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EDITORIAL

Editorial

Gambling can seriously damage your health

Simon Attard Montalto

Gambling is one of the earliest forms of entertainment and an ancient activity, possibly dating as far back as the middle pre-history Palaeolithic era (circa 50,000 years ago).[1] Dice, dating to before 3,000BC, have been discovered in ancient Mesopotamia (now Western Asia), gambling houses have been recorded in China in 1,000BC, early playing cards in the 800s AD, and the first casino opened in Venice, Italy in 1638.[1] Gambling, gaming and betting have been defined interchangeably but, arguably, equate to one another.[2] Gambling is known to become addictive, and is reinforced by repeated losses. It can be stratified, ranging from 'none', to 'occasional', 'recreational', 'at risk', 'problem' and finally 'pathological' gamblers. However, this is a continuum and all 'problem gamblers' started off as non-gamblers and 'worked their way up the ladder'. Gambling is mostly associated with male gender, and 'pathological gamblers' make up around 0.1-3.0 (median 1.5)% of any given western population, increasing to 2.3-13.0 (median 5.4)% if 'problem' and 'pathological' gamblers are combined.[3]

Problem gambling is intricately associated with health, social and financial problems.[4,5] The odd flutter may amount to a harmless folly, but habitual and compulsive betting has dire repercussions for the individual in terms of health, finances and secondary problems to fund increasing debt with, in some cases, recourse to criminal activity.[4-7] 'Problem' gambling has been estimated to cost the taxpayer in the UK around £1.2Bn per annum, mostly for additional NHS services.[8] The situation for gaming is similar to that of smoking and alcohol – all have a dire impact on individuals, families and society, yet governments 'tolerate' these, and 'balance' this tolerance by gambling-derived income and taxation.[9] That said, the global annual turnover of the betting/gambling industry is enormous, around $450 billion in 2020, and estimated to top a staggering $648 billion by 2027.[10]

Cover Picture:

'despising the poor)'

stoneware ceramics

By Joseph Agius

Joseph Agius is a senior staff nurse at the Fairyland Ward. He has been working there for the last 30 years. However, his hobby of ceramic sculpture has become his passion and he has established himself as one of Malta's foremost ceramists. He tends to favour a social neo-realist aesthetic. His profession as nurse exposes him to a world whose fabric at times includes pain, diseases, despair and death. World news is another source of inspiration. Agius chooses linguistic metaphors and figures of speech as springboards for his creations. The titles of his works have a metaphorical origin which Agius interprets as a narrative in clay.

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Hence, any tax 'hit' is easily absorbed with little impact on the industry itself and often, rather hypocritically, offset by exemptions and offshore tax-friendly sweeteners.[9,11]

The debate for and against gambling has smouldered for centuries, with governments, authoritative bodies and even religions taking widely divergent positions.[12] The 'modern' penchant for an inactive lifestyle encourages entertainment to be sought elsewhere, and the gambling community has been quick to exploit this niche and migrate gambling in diverse forms and guises on-line. High-street (any street!) betting/gambling outlets have mushroomed, in line with on-line betting websites. In 2020, COVID restrictions have not helped, and contributed toward increasing the growth of the industry's global earning by an estimated 5.6%.[10] A bet can be 'posted' on anything and everything, and at any time. Bets on the FIFA 2018 World Cup were estimated to have reached €136Bn,[13] whereas 26M Americans laid bets on the Super Bowl final in 2020, spending $6.8Bn.[14] Gambling advertising has become ubiquitous, particularly in association with sponsorship for individuals, teams, institutions and diverse sporting events. Betting-related advertising amounted to 17% of all advertising during the 2018 World Cup.[13] The sheer arrogance of intrusive betting advertising, often clothed in nauseatingly bombastic narrative, is astonishing. Promotional interruptions during key sporting events are commonplace, and Malta is not immune (remember the full-screen advert lasting almost a minute during the most recent world cup final?).

In its defence, in Malta as elsewhere, the industry and legislators have 'built in' numerous checks and balances ensuring regulation and with the aim of preventing excesses.[9,10,15,16] Similarly, this industry contributes significantly as an employer and toward the GDP: in 2019, Gaming employed approximately 7,500 persons, and added €1.56Bn, or 20% of the total, making it the third largest sector in Malta.[15] However, betting is, essentially, based on the concept of 'something for nothing' (or, at least, for very little). In reality, the hype and glamour surrounding mega-wins is all spin and simply adds gloss to the more down-to-earth (and sordid) reality: namely, that the overwhelmingly vast majority of punters lose their money. In its latest issue, whilst recognising Malta as a leading gaming jurisdiction that is home to many of the world's biggest online gambling affiliates, the *Global Gambling Statistics* reports: *". . . another interesting top 10 member is Malta. The small Mediterranean island boasts a small population but one of the largest per-capita losses anywhere in the world."*[16] Sobering words indeed.

The industry is extremely slick at publicising the 'big' (but rare!) wins (effectively, using these as their lure), whilst simply ignoring the vastly greater losses sustained by everybody else! This imbalance needs to be addressed, and it may be opportune to add, as with smoking, an official *caveat* on all betting advertising: **'Gambling can seriously damage your health'**!

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ORIGINAL ARTICLE

Assessing referrals to urology outreach in cases of acute urinary retention

Arthur Curmi, Jonathan Debattista, Gerald Busuttil, Kelvin Holmes, Keith Pace, John Sciberras

Introduction

Acute Urinary Retention (AUR) is the sudden and often painful inability to pass urine characterised by a palpable or percussible bladder. It constitutes 45% of all lower urinary tract consultations and is encountered in different medical specialties. A local guideline was set up to delineate the management of acute urinary retention (AUR) in July 2018. It describes the clinical features, investigations and treatment required according to the severity of the episode. The aim of this audit is to assess the demographics of patients making use of the Urology Outreach Unit (cases of AUR), and trends in investigations done, treatment chosen and outcomes on such patients.

Method

All patients older than 16 years of age who presented with AUR between March 2018 and September 2018 were included. Data was obtained from Urology TWOC forms and corroborated with the hospital online system.

Results

89 (37.6%) of the referrals were done from Accident and Emergency Department (A&E), and 86 (36.3%) were referred from Urology firms. Urinalysis and Microscopy was sent in 45.1% of cases. Renal profile (serum) was taken in 70.5% of cases. The most commonly used catheter type used was silicone (89.6%). Catheter size of 16F was used in 83.8% of the cases. The average days spent with the catheter in situ was 11.7 days. The average attempts at TWOC was 1.1 times (max of 3). 83.5% of patients were then advised to continue their medical therapy with appropriate follow up following a successful TWOC. The rest were scheduled for a repeat TWOC (13.1%), fitted with a long-term catheter (1.69%), advised regarding self-intermittent catheterisation (1.27%), or referred for TURP (0.42%).

Conclusion

This audit shows variable compliance to clinical guidelines. An active role of the clinician in the management and treatment of AUR might improve treatment and reduce the risk of further episodes of AUR.

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Background

A local guideline was set up to delineate the management of acute urinary retention (AUR) in July 2018. It describes the clinical features, investigations and treatment required according to the severity of the episode. For patients that are not admitted to hospital, or those that will be admitted, but will be discharged before an in-hospital trial without catheter (TWOC), a referral to Urology Outreach is to be organized. Key steps in the management of AUR are to be documented on the referral sheet to Urology Outreach, to ensure proper continuity of care. The aim of this audit is to assess the demographics of patients making use of the Urology Outreach Unit (cases of AUR), and trends in investigations done, treatment chosen and outcomes on such patients.

Methodology

Data was primarily obtained from Urology Outreach records. This was corroborated with data on hospital online systems. The audit period was from March 2018 to September 2018.

Inclusion criteria were include adults older the 16 years of age and at least 1 episode of AUR.

Results

Demographics: 237 entries were included in the audit, fitting the inclusion criteria above. 218 (92%) were male. Minimum age was 38 years, maximum of 93 years (average of 71 years).

Referral Source: The referrals were sent from various medical facilities. 89 (37.6%) were done from Accident and Emergency Department (A&E), and 86 (36.3%) were referred from Urology firms (Figure 1).

Characteristics of the episode: The cases were split evenly between painful AUR (118) and painless AUR (119). The residual volume was recorded on 71.3% of cases. Minimum residual volume was 135mL, and the maximum was 3000mL (average: 684.5mL). 16.9% of these patients were admitted; with length of stay varying from 1 day up to 23 days (average of 5 days).

Investigations: Urinalysis and Microscopy was sent in 45.1% of cases. Renal profile (serum) was taken in 70.5% of cases. Of note, the eGFR ranges were 8 up to 149 (average 74.1), with 50.2% of cases having an eGFR of more than 60.

Treatment: 222 entries (93.7%) had documented the insertion of a catheter. The catheter-type used was silicone (89.6%) (Figure 2). Of the total 222 catheters, 83.8% were 16F in size. With regards to medical treatment, 27.4% were not on any treatment prior to the event, and were not started on any treatment either. 48.5% were started on treatment. Documented changes in treatment can be seen in Figure 3

Figure 1 Referrals

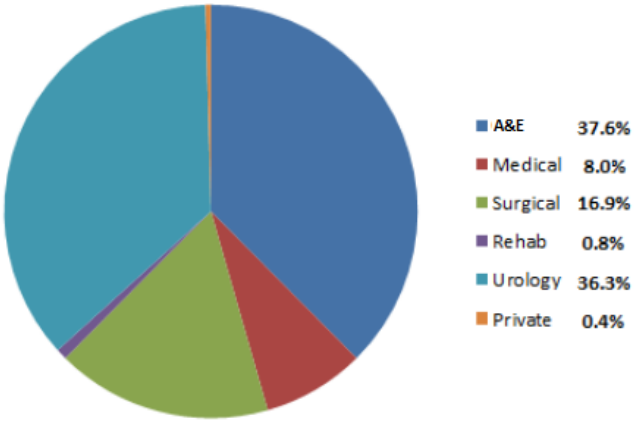


Figure 2 Type of catheter Used

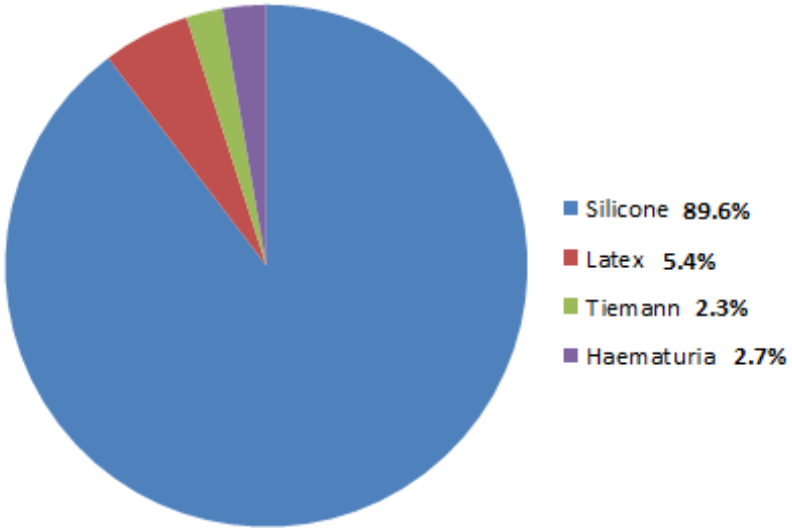
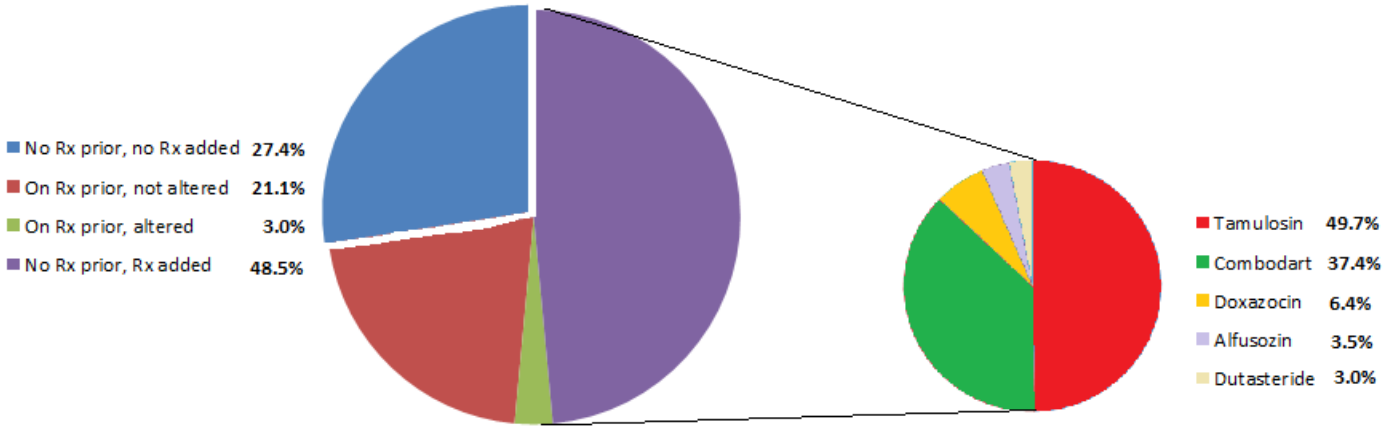


Figure 3 Treatment changes and type of treatment started



TWOC: The average days spent with the catheter in situ was 11.7 days (maximum documented of 49 days, and a minimum of 2). The average attempts at TWOC was 1.1 times (max of 3). The procedure was successful 83.5% of the time. The post-voiding residual (PVR) volumes ranged from 0mL up to 1000mL, the average being 154.97mL. In those TWOCs that were successful, the maximum PVR value was 690mL (average 97.82mL), and in those TWOCs that were not successful, the minimum was 150mL, the maximum was 1000mL, and the average was 486.31mL. The catheter residual was also documented; the average amount was 544.53mL (maximum of 1200mL, minimum of 250mL).

Outcome: 83.5% of patients (corresponding to successful TWOC cases) were then advised to continue their medical therapy with appropriate follow up. The remaining cases were either scheduled for a repeat TWOC (13.1%), fitted with a long-term catheter (1.69%), advised regarding self-intermittent

catheterisation (1.27%), and referred for TURP (0.42%).

Discussion

Acute Urinary Retention (AUR) is the sudden and often painful inability to pass urine characterised by a palpable or percussible bladder. Chronic Urinary Retention (CUR), on the other hand, is painless retention associated with high residual volumes after voiding. AUR is the most common urological emergency typically occurring in men between 60 and 80 years of age.[1] It constitutes 45% of all lower urinary tract consultations and is encountered in different medical specialties.[2] As expected the majority of our referrals were made from the emergency department (37.6%), urology (36.3%) and other surgical firms (16.9%). According to research, 10% of men over 70s and nearly a third over 80s will develop AUR.[3]

Obstruction occurring at or distal to the neck of the bladder may cause retention of urine. Obstruction may occur within the lower urinary tract itself (bladder stones, urethral strictures, prostate enlargement) or due to external compression of the bladder neck from a gastrointestinal or uterine mass. The most common cause in males is benign prostatic hyperplasia (BPH) with risk factors including advancing age, African American origin, increased body habitus, diabetes, alcohol consumption and a sedentary lifestyle.[1] Flaccidity or detrusor muscle failure can also cause incomplete bladder emptying leading to chronic urinary retention.[1] Other causes of AUR can be infective, inflammatory, pharmacologic or neurologic in origin. Thorough history taking and physical examination will often identify the underling etiology.

The diagnosis of AUR is aided by bladder ultrasonography. A volume equal or greater than 300mls in a patient who is unable to empty the bladder suggests retention.[4] Body habitus, previous surgery, scarring or tissue edema may give inaccurate bladder volumes.[1] Placement of a urethral catheter may, therefore, be required. It is considered to be the gold standard for measuring the post-voiding residual.[5] The amount of urine drained in the first 15 minutes after catheter insertion should be measured and recorded. In our case, the residual volume was recorded on 71.3% of the sheets. Urine should be tested for infection, and biochemistries evaluated to check for renal dysfunction and electrolyte imbalances.[6] Urinalysis was sent in 45.1% of cases, while serum renal profile was taken in 70.5% of cases.

Management of AUR should involve immediate and complete decompression of the urinary bladder through catheterisation in order to relieve patient discomfort.[7] The most commonly used catheter type was silicone (89.6%) followed by latex (5.4%). Silicone has a longer half-life so tends to be preferred for long-term use. First line urethral catheter should be 16 to 18 French in size. 83.8% of our cases had a 16 French catheter inserted. Smaller catheter sizes of 10 to 12 French may be used in cases involving a stricture. If urethral catheterisation fails, the urologist must be involved for consideration of catheterisation under vision, or suprapubic catheterisation. In circumstances where a urologist is not readily available, suprapubic aspiration via a needle under ultrasound guidance may be attempted. Contraindications to urethral catheterisation include recent urologic surgery such as urethral reconstruction and radical

prostatectomy. These group of patients should undergo suprapubic catheterisation.[8]

After the initial management patients are either admitted or discharged home and seen as outpatients. Patients with normal renal function and no significant comorbidities can be safely discharged home following catheterisation with a date for a later TWOC.[9] In our audit, 188 patients had an eGFR below 60 but only 40 patients (16.9%) were admitted to hospital. This might be due to pre-existing renal disease, and not new-onset renal dysfunction.

Although there is no general consensus when TWOC should be performed, in our audit removal of catheter was performed on day 11 on average. In the UK the majority of patients have their catheter removed on day 2 while in France TWOC is usually performed on day 3.[10] Some reports show that a prolonged duration of catheterization increased the chances of a successful TWOC.[11] Catheterisation for more than 3 days was actually associated with higher successful TWOC rates. However, prolonged catheterisation is associated with higher risk of complications including haematuria, urosepsis and urine leak so efforts should be made to reduce the duration of a urethral catheter.[12] This not only reduces comorbidities but also cuts down on healthcare costs. Reports state that there is a greater chance of successful TWOC if the patient is under 65 years of age, detrusor pressure is more than 35cm water, volume of urine drained is less than 1 litre at catheterisation and precipitating event is identified.[13] A TWOC is considered successful if the patient voids more than 100mls within 6 hours after removal of urinary catheter and the post-voiding residual volume is less than 200mls.[14] If removal of catheter is successful, patient needs follow up of lower urinary tract symptoms and treatment review.

Once the catheter is removed some patients will fail to pass urine normally and require re-catheterisation. These individuals may be managed by use of an indwelling catheter, self-intermittent catheterisation or considered for prostate surgery. Hence, measures to increase the rate of successful TWOCs are vital. The limited available research evidence implies that alpha blockers increase the rate of successful TWOCs. Data was statistically significant for tamsulosin, alfuzosin and silodosin.[13] They work by decreasing the smooth muscle tone of the prostate and increasing urinary flow with improvement of urinary symptoms. Tamsulosin which is given as 400mcg daily was the alpha blocker of choice (49.7%) while alfuzosin which is given as 10mg daily was used in 3.5% of the cases. Silodosin 8mg daily was not used at all. A combination of Tamsulosin and Finasteride (a 5-α-reductase inhibitor) was the second most preferred choice with 37.4% of cases. A combination therapy is usually preferred in men with very large prostates to maximize the prevention of further episodes of AUR.[15]

The number of TWOCs depend on patient characteristics, such as fitness to undergo surgery (like TURP) and also patient preference. In our audit 3 patients were referred for a third TWOC while another 2 patients were referred for a 4th TWOC. Surgical intervention is considered to be a last resort in the treatment of AUR. In males with BPH who fail a second TWOC, transurethral resection of the prostate (TURP) reduces AUR by 85 to 90 percent.[16] Surgery should be carried out until at least 30 days following the episode of AUR, to minimize the risk of surgical complications.[17] Out of 237 patients, only one (0.42%) was referred for TURP. This number could be an underrepresentation of the actual number of TURP referrals, since the decision

for TURP is often made at a later stage at outpatients after a series of failed TWOCs.

Recommendations

Clinicians should perform an appropriate evaluation. A urine sample and a renal profile should be taken in all cases of AUR and pre and post voiding residual checked with a bladder scanner. Moreover the practitioner must make sure that the residual is recorded appropriately in the TWOC form provided after insertion of the urinary. Intermittent self-catheterisation is another option. Although this can be difficult to employ from the emergency setting it can be used in patients who fail a TWOC whilst they are waiting for surgery. Adequate patient education about catheter care and importance of anti-sepsis should be provided. Involving patients in the decision-making process can also promote guideline use. Nurse should be aware about the contraindications of catheter insertion and must be able to recognize them. Clinicians need to be knowledgeable on how to perform suprapubic aspiration in cased where patient is in severe distress and urologist is not readily available. Coordination between the different members of the health care team is needed to improved patient outcomes.

Conclusion

This audit shows variable compliance to clinical guidelines. Hence, improvement both in the implementation and adherence to such guidelines is important as it improves the standard of care. An active role of the clinician in the management and treatment of AUR might improve treatment and reduce the risk of further episodes of AUR.

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Appendix A

Urinary Retention Management Guidelines

Department of Urology

Advisory, not mandatory

DEFINITION

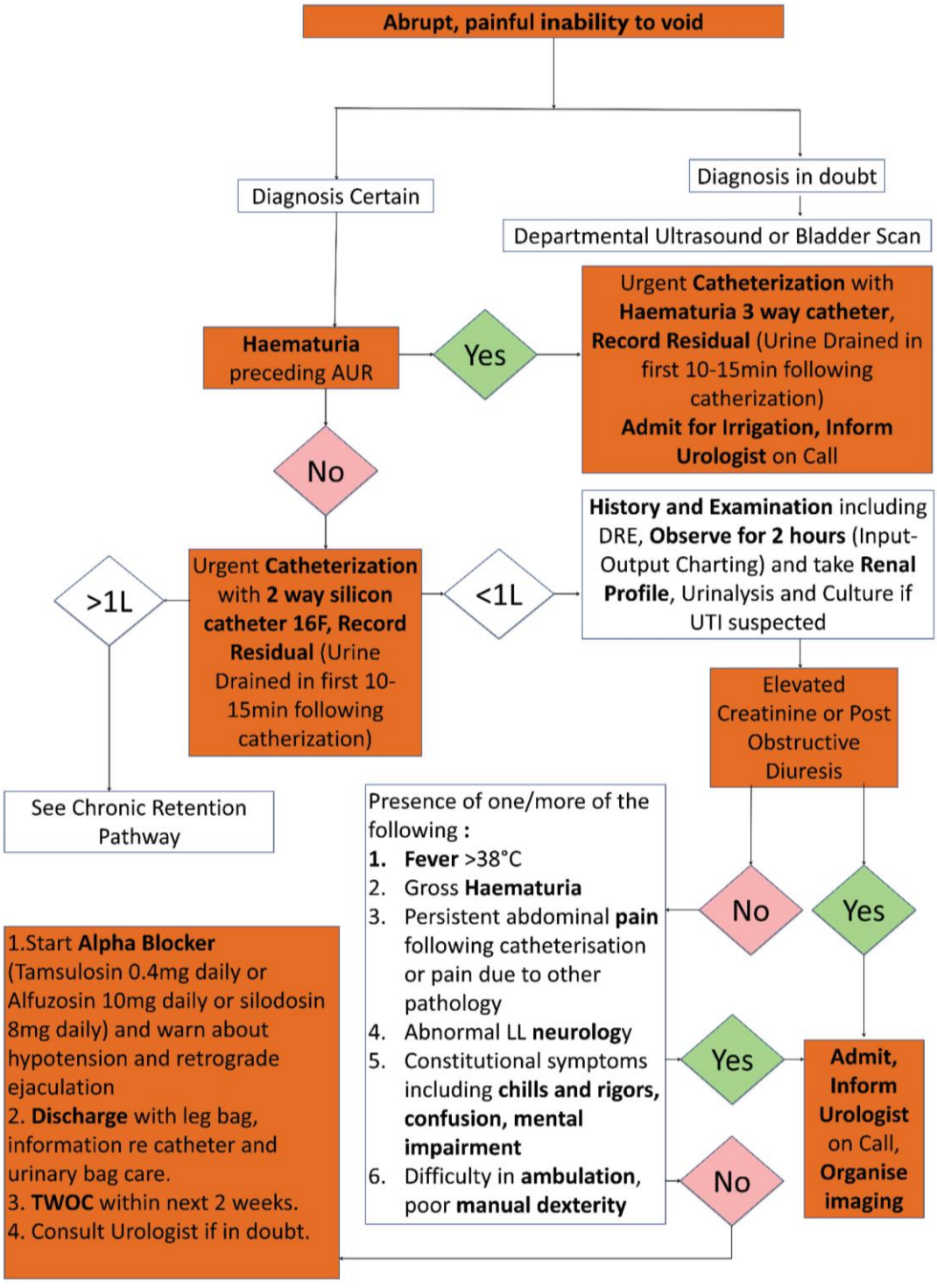
Acute Urinary Retention (AUR) is defined as a painful, palpable or percussable bladder, when the patient is unable to pass any urine. Whilst **Chronic Urinary Retention (CUR)** is said to occur when there is a non-painful bladder, which remains palpable or percussable after the patient has passed urine.

ACUTE URINARY RETENTION

AUR may be spontaneous or may be preceded by a trigger factor. In **spontaneous AUR** there is no trigger identified, with AUR being part of the natural history of Benign Prostatic Hyperplasia (BPH), usually after a long period of LUT symptoms (LUTS).

Triggered AUR may be preceded by bladder over-distension, surgery with general or regional anaesthesia, excess fluid intake, alcohol consumption, urinary tract infection, prostatic inflammation, faecal impaction, ano-rectal pain or use of drugs with sympathomimetic, anticholinergic or anti-histamine effects.

ACUTE URINARY RETENTION – MANAGEMENT PATHWAY



CHRONIC URINARY RETENTION

CUR is often defined by the volume of **post void residual (PVR).** However, there is **no consensus** on the cut off PVR and whilst some have defined it as a volume of 300mls, others have defined alternative PVRs as the cut off volumes or have given no cut off PVR at all.

CUR is classified as **High Pressure (HPCUR) or Low Pressure (LPCUR)** based on urodynamic findings.

LPCUR patients complaining of hesitancy, slow stream and incomplete emptying. These patients are usually followed up in an outpatient setting and only require catheterisation if symptomatic.

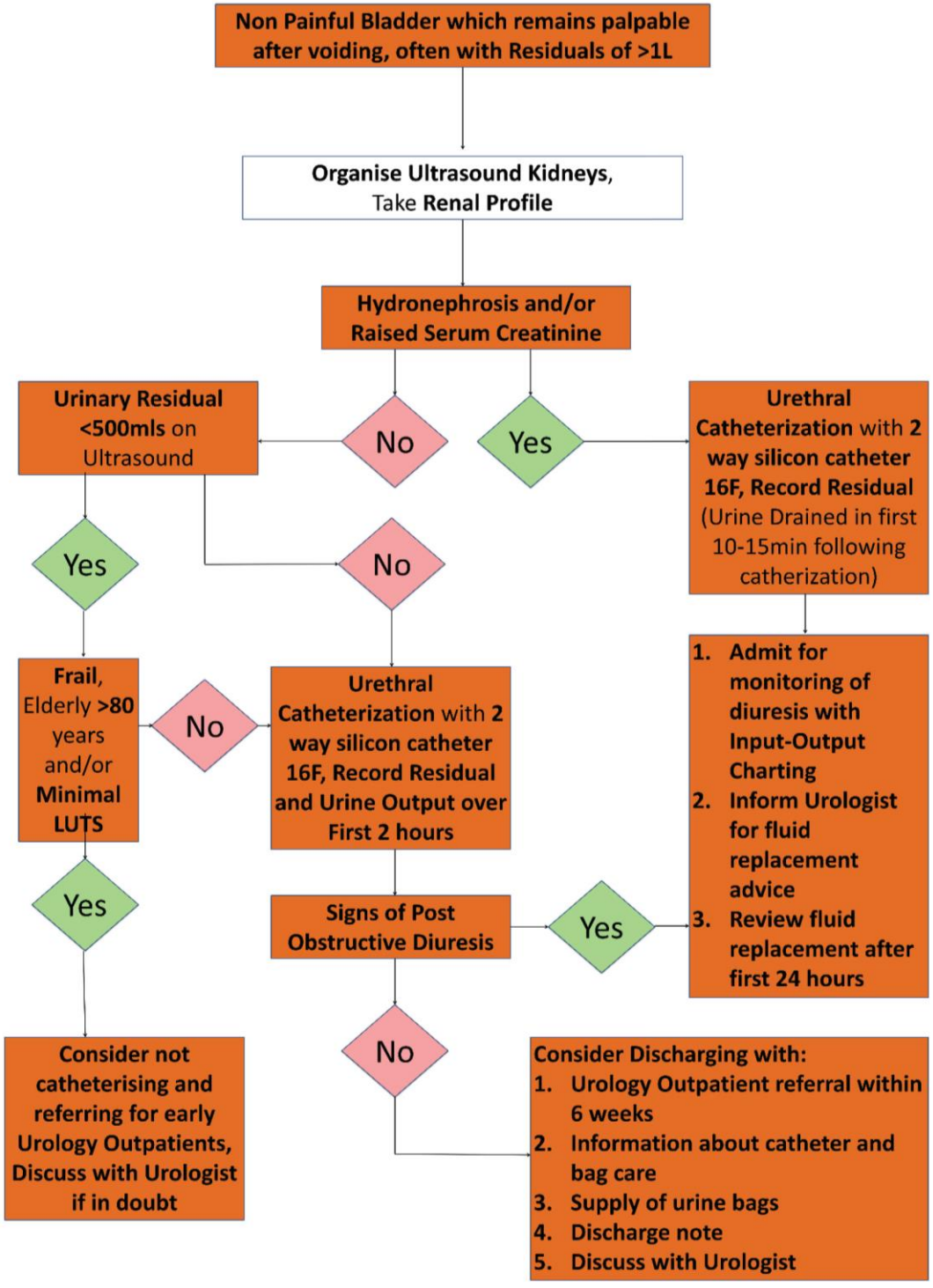
HPCUR patients complain of urgency. Their serum creatinine tends to be elevated and imaging reveals dilation of the upper urinary tracts. HPCUR patients require immediate catheterisation with careful recording of residual volumes and close monitoring of electrolytes as **inpatients**.

POST OBSTRUCTIVE DIURESIS

Urine production exceeding 200 mL per hour for 2 consecutive hours or producing greater than 3 L of urine in 24 hours is diagnostic of POD.

These patients require admission for close monitoring including input-output charting, daily weight and renal profile 12 hourly. They also require fluid replacement run at a negative balance, with fluid type tailored to serum and urinary electrolyte levels and hydration status. They will also benefit from consultation with a nephrologist.

ACUTE ON CHRONIC URINARY RETENTION MANAGEMENT PATHWAY



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ORIGINAL ARTICLE

Measuring Obstetric Anaesthesia workload – Empirical research using a Mixed Methods Design as part of a Quality and Safety Improvement Project

Petramay Attard Cortis Glenn Paul Abela

Background

Obstetric anaesthetists at Mater Dei Hospital considered the quality and safety of their work was deteriorating due to increasing workload. Literature suggests various ways of measuring this including the delivery rate, caesarian section rate, epidural rate, the obstetric anaesthesia activity index or a combination.

Objectives

The objectives were; to define the obstetric anaesthesia workload; to benchmark to standards set by international bodies; and to make evidence-based recommendations to improve safety and quality.

Methods

This single-centre study was performed between September 24 and November 20, 2017. It was an empirical research study using a mixed methods design. This allowed for data triangulation. Data was analyzed using SPSS.

Results

In 58 days, there were 669 births, 198 (29.6%) of which were by a lower segment Caesarean section (LSCS). On 30 days (52%), elective work over-ran, adding to the on-call workload. Average theatre cases in 24-hours were 3.81 ± 1.55. Epidural rate was 28.4% (*n*=190). The mean number of epidurals in a 24-hour period was 3.28 ± SD1.609. On 7 days (12%), not all requested epidurals were done because the anaesthetist was busy. Significant "hidden workload" was identified including patient reviews on 39 days (67%), vascular access outside theatre on 21 days (36%) and stand-by requests on 29 days (50%). There was no statistically significant difference between the work done on weekdays versus weekends.

Conclusions

We identified a significant amount of "hidden workload" in obstetric anaesthesia and workflow inefficiencies. Recommendations are being implemented to increase quality and safety of obstetric anaesthesia in Malta.

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Introduction

Malta is a Mediterranean island state with a population of around 470,000 people. It is currently experiencing a rapid population expansion due to immigration: a staggering 39% increase per 1000 inhabitant compared to an EU average of 2.1% per 1000 inhabitant.[1] It is mainly served by one tertiary general hospital with a 20-bedded intensive care unit, a theatre complex with 20 operating rooms and a labour ward with 9 suites and its own operating room.

Data from 2016 revealed a total of 4455 deliveries, the highest figure since 2000.[2] Delivery by Caesarean section was at 30.7% of all deliveries, up from 23.1% in 2000; 86.5% of these were done under a regional anaesthetic.[2-3] In 2014, epidural analgesia uptake stood at 26% of all deliveries, up from 6% in 2003.[3] Both the number of deliveries and the requests for anaesthetic procedures are set to continue increasing.

Obstetric anaesthesia is delivered by one on-call anaesthetist doing a 24-hour shift with dedicated consultant cover and junior trainee support from Monday to Saturday in the morning until 2PM. The on-call anaesthetist is either a non-consultant specialist or a senior trainee. Duties in obstetric anaesthesia are deemed notoriously work-intensive and anaesthetists during 24-hour shifts in labour ward often complain about the difficulty in delivering a safe service because of being over-worked and too tired. In addition, there is no separation of elective and emergency theatre work: both are carried out by the same anaesthetic team in the single labour ward operating room.

The aims of this study were to carry out a literature review of how anaesthetic services should be delivered in an obstetric setting; to carry out a literature review of how "workload" is assessed; if these do not return any results, or the methods identified therein are not feasible in our setting, set up a method to quantify and assess "workload"; assess the workload in our delivery suite using the parameters identified in earlier stages; and submit evidence-based recommendations to the departmental management for evaluation and implementation. This initiative served as a quality and safety improvement project in obstetric anaesthesia in Malta, following the concept of Safety-2, a model that aims to improve systems and processes to prevent the occurrence of errors or mistakes, rather than waiting for errors to occur and analysing them in retrospect (Safety-1).[4-5]

Materials and Methods

Permission to carry out this study was sought from, and granted by, the chairpersons of the departments of Anaesthesia and Intensive Care and of Obstetrics and Gynaecology, and the Data Protection Office, all at Mater Dei Hospital. Approval by the University of Malta Research Ethics Committee was not deemed necessary, as this was an internal data collection exercise with no patient involvement or intervention. The purpose of the study was explained to all anaesthetists working in obstetrics in writing and they all consented to participating in telephone interviews as part of this project.

A literature search was carried out to identify documents on the provision of anaesthetic services especially in obstetric anaesthesia. This was particularly important to select quality of care markers to which the obstetric anaesthesia service in Malta could be

compared. Also, a search for the terms "health workload", "workload in healthcare", "workload", "assessment of workload" was carried out on PubMed and Google Scholar.

The mixed-methods study design was used to develop a model to collect data in our setting and this included data triangulation, complementarity and expansion, three of the five main components of mixed method research.[6]

The first step in designing this study was to identify functioning databanks that were already in use and with which all labour ward staff were familiar. These were the operating theatre register, the obstetric anaesthesia activity logbook, the epidural analgesia record and the mothers' clinical notes. Although these involved writing down information manually, they were all filled out contemporaneously and their use was very well established. These databanks were used to devise a method to collect quantitative data that involved one databank serving as a primary source and another to cross-check it.

In addition, a number of activities that take a considerable amount of time but are never recorded were identified. These were: (1) standby for instrumental deliveries, (2) postoperative review of patients and (3) obtaining vascular access outside theatre. There were collectively termed "hidden workload". Interviewing the on-call anaesthetists was deemed the ideal way to gauge the amount of this work.

Three separate data collection protocols were written up each covering a different aspect of workload in obstetric anaesthesia. Analyzing the data from the three protocols together would allow building up an understanding of what was going on in labour ward. The protocol forms were:

- *Anaesthetist on-call questionnaire* – included questions on the work they did, including the hidden workload, and whether they felt subjectively busy during various shift times. This data was collected by one-to-one telephone interviews with on-call anaesthetists in the final thirty minutes of their 24-hour shift.
- *Epidural analgesia service workload* – included the grade of performing anaesthetist, the time of epidural request and the time of test dose administration for every epidural inserted in the previous 24-hour duty. Data was collected and cross-checked from the epidural record book, the anaesthesia procedures logbook and the midwifery notes.
- *Labour ward operating theatre workload* – included details on each individual theatre case, especially their timing, duration and level of urgency. Data was also collected on whether any cases had to be done in the main operating theatres (MOT), particularly the indication mandating such a transfer. This data was collected and cross-checked from the labour ward and MOT theatre registers, and the anaesthesia procedures logbook.

A working group consisting of anaesthetists with varying levels of experience was set up to serve both as a focus group and data collectors. Its members were informed about the purposes and methods of the initiative and trained in the completion of paper data collection forms. Three data collectors were assigned to a specific protocol i.e. one each for theatre cases, epidural service and anaesthetist on-call. A fourth was assigned to fill up gaps in cases of unavailability. Instructions on following the data collection protocols were written up overleaf on the

forms to serve as an aide-memoire and to further ensure standardization in data collection.

The project ran for 58 consecutive days (from September 24 to November 20, 2017) and data was collected prospectively every day. After the first three weeks, the working group was re-convened to discuss how data collection was progressing and deal with any problems. The unanimous decision was to continue with the data collection as planned with no changes to the protocols in place.

The data collected was inputted in MS Excel spreadsheet by one other member of the working group and was then analyzed by a separate professional statistician using SPSS.

RESULTS

The literature review identified three documents to be consulted for benchmarking our service: the OAA/AAGBI Guidelines for Obstetric Anaesthetic Services 2013, the Royal College of Anaesthetists Guidance on the Provision of Obstetric Anaesthesia Services 2019 and the WHO-WFSA International Standards for a Safe Practice of Anaesthesia.[7-9] At the time of writing, no similar European guideline was available. The authors are however aware of an ongoing effort by the European Board of Anaesthesiology to produce such recommendations (private correspondence).

Publications on evaluation of obstetric anaesthesia workload are limited. The 2005 AAGBI/OAA joint report arbitrarily defines "busy units" as those with over 5000 deliveries per year, an epidural rate above 35% and a Caesarean section rate above 25%.[10] Ginosar and colleagues devised the Obstetric Anaesthesia Activity Index (OAAI), a dimensionless number based on the number of deliveries and the number of epidurals carried out in a year.[11] However, the RCoA claims that "busy units" cannot be solely defined by crude figures, but must include other activities such as the number of regional anaesthetics provided for labour, the number of Caesarean sections and instrumental deliveries, any other procedures performed in the operating theatre, the number of critically ill obstetric patients and the number of patients seen at anaesthetic antenatal clinics.[8] Yentis and Robinson suggest using the "number of anaesthetic interventions" instead of delivery rate and the "regional anaesthesia rate" instead of rate epidural uptake, as markers of obstetric anaesthesia workload. The number of anaesthetic interventions is the sum of regional anaesthetics (spinal, epidural or CSE) done where the indication is "labour" and the number of Caesarean sections, instrumental deliveries and third stage or other procedure done in the operating theatre. The regional anaesthesia rate is defined as the number of women receiving a spinal, an epidural or a CSE for all indications divided by total number of deliveries.[12]

The methodology described above was used to collect raw data from our unit.

Labour ward operating theatre cases

During the study period there were 669 deliveries, 221 of which (33%) required theatre intervention. Most (198 cases, 90%) were lower segment Caesarean sections (LSCS): 113 were elective and 85 were emergency. Other theatre cases included suturing of birth canal tears (12 patients), manual removal of placenta (10 patients) and one instrumental delivery. LSCS rate was calculated at 29.6% of deliveries. Average number of theatre cases in 24-hours was 3.81 ± 1.55.

The commonest type of anaesthetic administered was the spinal block (152 cases, 68.8%), followed by the epidural anaesthetic (36 cases, 16.3%) and the general anaesthetic (27 patients, 12.2%). 97% of elective LSCS were done using regional anaesthesia (spinal or epidural top-up), with the remaining 3% performed under GA. For emergency LSCS, 70% were performed under regional anaesthesia, and 30% under GA. Average duration of time in theatre per case was 70.11 ± 18.86 minutes. Fisher Exact test revealed no statistically significant association between the number of cases done and the day of the week (p-value 0.773) (Figure 1). This was confirmed using time series analysis (Figure 2).

Figure 1 Total number of cases (y-axis) versus day of the week (x-axis)

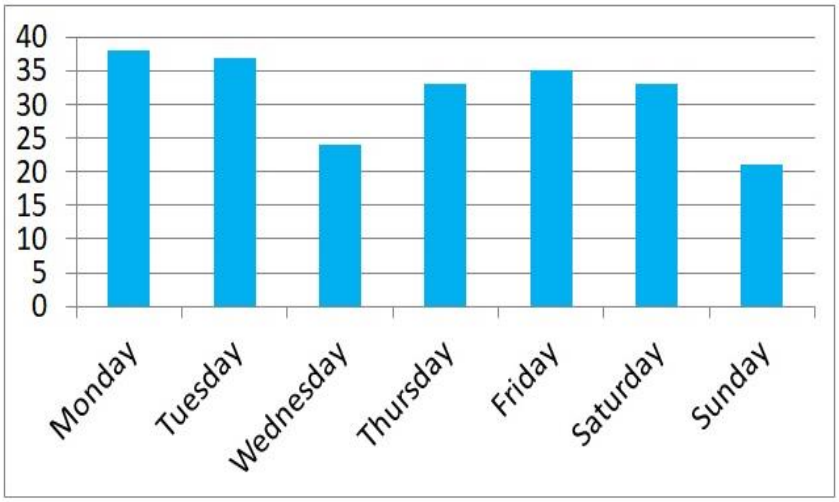
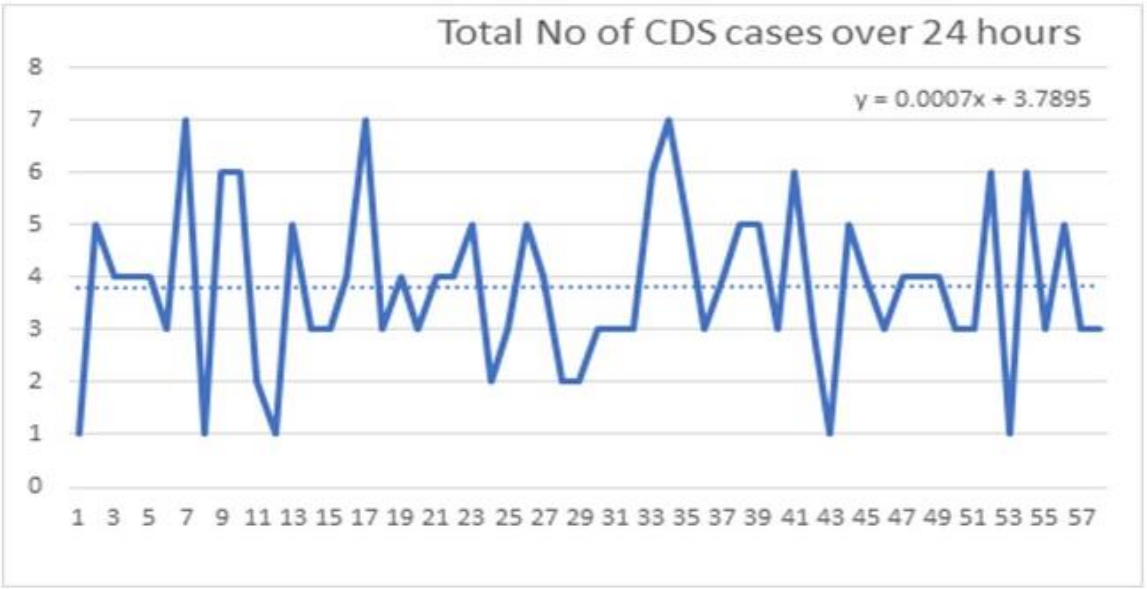


Figure 2 Total number of theatre cases per day (y-axis) versus study day (x-axis); time series analysis



Elective work overran past regular hours on 30 days (52%). Reasons for this included starting late in the morning (after 9:30am) and emergency work occupying the sole labour ward theatre (both 26% of study days), as well as elective LSCS lasting more than expected and poor scheduling of elective work (elective LSCS scheduled out-of-hours or on Sundays). There was no association between the number of epidurals done between 0800 to 1400 hours (regular hours) and elective work finishing after 1400 hours (encroaching on the on-call hours), using the Fisher Exact Test (p-value 0.656).

On two separate days, two parturients had to be transferred for urgent surgery to the main operating theatres as the labour ward theatre was occupied. In both occurrences, there were other cases being done in the labour ward operating room.

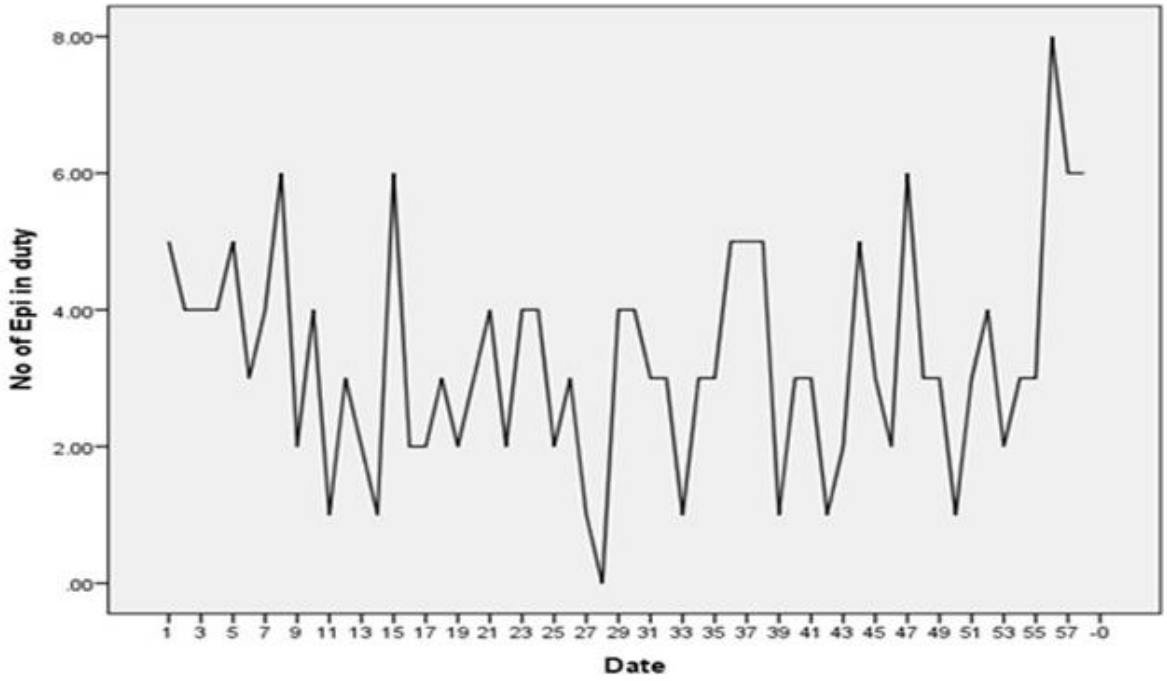
Epidural analgesia service

During the study period there were 190 labour epidurals i.e. 28.4% of total deliveries. The mean number of epidurals in a 24-hour period was 3.28 ± 1.609. The mean time in minutes between the anaesthetist being informed of the epidural request and the test dose being administered was 41 minutes (range 15 – 134 minutes). This time was over 60 minutes in 14 requested epidurals (7% of total epidurals), mainly due to the on-call anaesthetist being delayed by theatre work or due to increased technical difficulty of epidural insertion. On 7 days (12%), not all requested epidurals were done due to heavy workload.

Additional documented workload in relation to epidurals on the labour ward included documented patient reviews (*n*=38), bolus or top-up doses (*n*=37) and infusion refills (*n*=17). Most of the epidural analgesia workload was mainly carried by the non-consultant specialists (97 epidurals) and trainees (86 epidurals). One epidural blood patch for post-dural puncture headache was performed during this time.

There was no significant association between day of the week and time spent on epidurals (one-way ANOVA test, p-value 0.292) and this was confirmed using the Kruskal-Wallis test (p-value 0.203). Similarly, there was no association between the day of the week and the number of epidurals done (Fisher Exact test, p-value 0.055). This was also confirmed by time series analysis (Figure 3).

Figure 3 Total number of epidurals per day (y-axis) versus study day (x-axis); time series analysis



Anaesthetist on-call questionnaire

The 24-hour on-call obstetric anaesthesia duties were done by a non-consultant specialist on 49 days (84.5%) and by a senior trainee on 9 days (15.5%). On 18 days (31%), a junior trainee was assigned to this 24-hour duty in obstetrics.

On 90% of study days, the on-call anaesthetist felt that they were busy during the day, night or both. There was no association between how busy the on-call anaesthetist reported being and the presence of the junior trainee (Fisher Exact test, p-value 0.121) or their grade (non-consultant specialist or trainee) (Fisher Exact Test, p-value 0.701). Enough time for rest during the 24-hour shift was reported in 50% of days. Sub-group analysis revealed that the presence of the junior trainee changed the reported adequate rest rate from 45% to 61%. This allows us to infer that, although the presence of a junior trainee did not change the workload i.e. if the on-call anaesthetist reported being busy or not, it did allow the senior anaesthetist to report having better rest.

The hidden workload activities reported by the on-call anaesthetists included: patient reviews on 39 days (67%); vascular access outside of the operating theatre on 21 days (36%) and stand-by requests (for example, being present on the delivery suite in case of failed instrumental delivery) on 29 days (50%).

The on-call obstetric anaesthetist called the on-call consultant anaesthetist covering general anaesthesia on 7 days (12%) and they attended the delivery suite 3 times. Also, the on-call obstetric anaesthetist called for help from other non-consultant specialists covering the main theatres on separate 4 days (7%).

Further combined analysis

The mean duration of theatre and epidural-insertion related work was 400 ± 179 minutes per 24-hour period. This did not statistically correlate with time of the day, day of the week, a 1-in-6 pattern (most obstetrician shifts) or a

1-in-4 pattern (most midwifery shifts) using the Fisher Exact test.

A one-way ANOVA showed a significant association between the number of epidurals done and whether the anaesthetist on-call stated that they were busy during their shift (p=0.026). The suitability of the one-way ANOVA was confirmed using the Shapiro-Wilk test and Levene's test (p-value 0.450).

Discussion

Through this project, we identified six parameters that can be used to define how busy a maternity unit is. These are the delivery rate, the epidural rate, the rate of Caesarean sections, the Obstetric Anaesthesia Activity Index (OAAI), the anaesthetic interventions rate and the regional anaesthesia rate. Using these parameters only would indicate that our unit is a medium-sized delivery suite in terms of activity (Table 1).

Table 1 How busy is our obstetric unit?

	Threshold value or range identified in literature	MDH figures 2017
Delivery rate	5000	4210
Epidural rate	35%	28.4%
Caesarean rate	25%	29.5%
Obstetric Anaesthesia Activity Index (OAAI)	1.97 – 24.14	7.58
Regional anaesthesia rate	50–60%	52%
Number of anaesthetic interventions	Nil	2586.5

The fact that the time series analyses carried out were negative and that the mean duration of theatre cases and epidural insertion were not associated with day of the week, time of the day or colleagues' shift pattern demonstrates that our obstetric anaesthesia workload is unpredictable. This could be true for other units and makes appropriate staffing and of allocation of resources difficult. However, we did find a positive association between the number of epidural catheters inserted and on-call anaesthetists reporting they were busy. This correlates to the obstetric anaesthetists' clinical experience: epidural analgesia requires several steps and interventions that may stretch over a number of hours, including consenting the mother for the epidural catheter insertion, doing the procedure itself, setting up the analgesia programme, checking the quality of the block and troubleshooting any problems that may arise. These in turn vary from administering boluses and treating hypotension to re-positioning or re-inserting the epidural catheter itself.

This project demonstrated how hidden workload activities can take up considerable time: the on-call anaesthetist reported engaging in at least one such activity on most days of the study period. Any other attempts to quantify obstetric anaesthesia workload should take into account this work. Further areas of study can involve devising a unifying index that includes the delivery rate, the number of anaesthetic procedures, the number of regional anaesthetics and the hidden workload.

Defining the workload in obstetric anaesthesia can be a difficult task. Stand-alone numbers such as delivery rate and rate of epidural uptake, and the Obstetric Anaesthesia Activity Index derived from them, give a limited

indication of what really goes on as they do not take consideration the multiple activities that often go unrecorded. Using a mixed-method study design, we devised a model to collect data from several sources, including the anaesthetists finishing their on-calls in obstetrics. This in turn allowed us to compute standard figures (such as delivery rate, regional anaesthetics rate) and also quantify the hidden workload. We firmly believe this is an important component of the day-to-day work of the obstetric anaesthetist that cannot be ignored and contributes in no small way to the smooth running of and better quality of care in delivery suites.

Apart from computing the number of anaesthetic interventions carried out in our delivery suite we also recorded the duration of each procedure. Although the length of time a procedure is dependent on operator experience (in case of theatre intervention, that of the surgeons too), this is another important aspect that often goes ignored in evaluating the work intensity of a job. Furthermore, these time recordings allowed us to see how emergency work is impinging on elective cases and vice-versa, and by carrying out time-series analyses, to check if there is an association with other variables (time of day, day of the week, shift patterns).

The combined effort of literature reviews, interpretation of international guidelines and detailed data analysis as outlined above allowed us to write up several recommendations to the departmental management. These included separating the elective and emergency work and rostering different anaesthetists for each; stopping the scheduling of elective work out of regular hours; scheduling two anaesthetists fully trained in obstetric anaesthesia per 24-hour shift; and implementing a fully operational anaesthesia-led obstetric clinic for high-risk mothers.

The strengths of this project are that it ran prospectively, the study model used involved several steps of data triangulation to ensure the information retrieved was correct, and only one of the investigators inputted all data in respective spreadsheets. This was done to minimize errors and differences in data interpretation. Statistical analysis was then carried out by a professional statistician with an academic understanding of the best methods required to analyze the data and achieve our aims.

However, this study has several limitations. Primarily, data collection was not contemporaneous and depended on how well activities were recorded in the other databanks, rather than being directly observed. In the event an activity was not written up, it would have been missed by the data collectors. The on-call anaesthetists' survey was highly subjective as different people perceive being busy differently and if some anaesthetists did more on-calls than others during the study period, their answers would have skewed the results. Measuring the hidden workload depended on anaesthetists recall of events over the previous 24-hours. Also, the study period was short and even though it allowed us to better understand the level of anaesthetic activity in labour ward, the small numbers limited the statistical analysis.

Despite the study limitations, to the authors' knowledge, this is the first study that attempts to quantify obstetric anaesthesia workload not only by looking at standard data but also by identifying hidden workload, analyzing the duration of anaesthetic interventions and computing multiple statistical tests in order to establish associations between different

factors. In addition, the method used can be applied to other settings in order to distribute resources adequately and improve both working conditions and patient service and safety.

Summary Box

What is already known about this subject?

- Subjectively, obstetric anaesthetists in Malta considered the quality and safety of their work was deteriorating due to increasing workload.
- Various methods of measuring obstetric workload are reported in the literature.
- International guidance is available regarding safe staffing levels on obstetric units.

What are the new findings?

- The obstetric anaesthesia workload in Malta is defined using qualitative and quantitative methods, combining the various methods reported in the literature.
- Additional "Hidden workload" has been identified, defined and quantified.
- A preventative Safety-2 approach, as applied to obstetric anaesthesia in Malta, has allowed the development of recommendations to improve safety and quality of work.

Acknowledgements

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Presentation: Partial data was presented as an oral presentation during Euroanaesthesia 2019 in Vienna, Austria. Partial data was also presented as oral and poster presentations at the Malta Medical School Conference 2018.

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ORIGINAL ARTICLE

A comparison of intraoperative cell salvage use with cardiotomy suction in cardiothoracic surgery

Edward Muscat, Timothy Miggiani, David Sladden, Alexander Manche'

Introduction

Intraoperative cell salvage has been shown to be a safe and effective means of autologous blood recirculation in elective surgery. Most cardiac units now employ cell salvage for complex procedures but few use it routinely in all cardiac procedures requiring cardiopulmonary bypass.

Aim

To demonstrate if there was any haematological benefit of autologous transfusion using intra- operative cell salvage over single use of cardiotomy suction in patients undergoing cardiac surgery.

Methods

All patients who had operations performed by the cardiac surgical team over a twenty-month period formed part of this study including valve replacements and coronary artery bypass grafting. The patients were divided into two groups; the cell saver group and the control group. The haematological variations of these patients' blood results were analysed preoperatively, immediately post-operatively and 24 hours post-operatively.

Results

451 patients were operated on during this period. 230 patients in the control group and 221 patients in the cell saver group. Intra-operative cell salvage demonstrated better immediate post-operative haemoglobin levels (10.31 g/dL) compared to the non-cell saver group (9.99 g/dL). The p-value was 0.003 after comparison between pre-operative haemoglobin and post-operative haemoglobin in the cell saver group.

Conclusion

Intra-operative cell salvage demonstrated a minimal increment in haemoglobin levels in the immediate post-operative period when compared with cardiotomy suction alone. Even though the improvement in haemoglobin is only significant until 24 hours post-operation, overall this showed an improved haematological parameter in the immediate recovery period.

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Introduction

Major surgery, especially cardiac surgery, is a challenge to the hematopoietic system. It is well known that patients with cardiac disease, namely ischaemic heart disease and hypertrophic cardiomyopathy, cannot tolerate a decrement in haemoglobin and haematocrit levels. Cardiac surgery carries a high burden in terms of blood loss and transfusion requirement, and hence transfusion related injuries. The National Blood Service in the UK advocates that 10% of its stored blood supplies are used in cardiac surgery alone.[1] The continued use of allogeneic erythrocyte transfusions is associated with adverse effects such as myocardial ischaemia, acute lung injury and an overall raised mortality index.[2] According to various authors, a haemoglobin of 10 g/dl and a haematocrit of 30% indicated desirable goals in anaemic patients undergoing cardiac surgery.[3] Blood is a limited yet costly resource and it should be utilised as sparingly as possible. The autologous options for surgical blood conservation circumvent the transfusion of allogeneic blood. Options include preoperative autologous blood donation, intra-operative haemoconcentration and blood salvage.

The cardiotomy suction apparatus was introduced first in the 1960s as an extension of the intracardiac vent to allow blood lost during the operation to be returned via the cardiopulmonary bypass (CPB) circuit. The aim was to reduce blood loss and hence the need for allogeneic blood transfusions with its known risk of increased morbidity however this is not always the case as evidence suggests that recirculated cardiotomy suctioned blood neither reduces blood loss nor transfusion requirements.[4] Intra-operative cell salvage (ICS) during cardiac surgery is widely accepted; a meta-analysis of 31 trials showed that routine use reduced the transfusion of red cells by 40%.[5]

It works by collection, washing, and re-infusion. Collection involves the use of a double-lumen suction device. One lumen drains blood from the operative field and the other lumen adds a dose of heparinized saline to the drained blood. The anticoagulated blood is then passed through a filter, which is then collected in a reservoir. Centrifugation splits the blood into separate components. The red blood cells (RBCs) are then isolated and washed which are then filtered across a semi-permeable membrane. The free haemoglobin, plasma, platelets, white blood cells, and heparin become removed at this stage. The same RBCs are infused in normal saline transforming the haematocrit to 50–80%. Blood can then be transfused immediately or within a six-hour time frame.[6]

ICS is purported to feature benefits such as a decreased need for allogeneic blood transfusions and increased cost-effectiveness. It has been argued that ICS has financial benefits over erythrocyte transfusion in the setting of homologous blood is becoming more expensive. Furthermore, leucodepletion of blood in the post Creutzfeldt-Jakob disease era has quadrupled the cost of allogeneic blood transfusion.[7] It also avoids the potential side effects such as the transmission of viral illnesses, transfusion reactions and immunosuppressive infections associated with blood transfusions.[8] In addition, it can be associated with a lower risk of cerebral lipid embolism.[9]

The principal drawback of ICS in the literature is dilutional coagulopathy as blood that is salvaged lacks clotting factors. It has also been argued that since the introduction of drugs,

lower priming volumes and intravascular shunts blood loss has been minimised to the extent that ICS is no longer warranted.[1] At the time of writing this study there have been many publications highlighting the benefits of cell saver over cardiotomy suction but few recommend its routine use in cardiac surgery. Its use needs to be justified by analysing post-operative improvement in haemoglobin and haematocrit levels.

Therefore, the aim of our clinical study was to evaluate the effects of autologous cell saver blood transfusion on blood loss and changes in haemoglobin and haematocrit concentrations in the cardiac operations done in between over a one year period in Mater Dei Hospital in Malta. The literature has shown that the values of blood markers (number, size, function) produce changes during the early phase of cardiac surgery, steady recovery during the postoperative period achieving preoperative values 2-6 months after surgery.[10]

Materials and Methods

This study included all patients who had operations performed by the cardiac surgical team over a twenty-month period. Inclusion criteria consisted of all major cardiac surgical operations within this period including valve replacements (aortic and/or mitral). coronary artery bypass grafting (emergency or elective), aortic graft, cardiac tamponade and aortic root replacement. All patients underwent a general anaesthetic and standard practice of cardiopulmonary bypass.

The selected patients were organised into two groups namely the control (non-cell saver) and the cell saver groups. Data collection included patient demographics and hospital numbers, which were processed by the local hospital clinical manager software, iSoft, in order to retrieve their individual haematology results. The main focus of this study was primarily interpretation of trends of Haemoglobin (Hb) and Haematocrit (Hct). In order to accurately measure the trend of haematological variation throughout the patients' hospital stay blood results preoperatively, immediately post-operatively and 24 hours post-operatively (delayed) were obtained for analysis. All statistical analysis was performed using the SAS statistical software programme. We considered results to be significant at p value < 0.05.

The cell saver system was implemented in the year of 2015 in Mater Dei Hospital, Malta. Therefore, acquisition of control group patients was historical and occurred prior to the cell saver group being between January 2014 to September 2014. An equivalent number of control cases were recorded before the introduction of the cell saver machine and this included matching criteria. These weren't case matched on an individual basis however the average group demographics were consistent with similar risk factors and co-morbidities. Data for the cell saver group was collected prospectively as the operations were performed over time. The two cohorts were matched overall by a separate researcher prior to data collection of blood levels. All operations were performed by the same three cardiothoracic surgeons using relatively similar surgical methods and bypass times.

Results

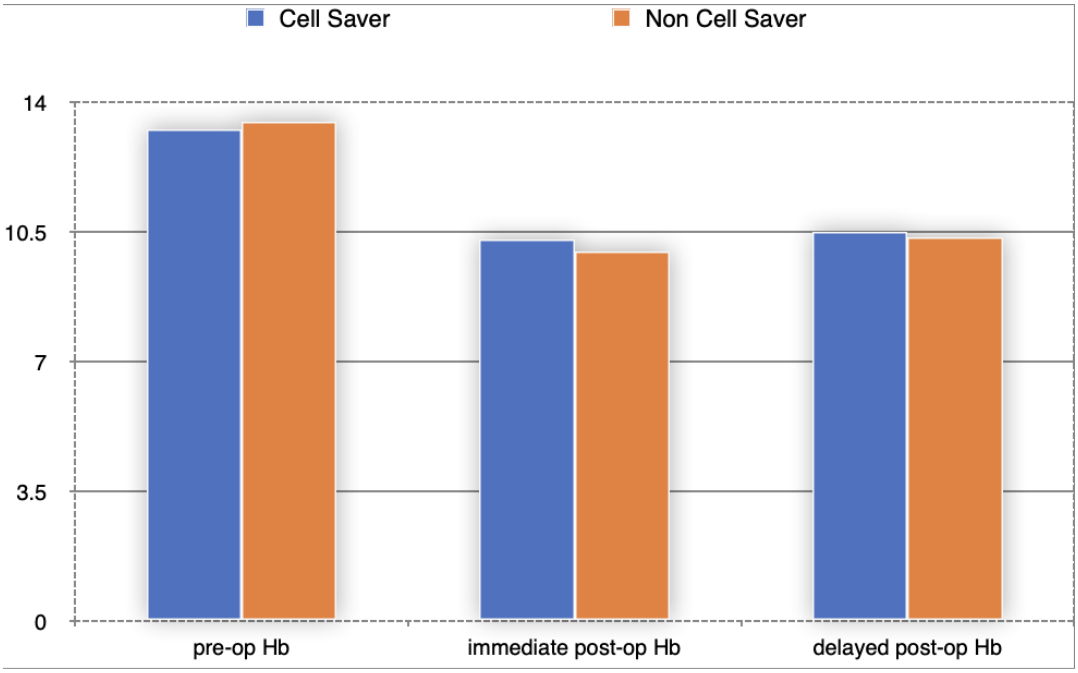
The total number of patients were 451 with a mean age of 64.75 years. 230 patients were in the control group and 221 patients in the cell saver group. The total number of operations is shown in table format in Table 1. The overall pre-operative haemoglobin mean was 13.28g/dL in the cell saver group and 13.47g/dL in the control group. The overall

mean preoperative haematocrit was 38.79% in the cell saver group and 39.15% in the control group. In both groups the average number of units of whole blood transfused to the patients were the same.

Table 1 Table including the categories of cases in this study

	Control	Cell saver
Total patients	230	221
Number of total AVR cases	54	60
Number of total MVR cases	17	27
CABG cases	169	139
Combined AVR + MVR cases	1	2
Combined CABG +VR	13	10

Figure 1 Bar graph showing the comparison of haemoglobin values between cell saver and non-cell saver cardiac operations pre and post-operation.



An important result from both group findings was mainly the *p*-value of 0.003 after comparison between pre-operative haemoglobin and post-operative haemoglobin in the cell saver group which is statistically significant for this study being that confidence intervals were all 95% *(Figure 1)*. The same cannot be said for delayed post-operative haemoglobin which did not show any statistical significance when comparing pre-operative haemoglobin *(p*=0.143*)*. Therefore, an increment was found amongst the cell saver

patients compared to control group patients in terms of immediate post-operative haemoglobin levels considering the pre-operative Hb even was lower for the cell saver grouped patients. Minor haematocrit difference was observed between both groups both immediately post-operation *(p*=0.643*)* and delayed post- operation *(p*=0.766*).*

Discussion

Intraoperative autologous red cell salvage during cardiac surgery is an attractive alternative to the continued single use of cardiotomy suction. From our study we have observed that ICS was associated with better post-operative haemoglobin results compared to the control group in the immediate post-operative period. Similar results were also mentioned by Marcoux et al in his study where post-operative haemoglobin concentrations, in cardiac surgical patients, were significantly higher in the ICS group consequently spending significantly less time in the Intensive Care Unit (ICU).[11] In terms of delayed post-operative haemoglobin results both groups had similar results with the cell saver group having haemoglobin levels that were, again, slightly higher.

When first introduced in the 1980s, some authors had opposing views against the use of ICS, because it would neither decrease the costs nor the requirement of autologous blood. Since then, several studies have emerged highlighting the advantages in the use of ICS being that it increases haemoglobin concentration and utilizes less use of allogenic blood transfusion in the post-operative period.[12] Several other studies have shown advantages in the use of the cell salver. Almeida et Leitao also mentioned that use of a cell saver mechanism results in shorter hospitalization time in ICU (one day less) and a reduction of the use of red blood cell units during inpatient stay for cardiac surgical patients.

Currently, misconceptions regarding the use of cell saver systems portray them as expensive, ineffective, and inappropriate for use in certain clinical situations. Several authors have demonstrated that the lack of use of red blood cells in the postoperative period decreases not only the morbidity but also intra and postoperative mortality. In a recent study, Coté et. al. retrospectively analysed outcomes of ICS in cardiac surgery revealing ICS group were less likely than the control group to be exposed to packed red blood cells, coagulation products or any blood products in the peri-operative period.[13] Since whole blood transfusion is used after cardiac surgery as a means to enhance cardiac output it was not analysed as a variable for cell saver performance in our study. Both groups had cardiotomy suction available providing an added benefit. In our study we had not noticed any significant difference in the number of units of blood products between both groups but as this is a pilot study of cardiac operations the patients received similar transfusion units post operatively and perhaps the team will become more confident in the ability of the cell saver system over the years. However, despite this postoperative hemoglobin levels increased in the cell saver group in the immediate setting. Few ICS studies stated as to whether or not remaining cardiopulmonary bypass contents were processed through the cell saver via cardiotomy suction. Those of which that did found a significant decrease in red blood cell transfusion and a decrease in postoperative chest tube drainage.[14] Interestingly, a randomised controlled trial (RCT) by Westerberg et al. comparing re-transfusion of ICS and cardiotomy suctioned

blood effects in cardiac surgery showed cardiotomy suctioned blood being quite vasoactive decreasing the mean arterial pressure (MAP). The vasodilation was proportional to the release of inflammatory cytokines from cardiotomy suctioned blood and this is significantly reduced by using it alongside ICS.[15]

Cardiopulmonary suction alone involves a highly turbulent flow of the suction which causes shear stresses at the air-fluid interface resulting in the stimulation of humoral cascades as part of the systemic inflammatory response. The shearing stress caused by a cardiotomy suction results in an increased amount of free haemoglobin due to mechanical haemolysis.[7] Perhaps this is as to why there is a slight difference between the cell saver and control group blood results. It is well documented that not only does the single use of the cardiotomy suction in cardiopulmonary bypass (CPB) surgery is associated with a systemic inflammatory response but also a resulting coagulopathy as it exacerbates the microembolic load. High quantities of free haemoglobin can cause platelet disfunction and damage to renal tubular cells. Processing cardiotomy suctioned blood with a cell saver device is important factor to effectively reduce these inflammatory responses, yet this in itself might also have potential harmful effects for the patient[16]. In terms of safety with cell saver we know that heparin coated CPB circuit with the uncoated cardiotomy reservoir may be less biocompatible than the identical CPB set used together with cell saver mechanism. Borowiec et. al mentioned that cardiotomy suction produces a marked reduced ability to produce oxygen free radicals by the whole blood at 45 minutes of CPB.[17] Fat microembolic load is decreased by the cell saver by as much as 85%.[18] In a prospective randomised trial analysing fat percentage in recirculated blood in cardiac surgery the percentage reduction in fat weight achieved by cell saver and cardiotomy suction alone was 87% and 45% respectively.[19]

In a RCT by Lau et al. recirculation of blood in the operative field significantly decreased the number of packed cells, platelets, and total blood products received in the test group when compared with the control group.[20] 200 patients were randomised prospectively undergoing first time CABG to control or cell salvage (washed). The cell salvage group was significantly less likely to receive a homologous blood transfusion and they received significantly fewer units of blood or platelets than controls. Larger systematic reviews have been completed to address this clinical question.[21] The Cochrane systematic review of Carless et al. did not differentiate between studies with washed and unwashed blood, but overall a similar result suggesting benefit of this technology.[22]

Fat particles have been linked with neurologic disfunction associated with CPB which have been due to the presence of small capillary and arteriolar dilatations (SCADs) shown in the brain in post- mortem studies. Unprocessed cardiotomy blood has also resulted in the production of thrombin during cardiac surgery including markers of inflammation such as tumor necrosis factor, interleukin-6 (IL-6), complement and neuron-specific enolase.[23] Even though the use of cardiotomy suctioned blood poses a microvascular risk, Rubens et.al stated that there is no clinical evidence of any neurologic benefit with this approach in terms of postoperative cognitive function.[24] This decrease in blood product utilization translated into a significant cost savings per patient in the available literature. We have not

analysed cost in this study as the cell saver device was initially a donation to the local department but it would be an interesting feature to do so in the future. In the same RCT Rubens et.al also stated there was less postoperative bleeding and less use of blood transfusions amongst the cell saver group in cardiac surgery.[24] Our results are fairly consistent with other studies demonstrating that ICS results in increased post-operative haemoglobin rates, especially in cardiac surgical patients. Cardiac surgery patients are most at risk of myocardial ischaemia when haemoglobin levels fall and as a consequence are also at most risk of transfusion related complications especially acute lung injury.

It has been suggested that cardiotomy suction alone produces an unbalanced ratio of pro and anti-inflammatory cytokines. A RCT by Gabel et. al discovered that cell savage in combination with cardiotomy suction decreased the concentrations for such cytokines improving the postoperative balance.[25] Damgaard et al. suggested that ICS decreases circulatory levels of pro-inflammatory markers IL-6 and IL-8 and increased immediate Hb levels at 6 hours post CPB[26]. Engels et al supports this with his RCT of inflammatory cytokines in cardiac surgery which indicated lower levels of Clara cell 16 kD proteins (CC16) resulting in less lung injury in the ICS group compared to controls. The ICS group had shorter ventilation times.[27]

Cell salvage is not however entirely without its problems. The air-fluid interface remains, however, the presence of heparin at the tip of the suction reduces the activation of the clotting and inflammatory cascades. It is almost predicable that if very large volumes of blood are processed through a cell saver it will deplete that volume of blood of platelets and clotting factors, careful monitoring and replacement of these may be necessary[6]. Shen et. al performed a RCT on high-risk cardiac surgical patients and discovered that ICS could impair blood coagulation and found excessive bleeding post operatively in this group[28]. Even though complications associated with the use of ICS are rare, studies have shown no overt increase in the rate of complications in patients who receive ICS.[29]

Conclusion

This study recommends the use of the cell saver system in cardiac surgery to reduce the probability of severe postoperative anaemia. As also stated by the ASA guidelines, we support the recommendation to keep its availability for immediate use 24 hours a day in any center undertaking surgery where blood loss is a recognised potential complication.[30] Although the use of ICS did not decrease the rate of red blood cell transfusion there were higher postoperative hemoglobin levels in immediate post-operative settings compared with cardiotomy suction alone. The literature seems to support use of combined ICS with cardiotomy suction as they effectively decrease inflammatory cytokines which can cause complications. However, excess cell saver use alone may decrease circulating clotting factors in high risk bleeding cardiac surgery.[31] Therefore, we do not recommend cell saver use without cardiotomy suction in cardiac surgery. It would be worth comparing both groups in terms of post-operative bleeding in future cohorts.

Summary Box

What is already known about this subject:

- Benefits of ICS include less time in ICU, shorter ventilation times and a shorter hospital stay in surgical patients.

- ICS causes a depletion of clotting factor and platelets due to hemofiltation of recirculated blood.
- Cardiotomy suction alone causes mechanical hemolysis increasing transfusion requirements whilst maintaining clotting factors.

What are the new findings:

- Immediate post-operative haemoglobin levels are increased with the use of ICS in cardiac surgery compared with cardiotomy suction alone.
- No significant changes in hemoglobin found in the late post-operative period using the cell

  saver. No significant changes in hematocrit using a cell saver mechanism.
- An addition to the literature to support a combination of cell saver mechanism with cardiotomy suction in cardiac surgery.

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ORIGINAL ARTICLE

Metastatic melanoma mortality in Malta

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Background

There are currently no studies looking specifically at the characteristics of the primary melanoma in patients who died of metastatic melanoma in Malta. This retrospective study looks at the demographics of these patients and the characteristics of their primary melanoma.

Method

Mortality data secondary to metastatic melanoma between 2007 and 2016 was gathered from the Malta National Mortality Registry. All patients whose death certificates had metastatic melanoma as the cause of death were included. Further data on histology and imaging was gathered from the Malta National Cancer Registry and the hospital electronic database.

Results

There were 87 recorded deaths (45 male; 42 female) in Malta secondary to metastatic melanoma between 2007 and 2016, with an average age at diagnosis of the primary melanoma of 64.3 years (range 23-92 years), average age at death of 67.9 years (range 28-96 years) and an average duration of survival after diagnosis of primary melanoma of 34.7 months (range 1-180 months). The commonest histological subtype of the primary cutaneous melanoma was nodular. The commonest site for the primary cutaneous melanoma was the back. The mean Breslow thickness was 4.23mm (range 0.3-13mm). The commonest site of metastasis was to distant lymph nodes, followed by the skin, liver and lung.

Conclusion

Mortality secondary to metastatic melanoma is prevalent in the over 60 age group, with the back being the commonest site of the primary melanoma. Identification of patients who are at higher risk of death from melanoma in Malta allows for their more effective targeting in local melanoma screening and education campaigns.

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Introduction

Melanoma is the most serious form of skin cancer, due to the significant risk of metastasis and death. Risk factors for cutaneous melanoma include sun exposure, increasing number of moles on the skin, the presence of atypical moles, fair skin, family or personal history of melanoma, immunosuppression and increasing age.[1] The ABCDE (asymmetry, border, colour change, diameter, evolution) pattern and the ugly duckling sign are useful educational tools to help the general public pick up any warning signs for melanoma.[2]

The Maltese islands have a high UV index for several months of the year with the population being exposed to intense sunlight particularly in the spring and summer months. The majority of the population is of skin phototype II to IV.[3] This means that a significant percentage of the population is susceptible to skin burning when exposed to the sun, which is a risk factor for the development of melanoma. In Malta, melanoma incidence has been on the increase over the past twenty years,[4] a trend which has been observed in white populations worldwide.[5-8] The standardised incidence for primary invasive cutaneous malignant melanoma in Malta increased from 3.7 per 100,000 population per year for males and 5.1 for females between 1993-1997, to 10.1 per 100,000 population per year for males and 12.1 for females in 2017.[4] Despite this, mortality from melanoma has remained stable between 2007 and 2017,[4] presumably because the increased incidence is mainly for thin melanomas of low metastasizing potential.[6]

Established bad prognostic factors indicating a higher risk of death in patients with cutaneous melanoma include increasing tumour thickness (Breslow thickness), ulceration, mitotic rate, number of metastatic nodes, clinically apparent nodal metastasis and visceral metastasis.[9]

Traditionally, the treatment of cutaneous melanoma has involved surgical excision with narrow margins, followed by wider surgical excision with margins guided by the Breslow thickness (Table 1).[10] Sentinel lymph node biopsy (SLNB), performed at the time of the wider excision,[10] is offered to patients depending on the Breslow thickness (>1mm) and other high risk factors. SLNB for melanoma has been offered in Malta since May 2010. Further investigation (blood tests, ultrasound, CT, PET scans etc) would be indicated according to the prognosis of the patient; most patients with thin melanomas (Breslow thickness <1 mm) would be treated only with surgery and close clinical follow up.

Table 1 Recommended excision margins of a primary melanoma depending on depth of invasion.

Breslow thickness, mm	Recommended excision margin, cm
In situ	0.5
≤ 1.0	1
1.01-2.00	1-2
2.01-4.00	1-2
> 4.0	2

There are no studies looking specifically at the demographics of patients dying of metastatic melanoma in Malta, or the characteristics of their primary melanoma. This retrospective study aims to look at these factors, to help identify the patients who are at a higher risk of death from melanoma in Malta, so they may be targeted more effectively in local melanoma screening and education campaigns.

Methods

Data for this study was collected retrospectively from the Malta National Mortality Registry. All patients whose death certificates listed metastatic melanoma as the cause of death between 2007 and 2016 were included in the study. Further data on histology and imaging was gathered from the Malta National Cancer Registry and the hospital electronic database when available. Data collected included demographic details, date of diagnosis of the primary melanoma, date of death, melanoma histological subtype, site of primary melanoma, Breslow thickness, Clark's level, presence of ulceration, lymph node involvement including sentinel lymph node biopsy result and site of distant metastasis when imaging was available.

Results

There were 87 recorded deaths (45 were male and 42 were female) secondary to metastatic melanoma in the ten-year period between 2007 and 2016. The primary melanoma was identified histologically in 57 cases (66%), whilst 24 cases (27%) had confirmed metastatic melanoma on histology and imaging, but the primary melanoma was not identified. The remaining 6 cases (7%) originated from an extra-cutaneous primary site. The commonest histological subtype of the primary cutaneous melanoma was nodular followed by superficial spreading and acral melanoma (Table 2a). The commonest site for the primary melanoma was the back, followed by the hands and feet (acral), followed by the legs (Table 2b).

Table 2a Histological subtype of the primary melanoma

Melanoma histological subtype	Percentage (number of cases,n=87) Male(M), Female (F)
Nodular	25% (*n*=22; M16:F6)
Superficial spreading	17% (*n*=15; M8: F7)
Acral lentiginous	15% (*n*=13; M3:F10)
Other (balloon cell ,mucosal, desmoplastic, choroidal)	7% (*n*=6; M2:F1)
Not available/Primary not identified	36% (*n*=31; M15:F16)

Table 2b Site of the primary melanoma

Site of primary	Percentage (number of cases, n=87) Male(M), Female (F)
Back	22% (*n*=19; M13:F6)
Acral	15% (*n*=13; M10:F3)
Legs	13% (*n*=11; M5:F6)
Arms	9% (*n*=8; M4:F4)
Head and neck	7% (*n*=6; M5:F1)
Chest and abdomen	5% (*n*=4; M3:F1)
Choroidal (eye)	2% (*n*=2; M0:F2)
Genital	2% (*n*=2; M1:F1)
Paranasal sinus	1% (*n*=1; M1:F0)
Oral	1% (*n*=1; M1:F0)
Lung pleura	1% (n=1) (M0:F1)
Anal	1% (n=1) (M1:F0)
Not available/Primary not identified	21% (n=18)

The average age at diagnosis of the primary melanoma was 64.3 years (range 23-92 years, median 65 years), the average age at death was 67.9 years (range 28-96 years, median 69 years) and the average duration of survival after diagnosis of the primary melanoma was 34.7 months (range 1-180 months, median 19 months).

Table 3 shows the Breslow thickness and Clark's level in the 57 cases (66%) where histology of the primary melanoma was identified. The mean Breslow thickness was 4.35mm (range 0.3-13mm). Ulceration was present in 21 cases. Five patients who died of metastatic melanoma had a primary cutaneous melanoma with a Breslow thickness <1mm. Their characteristics are shown in Table 4.

A sentinel lymph node biopsy result was available in a total of 30 cases; 28 of these were positive while 2 were negative. The 2 cases that presented with a negative sentinel lymph node biopsy and eventual metastasis had their primary melanoma on the back and a Breslow thickness of 3.5 mm and 12 mm respectively. The commonest sites of distant metastasis were to distant lymph nodes, liver and skin (Table 5).

Table 3 Breslow thickness and Clark's level of the primary melanoma

Breslow thickness	Percentage (number of cases, n=57)
In situ	0% (*n*=0)
0.1 – 1.0mm	8% (*n*=5)
1.01 – 2.0mm	18% (*n*=10)
2.01 – 4.0mm	32% (*n*=18)
>4.0mm	42% (*n*=24)
Clark level	**Percentage (number of cases, n=57)**
1	0% (*n*=0)
2	4% (*n*=2)
3	25% (*n*=14)
4	56% (*n*=32)
5	15% (*n*=9)

Table 4 Data for patients with a Breslow thickness between 0.1-1mm (*n*=5)

Sex	Months between diagnosis and death	Melanoma type	Primary Melanoma Site	Breslow Thickness	Clark's Level	Ulceration present (Y/N)	Site of documented metastasis
F	39	Superficial spreading melanoma	Left foot	0.3	2	N	Leg
M	7	Superficial spreading melanoma	Left leg	0.7	3	N	Brain
F	138	Not available	Chest	0.8	3	N	Axillary lymph node
F	15	Invasive superficial spreading malignant melanoma	Right leg	0.93	3	N	Inguinal lymph node
F	38	Invasive superficial spreading malignant melanoma	Left flank	0.93	3	N	N/A

Table 5 Documented sites of metastasis (The same patient might have had two or more distant metastasis sites. Data on the site of metastasis was not available in 39 cases)

Site of metastasis	Number (*n*=48)
Distant lymph nodes	33
Liver	8
Skin	7
Lung	6
Bone	5
Brain	2
Bowel	2

Discussion

Our study shows that death from melanoma in Malta, as seen in other countries, is more common in the older age groups, with an average age at death of 67.9 years, occurring within an average of 34.7 months of diagnosis of the primary melanoma. Older people also show a higher incidence of melanoma, in Malta as well as worldwide, where melanoma incidence (age standardised) rates peak at the seventh and eighth decades of life.[11]

The commonest histological type of melanoma causing metastasis and death in our cohort was nodular melanoma, followed by superficial spreading and acral melanoma. This does not come as a surprise as, although superficial spreading melanomas are the commonest form of melanoma, they tend to be diagnosed at less than 1 mm thickness, as opposed to nodular melanomas that tend to be thicker than 2 mm at the time of diagnosis and would therefore be associated with a worse prognosis.

The back was the commonest skin site for the primary melanoma leading to death in our cohort. Among Caucasian populations, including the Maltese population, melanoma is more frequently reported on the backs and shoulders in men and on the lower limbs in women.[5-6,11] The back should be emphasized in educational campaigns so that patients ensure that this part of their body is checked regularly by other family members, their doctor or friends, or else with the use of a mirror. Mole mapping in selected cases can be useful as a baseline photographic record for long-term screening in order to allow objective comparison and early detection of any changes in pigmented lesions, especially in areas that are difficult to monitor. The primary melanoma leading to metastasis was never identified in 27%(*n*=24) of cases. This could be due to regression of the primary tumour or due to patients presenting at a terminal stage or the melanoma occurring in an inaccessible site.

As expected, thick primary melanomas correlated with an increased risk of death. The mean Breslow thickness in our cohort was 4.35mm and we had no patients dying of

metastatic melanoma who had presented with an *in situ* primary melanoma. However, 8% of the total deaths due to melanoma in our cohort had a primary melanoma with Breslow thickness of only 0.3 to 1 mm and showed no ulceration. Internationally, patients with a primary melanoma with Breslow thickness <1 mm have a 95% 5-year survival rate.[12] Our results do remind us that patients in the thin melanoma category may – rarely – still develop metastases and die from them.

Sentinel lymph node biopsy carried out in our cohort was positive in 38 cases and negative in only 2. Several international large-scale studies have reported a relatively high false-negative rate for SLNB (5.6-21%).[13] The false negative rate of SLNB biopsy in Malta cannot be determined from this study as we only studied patients who died of melanoma. However, our results do highlight the small possibility of a false negative result with a SLNB biopsy, which should be communicated to the patient.

A limitation of the study is the small number of patients, despite including the whole population on the islands over a 10-year period. Data on the primary melanoma was unavailable in about one fourth of cases since these patients were diagnosed at the metastatic stage. Patients included in the study had metastatic melanoma as the primary cause of death on their death certificate. However, co-morbidities which may have contributed to death were not taken into account in this study. The site of metastasis was unavailable or undocumented in a number of cases and patients may have had undocumented metastases elsewhere.

In recent years, the management of melanoma has undergone some very important changes. Up to a few years ago, due to the absence of effective systemic therapy options, surgery was viewed as the only potential curative treatment. A big leap in the treatment of metastatic melanoma occurred with the advancement of new systemic therapies, including immunotherapy with cell cycle checkpoint inhibitors (e.g. nivolumab and pembrolizumab) and targeted therapies aimed at BRAF and MEK mutations (including dabrafenib and trametinib), which may also be used in the adjuvant setting. These treatments became available in Malta in recent years. There has also been a move away from performing complete lymph node dissection in patients with a positive sentinel lymph node (clinically occult disease), as no overall survival benefit was shown over observation with nodal basin ultrasound surveillance in two large prospective randomized phase III studies (MSLT-II and DeCOG).[14] These patients would now be offered adjuvant therapy, so the role of SLNB is changing from that of a prognostic indicator to one that influences access to adjuvant treatment.[15] The American Joint Committee on Cancer (AJCC) published the eighth edition of its staging system for melanoma in 2017,[12] to move towards a 'more personalized' approach to the treatment of melanoma. It is hoped that future studies on melanoma mortality in Malta will reflect the positive influence of these new management strategies.

Finally, local campaigns to advise the public not to overexpose their skin to the sun should also be continued and promoted, together with campaigns to encourage earlier detection and treatment of melanomas when they present on the skin or accessible parts of the body. With this three-pronged approach of primary prevention of melanoma, early detection and treatment, and improved management of patients with metastatic

melanoma, we hope that as few patients as possible will succumb to this cancer.

Conclusion

This study has provided more local data on melanoma to help in the fight against this cancer. It confirms that death from melanoma is highest in patients over 60 years of age. It also highlights the importance for individuals to have their backs checked since this is the commonest primary melanoma site leading to mortality.

Summary Box

What is known:

- Melanoma causes significant mortality
- Early diagnosis is key
- Latest guidelines on staging updated
- New treatments available

New findings:

- There has been a rise in melanoma incidence but not mortality in Malta over the past 10 years
- Death from melanoma in Malta is commonest in the over 60 age group.
- The characteristics of the primary melanoma leading to metastatic melanoma in Malta have been identified. The commonest site for the primary was the back, with nodular melanoma being the commonest histological type.

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ORIGINAL ARTICLE

Anterior resection syndrome: Contributing factors and its impact on quality of life

Svetlana Doris Brincat, Josef Lauri, Charles Cini

BACKGROUND

In Europe, colorectal cancer is the second most common cancer in women and third most common in men. Around half of all colorectal cancer cases affect the rectum. Surgery is the main curative therapy for rectal cancer however this is associated with bowel functional disturbances post anterior resection. The wide spectrum of symptoms following resection and restitution of rectum is what constitutes anterior resection syndrome. The aims of the study were to evaluate the incidence of anterior resection syndrome, identify correlation with clinical variables and its impact on quality of life.

METHODS

Adult patients who had undergone anterior resection between January 2014 and December 2016 were recruited. Variable factors for low anterior resection syndrome (LARS) were collected retrospectively from clinical records. Data was collected using validated questionnaires, namely LARS scale and EORTC QLQ-C30. Statistical analysis included ordinal logistic regression, one-way ANOVA and Scheffe post-hoc test.

RESULTS

Between January 2014 and December 2016, 179 patients underwent undergone anterior resection, with 55 patients fulfilling the inclusion criteria. Symptoms of LARS were identified in 51% of patients (n=27); with 23% (n=13) classified as minor and 28% (n=15) as major. Ordinal logistic regression showed that distance from anal verge (p=0.02), preoperative radiotherapy (p=0.01) and presence of stoma (p=0.02) were significantly associated with LARS. Patients with major LARS experienced a significant decrease in their quality of life.

DISCUSSION

Following anterior resection, patients may suffer from LARS adversely impacting their quality of life. Identification of factors contributing to LARS and its impact on the quality of life allows for better patients stratification in treatment groups and provision of individualised management plan.

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Introduction

In Europe, colorectal cancer is the second most common cancer in women after breast cancer and third most common cancer in men following lung and prostate cancer. It accounts to 9.7% of all cancers worldwide with 1.8 million new cases diagnosed annually. Around half of all colorectal cancer cases affect the rectum.[1] Surgery is the main curative therapy for rectal cancer. This involves either an abdominal perineal resection (AP) or a sphincter-sparing resection. Improvements in pre-operative staging and surgical techniques have led to the advent of low and ultra-low anterior resection, both being sphincter sparing surgeries for patients who might have otherwise undergone an AP resection. Hence for patients in whom a negative distal margin can be achieved, low anterior resection is preferred as it maintains bowel continence and avoids a permanent colostomy. However, bowel functional disturbances constitute a major problem for many surviving rectal cancer patients following anterior resection. The wide spectrum of symptoms following resection and restitution of rectum is what constitutes low anterior resection syndrome (LARS).[2]

Studies have shown that anterior resection syndrome may be attributed to sphincter injury, denervation during pelvic dissection associated with altered rectal sensation, low coloanal anastomosis as well as reduced capacity and compliance of rectal remnant.[3] Anterior resection syndrome constitutes fecal incontinence or urgency, frequent or fragmented bowel movements, emptying difficulties and increased intestinal gas. Although most of the functional impairments are clinically recovered following one year after surgery, long term studies report the presence of bowel dysfunction for years following resection. This dysfunction varies in its symptoms and severity and may have significant impact on patient's quality of life.[4-5] Hence, the aims of the study were to evaluate the incidence of anterior resection syndrome, identify correlation between anterior resection syndrome and clinical variables and evaluate the impact of anterior resection syndrome on quality of life.

Materials and Methods

All adult patients, under the care of all surgical firms at the national acute hospital in Malta, who had undergone anterior resection for rectal cancer between January 2014 and December 2016 were included. Approval from data protection unit at Mater Dei hospital was sought to obtain access to patient's details and files for data collection. Approval from local research ethics committee and the patients' caring consultants was obtained. The study was also registered with ClinicalTrials.gov.

Patients were recruited from data recorded in operation record sheets. Patients were excluded if they met the below criteria:

- colon cancer >15cm from anal verge
- permanent stoma
- known disseminated or recurrent disease
- patient without restitution of bowel continuity after one year

All patients were sent a letter by ordinary mail which contained an information sheet and a consent form describing the study aim and declaration of its confidentiality. It also contained 2 validated questionnaires: LARS scale questionnaire and EORTC QLQ-30.[6-7]

The LARS score is a validated five-score questionnaire focusing on bowel symptoms. According to the score patients are grouped into non-LARS (if score obtained is 0-20

points), minor LARS (21-29 points) and major LARS (30-42 points).[6] Hence, it enables quantification of the severity of intestinal and defecatory dysfunction following anterior resection. The EORTC QLQ-30 is a validated 30-item questionnaire designed to assess quality of life in cancer patients. The higher the score was suggestive of better quality of life and better functioning level.[7]

Participants were asked to return the consent form and the questionnaire in a paid self-addressed envelope. Patients who failed to answer the questionnaire were contacted by phone and encouraged to participate to increase the response rate.

The following data on patients' demographic (age, sex, comorbidities), tumour related factors (distance from anal verge, histological and MRI based TNM staging) and stoma related data (presence, type, time before closure) were collected. iSoft Clinical Manager (iCM) and electronic case summaries were used to collect clinical variables. The cancer staging was based on American Joint Commission on Cancer (AJCC) Tumor Node metastasis (TNM) classification system. Analysis was performed using IBM SPSS® Statistics. The relationship between possible risk factors and the severity of LARS as the dependent variable was analysed using ordinal logistic regression. Categorical variables were assessed using one-way ANOVA. Scheffe post-hoc test was used for analysis of variance. Statistical significance was set at $p<0.05$. The study has been reported in line with the STROCSS criteria.

Results

179 patients had anterior resection between January 2014 and December 2016; out of which 124 patients failed to fit the inclusion criteria hence, 57 patients were eligible to participate. Only 1 patient failed to return the questionnaire and one questionnaire was invalid as several answers were selected simultaneously. Thus the study population was composed of 55 patients (Figure 1).

Table 1 shows the demographic and therapeutic characteristics of the studied participants. Most of the participants were male (69%, *n*=38) and had an overall mean age of 65 years. One quarter of the patients were diabetic (25%, *n*=14), 71% (*n*=39) received neoadjuvant therapy whilst 44% (*n*=44) had adjuvant therapy as decided by the multidisciplinary team. In most patients rectal cancer was between 5-10cm from anal verge (60%, *n*=33). Most patients had T3 disease with no lymph node involvement. (Table 2). Sixty-four percent of procedures (*n*=35) were performed using an open technique, with laparoscopy being employed in one third of patients. Four percent of patients (*n*=2) required conversion to open with adhesion being the reasons for conversion. A defunctioning stoma was created in 51% of patients (*n*=28) with the majority of these having loop ileostomy. Stoma reversal was performed with a mean of 215 days after primary surgery.

LARS symptoms were identified in 51% of patients (*n*=27); classified as minor in 23% of patients (*n*=13) and major in 28% of patients (*n*=15) (Figure 2). The mean time from surgery to patients assessment of LARS though the questionnaire was 995 days.

Figure 1 Flow chart of patient selection

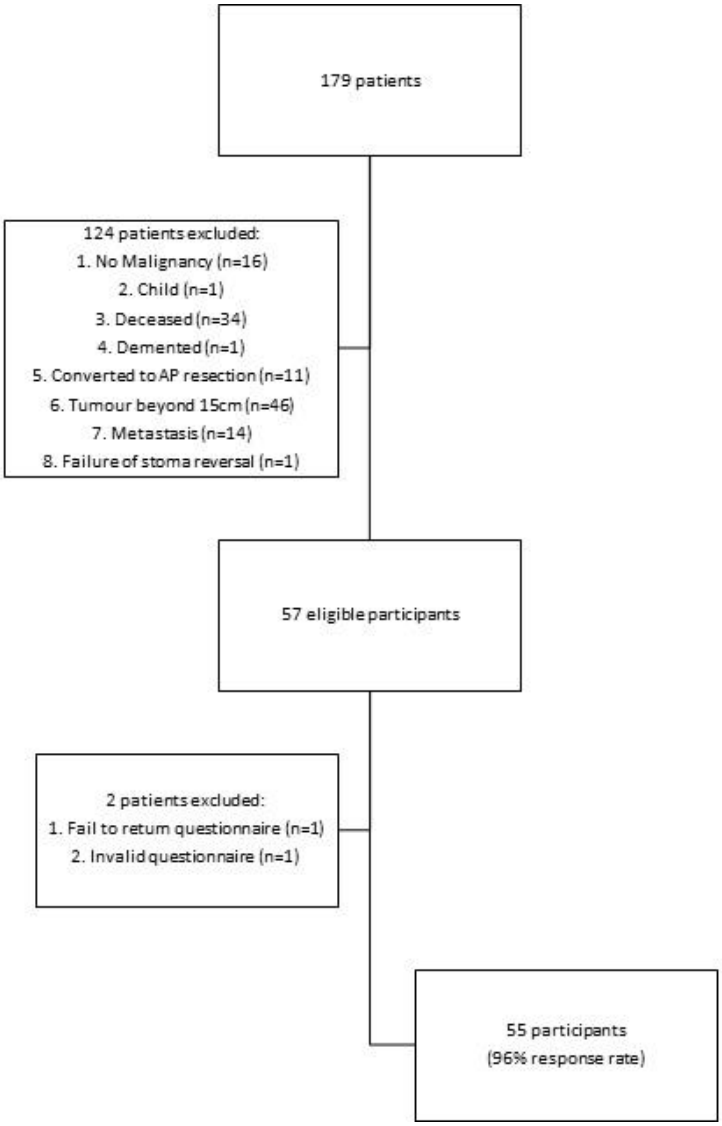
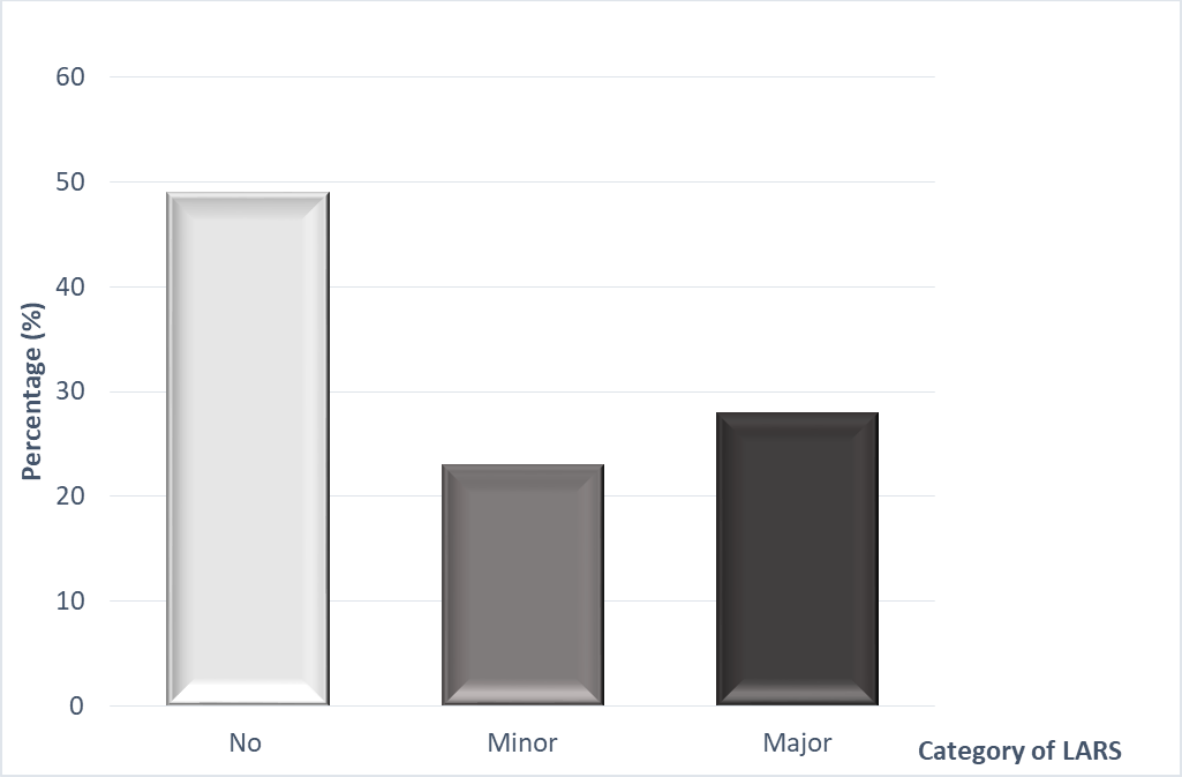


Table 1 Patients' demographic and therapeutic characteristics

	Frequency (*n*=55)	Percentage (%)
Gender		
Male	38	69
Female	17	31
Mean Age (years)	65 years	
Diabetes mellitus		
Yes	14	25
No	41	75
Hypertension		
Yes	29	53
No	26	47
Neoadjuvant therapy		
Pre-operative radiotherapy	39	71
Pre-operative chemotherapy	26	47
Adjuvant therapy		
Post-operative radiotherapy	0	0
Post-operative chemotherapy	24	44
Distance from anal verge (cm)		
<5	1	2
5-10	33	60
10-15	21	38
Surgical technique		
Open	35	64
Laparoscopic	18	33
Conversion to open	2	4
Presence of stoma		
Ileostomy	26	47
Colostomy	2	4
No stoma	27	49

Figure 2 Stratification of patients according to LARS symtoms



3.1 Association

Our logistic analysis showed a significant association of LARS with distance from anal verge (OR3.55, 95% CI 1.22-10.28; *p*=0.02), preoperative radiotherapy (OR 4.66, 95% CI 1.44-15.15; *p*=0.01) and presence of stoma (OR3.36, 95%CI 1.21-9.30; *p*=0.02). No significant association was found between gender, diabetes mellitus, tumour staging, surgical technique and interval from stoma reversal (Table 2).

3.2 Quality of life

The larger difference in mean quality of life scores was between the Major LARS group and each of the other two groups as demonstrated in Figure 3. One-way ANOVA analysing quality of life by LARS showed that these differences in quality of life score are statistically significant. The Scheffe post-hoc test ascertained that the significant difference lies between the No LARS and the Major LARS groups (*p*<0.0005; 95% CI 0.81 - 1.94) and between the Minor LARS and the Major LARS groups (*p*<0.01; 95% CI 0.39 - 1.64) (Figure 4).

Table 2 Histopathological staging and MRI staging of patients with rectal tumour

	Frequency (n=55)	Percentage (%)
Pathological stage, T		
T0	10	18
T1	4	7
T2	16	29
T3	23	42
T4	2	4
Pathology, N		
N0	33	60
N1	17	31
N2	5	9
MRI stage, T		
No MRI	8	15
T0	2	4
T1	0	0
T2	16	29
T3	27	49
T4	2	4
MRI stage, N		
N0	26	47
N1	13	24
N2	8	15

Figure 3 Box plot demonstrating quality of life based on LARS score category

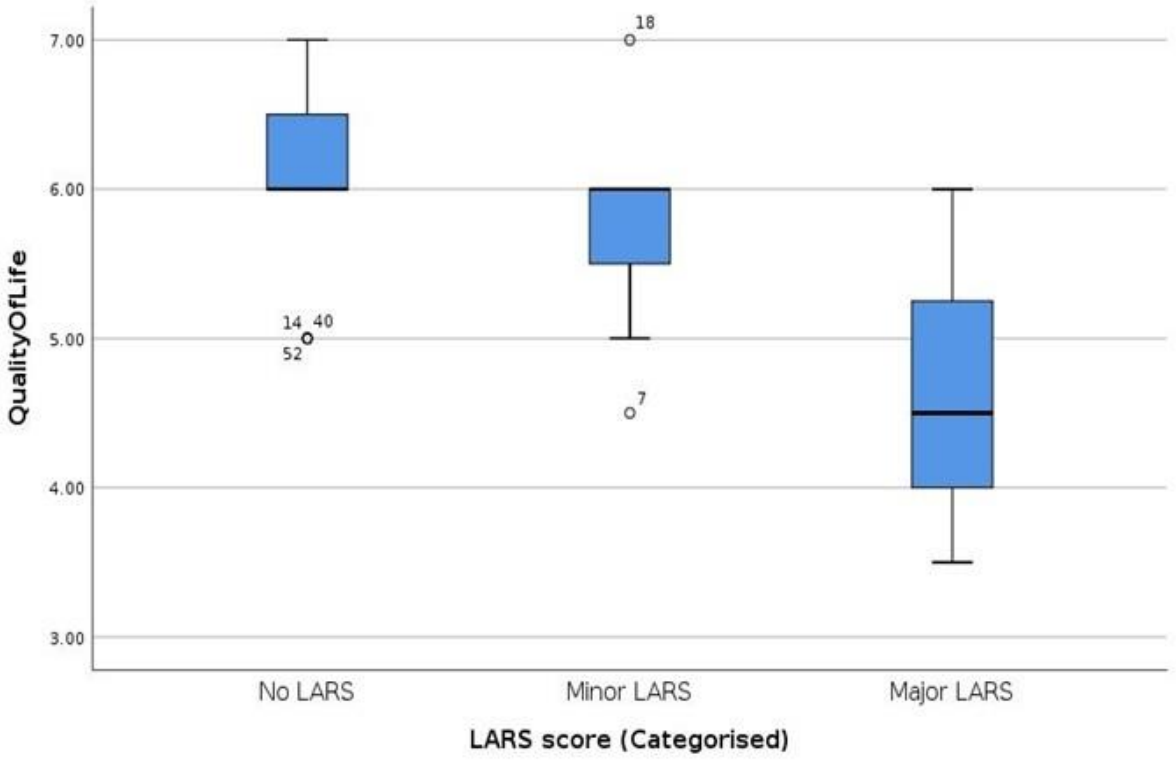


Figure 4 Scheffe post-hoc test demonstrating quality of life according to different LARS categories.

QualityOfLife
Scheffe

(I) LARS score (Categorised)	(J) LARS score (Categorised)	Mean Difference (I-J)	Std. Error	Sig.	95% Confidence Interval	
					Lower Bound	Upper Bound
No LARS	Minor LARS	.35714	.24724	.360	-.2659	.9802
	Major LARS	1.37143*	.22388	.000	.8072	1.9356
Minor LARS	No LARS	-.35714	.24724	.360	-.9802	.2659
	Major LARS	1.01429*	.24970	.001	.3851	1.6435
Major LARS	No LARS	-1.37143*	.22388	.000	-1.9356	-.8072
	Minor LARS	-1.01429*	.24970	.001	-1.6435	-.3851

*. The mean difference is significant at the 0.05 level.

Discussion

In our study, more than half the patients who underwent anterior resection for rectal cancer presented with anterior resection syndrome. Of these, 28% of these experienced major symptoms even after one year post operatively. Although functional bowel changes are more severe in the initial 12 months postoperatively, after which stabilisation in symptoms is achieved, this study demonstrates that the symptoms experienced in LARS are not transient with its effects persisting following one year post operatively. This is comparable to other international studies.[4,8-10]

Literature demonstrates multiple factors which may contribute to LARS. These include the patient's age,[3] gender,[3,8,11] surgical techniques,[11-12] presence of stoma,[9,11,13-14] level of anastomosis[4,11,15] and radiotherapy.[9,11] Consistent with other literature, our study showed that distance from anal verge (p=0.02), preoperative radiotherapy (p=0.01) and presence of stoma (p=0.02) are significantly associated with LARS. Pre-operative radiotherapy and presence of stoma may not have a direct causal relationship to LARS but may be a co-variant of the distance from anal verge. Patients who have a rectal tumour at low distance from anal verge are more likely to have a protective temporary stoma to secure anastomosis and receive neo-adjuvant therapy hence further contributing to LARS. Conversely, patients who have distal sited tumours have a decrease in rectal capacity and reservoir following resection whilst radiotherapy is known to cause pelvic nerve damage, suggesting their independent aspect in contributing to LARS.

LARS was noted to exert significant impact on patient's quality of life. Our study showed that the perception of quality of life was significantly worse in patients who were classified to have major LARS compared to those who did not suffer from LARS or had minor LARS symptoms. This is consistent with the study by Juul et al. which assessed the effect of LARS across multiple European countries.[16]

The strengths of the study include the use of validated scores for classification of LARS and quality of life increasing the validity of the results. This study had a response rate of 96% suggesting adequate representation of the population studied. As the study was performed by filling in an anonymous questionnaire, the patients were more likely to express their symptoms rather than by patient's interview; hence being representative of the true incidence of LARS and its impact on quality of life. Nevertheless, the limitations of this study include its retrospective study design and the small study population.

This study adds to the understanding of the contributing factors leading to LARS, the long term effects of this syndrome post-operatively and its impact on quality of life. Based on our study findings, the factors contributing to LARS are noted to be largely non-modifiable. Hence, adequate consideration should be given in the pre-operative counselling and post-operative identification of the syndrome and management of bowel dysfunction.

Conclusion

With the improved surgical techniques, colorectal procedures which achieve adequate surgical margin and total mesorectal excision are the current surgical standard for rectal carcinoma. However restoration of bowel continuity does not mean satisfactory bowel function. More than half the patients who had anterior resection suffer from LARS at least one year after surgery. Given its impact on patient's quality of life, pre-operative counselling on bowel dysfunction is crucial in patients who are scheduled to undergo anterior resection. Additionally, patients should be adequately evaluated during postoperative follow-up to enable early identification of the syndrome and provide a patient-tailored management approach.

Summary box

Facts already known:

- In Europe, colorectal cancer is the second most common cancer in women and third most common in men.
- Around half of all colorectal cancer cases affect the rectum.
- Anterior resection is a sphincter sparing surgery for the treatment of rectal cancer.

New findings:

- The effects of low anterior resection syndrome (LARS) are not transient with its effects persisting 1 year post operatively.
- The distance from anal verge, preoperative radiotherapy and presence of stoma are significantly associated with LARS.
- Patients suffering from major LARS have a significant decrease in their quality of life

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ORIGINAL ARTICLE

Audit to benchmark the epidemiology of hand and wrist fractures in Malta

Simon Gouder, Caroline Gouder, Lorraine Attard

Introduction

Hand and distal forearm fractures are among the most common injuries worldwide. To date there is no data on the extent of hand and wrist fractures diagnosed radiologically in Malta.

This audit aimed to quantify and analyse all hand and distal forearm fractures presenting at the Accident & Emergency (A&E) Department at Mater Dei Hospital. This would be done to establish the amount of hand and wrist injuries, to calculate the potential number of patients requiring specialist hand therapy services and to understand the requirements of the A&E department in the area of hand injuries.

Methods

Baseline data was obtained from analysing all orthopaedic X rays over three consecutive months taken in the local A&E department during the study period. Data on hand and distal forearm fractures was analysed.

Results

Results confirm that 18.6% (*n*=986) of all orthopaedic X-Rays were of the wrist and hand, 37% of which had confirmed fractures. Distal forearm fractures amounted to 58.4% (*n*=213) of all hand and wrist fractures. The most commonly injured hand bone was the 5th metacarpal in 24.3%, and 5.9% of all wrist fractures were scaphoid fractures.

Discussion

Our findings represent our local scenario. In view of an ageing and increasing Maltese population, one should expect numbers of hand and wrist fractures to increase. This data will help ensure the service is prepared with adequate specialised staffing levels to manage these cases. Education programmes that could advise on strategies to prevent such fractures by reducing falls and collaboration with government entities to assist in such prevention, better workplace health and safety and treating osteoporosis early is of crucial.

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Introduction

Hand and distal forearm fractures are the most common types of fractures worldwide. [1] A number of authors have studied the patterns of hand injuries in various Accident and Emergency (A&E) departments around the world.[2-3] Studies have taken into account the parts of the hand or wrist,[4] days of the week on which these injuries have occurred,[2] as well as the demographics of the patients attending the A&E department with such injuries. [5] It is estimated that there are around 16. per 10000 cases of distal forearm fractures in the United States annually.[6] Out of the total number of both fractures and dislocations, 28% occur in the hand while when taking only fractures, 20% of the total number of fractures occurred in the hand.[2,7]

Studies report that males, especially younger males tend to be more at risk of hand and distal forearm injuries [4] following accidents at work and sports injuries. These injuries could have a bearing on socioeconomic factors if the injured individual is required to periodically stop working. Fractures of the hand and distal forearm also have a large economic burden on the health service due to their high frequency and treatment required.[3,8,9]

In order to understand patterns of hand and wrist injuries, a number of studies looked into patient records and radiological images.[2,4,10,11] To date, in Malta, the number of hand and wrist X-rays and injuries diagnosed radiologically has never been studied.

According to the latest estimates in 2017, Malta has a population of 475,701 and there are approximately 5100 more males than females. Statistics show an overall increasing population with an increase of 10000 people between the ends of 2015 and 2016.[12] Malta has an increasing elderly population together with an increasing life expectancy and an increase in population by immigration.

Therefore, the primary objective of this audit was to quantify and analyse all the orthopaedic X-rays taken in the local A&E department over a period of three consecutive months to establish the amount of hand and wrist injuries, and the potential number of patients requiring specialist hand therapy services. This data would then be presented to hospital management to inform staffing level requirements in this area of interest, including the number of physiotherapists and occupational therapists employed with the necessary hand therapy training. They would also give an understanding of the requirements of the A&E department in the area of hand injuries such as orthopaedic surgeons, physiotherapists and occupational therapists available to offer immediate care when necessary.

A secondary objective was to obtain baseline data on hand and wrist fractures to be able to compare future trends in Malta. Understanding patterns of injury could be used to better understand potential input of the physiotherapists and occupational therapists in terms of education and prevention.

Materials and Methods

A descriptive retrospective audit was carried out by reviewing X-rays ordered by physicians at the A&E Department at Mater Dei Hospital, the only public general hospital in Malta. Permission to perform this audit was obtained from the Chairman of the A&E department as well as from Director of Information Technology at Mater Dei Hospital as per Maltese ethical approval requirements.

Patient identification details were kept confidential.

The X-rays for all orthopaedic adult and paediatric patients were reviewed on the Hospital's Patient Archiving and Communication System (PACS) (GE Healthcare Centricity Universal Viewer), for a period of 3 months between 1st of February 2018 and 30th of April 2018. Eventually, X-rays for the hand and distal forearm were extracted including distal forearm, carpal bones, metacarpals and phalanges. The number of different fractures were recorded from these X-rays. Patient information including gender, age and the mechanism of injury available on the X-ray requests was noted.

In order to compare data obtained in Malta to that in similar audits around the world, a thorough literature search was completed. All published data readily available was utilized. Much of the literature data available was older than 10 years, however, it was still used for analyses and comparison.

Results

A total of 5302 orthopaedic X-rays were ordered at the A&E department during the study period of which, 986 (18.6%) were hand and distal forearm X-rays. Of these, 365 (37%) had a reported fracture. The data of these patients was reviewed. The results obtained are illustrated in the tables below.

The demographic data and characteristics of all wrist, carpus and hand fractures (*n*=365) is shown in Table 1. Men sustained 55% of the injuries and the most common fracture was of the distal forearm (58.4%) and more commonly, the left hand was injured.

Table 2 highlights the large age range of the population who sustained these injuries. Small peaks are seen in the age group 21-30 ,51-61 and 71 to 80.

Table 3 shows the demographic data and characteristics of distal forearm fractures (*n*=213). The largest number were sustained by men (59.6%) and distal radius fractures (63.8%) were most common.

Reviewing distal forearm fracture data (Table 4) more closely illustrates a range of age groups who experience this injury. However, the most common age group was 71 to 80

Table 5 shows the demographic data and characteristics of hand and carpus fractures presenting (*n*=136). These were found predominantly in males (77.2%), with an equal left to right hand distribution.

Table 6 shows the age groups for all patients who suffered a carpus or hand fracture and highlights as expected that the largest number (30%) were found within the 21 to 30 age group.

Table 1 Demographic data and characteristics of all fractures (*n*=365)

	n (%)
Mean age (years): 46	
Males	202 (55)
Females	163 (45)
Right Upper Limb	176 (48)
Left Upper Limb	189 (52)
Distal Forearm Fractures	213 (58.4)
Hand and Carpus Fractures	152 (41.6)

Table 2 Age groups for all fractures (*n*=365)

Age Group	n (%)
0 to 10	28 (7.7)
11 to 20	45 (12.3)
21 to 30	54 (14.8)
31 to 40	35 (9.6)
41 to 50	34 (9.3)
51 to 60	47 (12.9)
61 to 70	38 (10.4)
71 to 80	46 (12.6)
81 to 90	33 (9)
90+	5 (1.4)

Table 3 Demographic data and characteristics of distal forearm fractures (*n*=213)

	n (%)
Mean age (years): 51.5	
Males	127 (59.6)
Females	86 (40.4)
Fracture on left side	**114 (53.5)**
Distal Radius Fractures	136 (63.8)
Distal Radius and Distal Ulna Fractures	25 (11.7)
Distal Radius Fracture and Ulna Styloid	49 (23)
Distal Ulna Fracture	2 (1)
Ulna Styloid Fracture	1 (0.5)

Table 4 Age groups for distal forearm fractures (*n*=213)

Age Group	n (%)
0 to 10	21 (9.9)
11 to 20	27 (12.7)
21 to 30	11 (5.2)
31 to 40	11 (5.2)
41 to 50	15 (7)
51 to 60	30 (14.1)
61 to 70	32 (15)
71 to 80	36 (16.9)
81 to 90	25 (11.7)
90+	5 (2.3)

Table 5 Demographic data and characteristics of hand and carpus fractures (*n*=136)

	n (%)
Mean age 38.8	
Males	105 (77.2)
Females	31 (22.8)
Right:Left Distribution 1:1	

Table 6 Age groups for all carpus and hand fractures (*n*=136)

Age Group	n (%)
0 to 10	7 (5.1)
11 to 20	16 (11.8)
21 to 30	41 (30.1)
31 to 40	20 (14.7)
41 to 50	16 (11.8)
51 to 60	15 (11)
61 to 70	6 (4.4)
71 to 80	8 (5.9)
81 to 90	7 (5.1)
90+	0 (0)

Investigating the 136 carpus and hand fractures further in Table 7 highlights the most common bone injured was the 5th metacarpal (27.2%), followed by the proximal phalanx of the little finger (11%). Nine patients suffered two co-existing fractures and one patient suffered three. In the analysis, these are considered as separate injuries.

Table 7 Fractures in the carpus and hand (*n*=136)

Bone Fracture	n (%)
1st Metacarpal	5 (3.7)
2nd Metacarpal	9 (6.6)
3rd Metacarpal	3 (2.2)
4th Metacarpal	3 (2.2)
5th Metacarpal	37 (27.2)
Proximal Phalanx Index Finger	2 (1.5)
Proximal Phalanx Middle Finger	2 (1.5)
Proximal Phalanx Ring Finger	2 (1.5)
Proximal Phalanx Little Finger	15 (11)
Distal Phalanx Thumb Finger	4 (2.9)
Distal Phalanx Index Finger	7 (5.1)
Distal Phalanx Middle Finger	8 (5.9)
Distal Phalanx Ring Finger	8 (5.9)
Distal Phalanx Little Finger	10 (7.4)
Middle phalanx Little Finger	2 (1.5)
Middle Phalanx Middle Finger	2 (1.5)
Middle Phalanx Ring Finger	5 (3.7)
Scaphoid	8 (5.9)
Triquetrum	3 (2.2)
Pisiform	1 (0.7)

The data analysis also reviewed the documented mechanism of injury for all hand and forearm fractures sustained during this three-month period (Table 8). The largest number of fractures (46.6%) occurred due to falls followed by (40.3%) listed under the general term of trauma with no details of the type of trauma suffered.

Table 8 Mechanism of Injury for all fractures audited (*n*=365)

Mechanism of Injury	n (%)
Amputation	4 (1.1)
Crush Injury	14 (3.8)
Fall	170 (46.6)
Fight	2 (0.5)
Hit	3 (0.8)
LCW	4 (1.1)
Mallet	1 (0.3)
MVA	11 (3)
Pain	1 (0.3)
Punch	4 (1.1)
Sports Injury	2 (0.5)
Trauma	147 (40.3)
Twisting	1 (0.3)
Swelling	1 (0.3)

Discussion

This audit provided baseline data of current hand and wrist fractures within the small population of the island of Malta, which can be used for comparison in future repeat studies. Studies around the world have shown changing patterns of distal forearm fractures.[13]

In Malta, the number of hand and wrist fractures confirmed from the total number of orthopaedic X-rays is slightly higher than those confirmed in a similar audit in Saudi Arabia.[4]

The gender distribution data of the hand and forearm fractures in Malta is 1.2:1. However, data from Saudi Arabia showed a higher male dominance a 2.8:1 ratio [4], and Amsterdam 1.8:1[7]. If the Malta data is analysed for the hand injuries only (excluding wrist joint

injuries) the male to female ratio changes to 3.2:1 male to female ratio. This therefore shows a much higher incidence among males, similar to another international audit identifying a distribution of 3:1.[2] This is probably due to injuries in manual jobs performed more commonly by males in addition to certain sports.

Fractures of the distal forearm

In Malta, fractures of the distal forearm of the total fractures of the hand and wrist is quite a high percentage when compared to other studies which reported 30% in the distal forearm while another reported an incidence of 44%.[3,4]

The gender distribution for specifically distal radius fractures is of 1.5:1 female to male ratio. In Oslo, the female to male ratio is of 3.5:1 showing a much higher distribution among females compared to our cohort,[8] possibly due to a higher incidence of osteoporotic fractures in Oslo. The causes are not properly understood[8] In this audit, the male to female ratio for the age group above 50 is in line with the estimated worldwide ratio for distal forearm fractures.[1] The large number of distal forearm fractures in the 60+ age group occur in females, possibly explained by a decrease in bone mineral density (BMD) in post-menopausal females compared to males. Women over 65 were 4.88 times more likely to have a fracture of the distal forearm when compared to males,[14] similar to that found in this audit, showing that women above 60 are 4.2 times more likely to suffer such a fracture. This is important when considering that life expectancy for Maltese females is 83.3 years and there is an increasingly ageing population.[15]

The peak age for a fracture of the distal radius in Malta was found to be in the 71 and 80 age group, followed by the decade between 61 and 70. This is an important issue for such patients since a higher incidence of osteoporotic fractures and increased mortality has been documented for these types of fractures.[1] In the younger population, the peak age group occurs between ages 11 and 20, possibly due to more people participating in sports activities. The incidence then decreases and increases again after 50 years of age. The peak incidence in Malta is similar to that in Saudi Arabia,[4] the 70+ age group, and in Oslo, also showing a peak in the 70 to 80 age group.[8] There is a significant difference from the audit in the United States where a peak is seen in the 5 to 14 year age group and a reduction in the numbers following that age group.[7] This highlights the need to further understand the incidence of fractures in Malta in the distal forearm.

Analysis of the mechanism of injury revealed that 65% of all fractures of the distal forearm occurred due to a fall, which is the most common mechanism of injury.[3] 40% of X-Rays requested identified the mechanism of injury to be trauma, with no further description of the type of trauma. It is noted that a proportion of those described as trauma could also have suffered a fall, which would result in a higher number of injuries with this mechanism.

Fractures of the hand

Locally, the most commonly injured bone in the hand was the 5th metacarpal responsible for 24.3% followed by fractures of the little finger. This is in line with other reported studies were the 5th metacarpal was also the most commonly fractured bone with the little finger suffering most fractures.[2,10,16] Our audit shows that 60% of fractures of the

metacarpals occur in the right hand in line with other reports.[4,7]

The phalanges are the most commonly injured group of bones, as the distal aspect of the hand is more susceptible to injuries similar to our local results. [4,7] Interestingly 85.7% of fractures of the metacarpals in Malta occurred in males.

In Malta, the peak occurs in the 31 to 40 years old age group followed by a steady decline in the numbers of hand injuries, similar to the audit in Amsterdam[5] and British Columbia[17]. In another audit, the peak observed was in the age group between 11 to 20 years followed by a decline.[2]

The most common age group for fractures of the phalanges was in the 21 to 30 age group. This is similar to that reported by an audit in Groningen.[5] In Malta, males were 3.1 times more likely to injure the phalanges, higher than results in Groningen where there was a 2.5 times in males compared to females.[5]

Reviewing hand fractures data alone highlighted 75.7% occurred in males of a range of ages, similar to that observed in an audit in British Columbia.[17] It could be speculated that these occurred due to manual labour, however, more information is needed to confirm this. These injuries are likely to result in the need for time off work and have economic implications. Early rehabilitation is essential as this group of people need to return to work as soon as possible with little or no disability, ideally to the same job. Studies have found that 41% of hand injuries occur due to sport injuries and fighting and only 9% occur at work, therefore these facts could explain why the younger population tend to suffer such fractures.[2,17] The impact of these fractures would affect the income of these patients and their families.

More detail of the patients mechanism of injury for these fractures was not available on the X ray request forms studied in this data collection but would have informed this discussion further. How many injuries were sustained due to sports/hobbies or occupational injuries? Common finger injuries in young children occur when their hands get stuck in doors.[5] Keeping these mechanisms in mind would be useful when planning prevention strategies.

Carpal Fractures

The most commonly injured carpal bone in previous studies is the scaphoid.[7,17] They are reported to constitute 5%[7] to 10.6%[17] of all hand fractures. In this audit, 5.9% of all hand fractures were scaphoid fractures. In this group, 83.3% were males while 16.7% were females.

The most common mechanism of injury reported in this audit are trauma and falls which make up 83.3% (10) of the mechanisms described. The literature confirms that younger people have a larger chance of suffering a fracture scaphoid other than a Colles' fracture following a fall.[18]

Hand Dominance

Although 90% of the world's population is right handed dominant. [18] this audit data showed a fairly equal distribution of hand injuries on the left and right side with slightly more on the left. This finding is similar to previous studies,[2,7] implying that dominance does not equate to an increased risk of injury on one side or another. However, fractures of the distal radius occurred more commonly on the left possibly due to lower bone mass on the non-dominant hand.[11] When looking at distal radius fractures, there is also a slight difference as left-sided fractures where

slightly more common locally similar to an audit in Riyadh.[4] Hand dominance is an important issue for the therapist during rehabilitation. This is important due to occupational issues and even in the case of students who need to write frequently. The non-dominant hand tends to be weaker than the dominant hand in right hand dominant people,[20] and therefore might lead to a longer rehabilitation period.

Role of the Hand Therapy Service

The physiotherapists and occupational therapists working in the hand therapy service, as well as rehabilitating patients post injury have a vital role providing advice on accident and fall prevention. In the 60+ age groups, the percentage of fractures of the distal forearm rose to 75% compared to the age group below 60, which shows a further increase in the risk of such injuries due to falls. Due to favourable weather conditions in Malta throughout most of the year it is very common for the population of all age groups to go out frequently, possibly leading to an increased risk of falls and consequent fractures. The data helps inform potential risk factors and Professionals working in hand therapy may now embark on educational programmes which could include visiting day centres and local councils, advising retirement homes and media appearances to help reduce potential falls. Future similar audits should be carried out to compare the impact of prevention strategies, such as fall prevention programmes.

Diagnosing and treating osteoporotic fractures ensures that these patients are also managed to prevent further fractures.[1] Fractures of the distal radius in the elderly could actually be used as a predictor for other types of fractures.[12]

Limitations

The largest limitation of this audit is that the mechanism of injury reported on the X-ray request was not recorded in enough detail to clearly inform the discussion. Information taken from the PACS was discovered to be too generic. It has since been suggested that more details about the mechanism of injury are documented when requesting imaging to better understand the reasons behind such injuries and inform further audits. Ideally, patients should have been interviewed to obtain more details of the mechanism of injury, any medication, smoking history and occupation to provide more information regarding causes of fractures.

The audit should, ideally, be performed over a year in order to understand seasonal variation for these injuries. However, this audit provided an initial snapshot of the situation in Malta which has helped in service planning.

Conclusion

Since Mater Dei Hospital caters for the majority of the Maltese population, this audit reflects and benchmarks the situation across Malta. The data analysed demonstrates similar patterns of hand and forearm injuries when compared to the available literature. Data was found to have similar trends to theses international studies suggesting that Malta can follow international management strategies when dealing with distal forearm, carpal and hand fractures.

Following the setup of an official hand therapy service in 2010, currently manned by 3 physiotherapists and 3 occupational therapists, this audit gives us an indication of the staffing levels required, for capacity building and the need for further training to

keep up with the demands on the service keeping in mind the increasing population.

The most common fractures include the distal radius in the elderly and the 5th metacarpal in the younger population. As well as providing effective early rehabilitation after these fractures it is important to implement strategies to prevent such fractures. Involvement in education programmes and collaboration with government entities, better workplace health and safety and early treatment for potential osteoporosis. In view of an ageing and increasing Maltese population, one should expect that the numbers of hand and wrist fractures will increase and therefore, the service must ensure preparedness with adequate numbers of trained therapists to manage these cases. Therapists in Malta also need to play a larger role in development of prevention strategies both for the elderly population and the younger working population. Prevention is of utmost importance to limit the burden both economically health services as well as on the patient's.

This audit successfully provided a baseline of such fractures and calls for repeat analysis in the future to compare trends and patterns.

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REVIEW ARTICLE

The use of high flow nasal oxygen in COPD patients

Nicole Sciberras

High flow nasal oxygen (HFNO) is one of the interventions a physician may opt to prescribe in hypoxemic patients. It involves the delivery of heated and humidified oxygen at rates of up to 60L/min via large bore nasal cannulae in a controlled manner, with variables such as the fraction of inspired oxygen (FiO2) which may be controlled independently. The set-up of HFNO consists of an oxygen generator, a flow meter, a humidifier and wide bore nasal cannulae (figure 1). There are 5 physiologic mechanisms that are believed to be responsible for the efficacy of HFNO. These include physiological dead space washout of waste gases including carbon dioxide (CO2), decreased respiratory rate, positive end-expiratory pressure, increased tidal volume and increased end-expiratory volume. These mechanisms account for the multiple applications of HFNO in hypoxemic patients, both in the acute and chronic settings. The use of HFNO in the management of COPD has risen along the years. It plays a role in both acute and stable COPD patients, however, the present evidence is insufficient for HFNO to be utilised preferentially especially in the acute setting. Larger scale studies are necessary to establish its role especially in these scenarios where NIV is currently recommended as the first line mode of oxygenation and HFNO is reserved for those unable to tolerate NIV.

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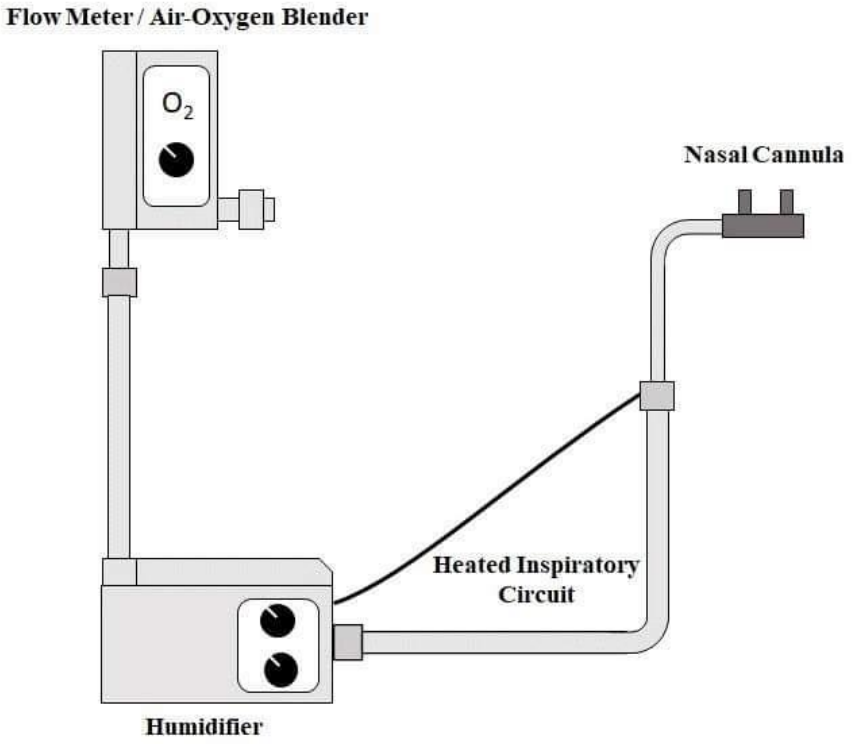
Figure 1 Set-up of high flow nasal oxygen



Introduction

High flow nasal oxygen (HFNO) is one of the interventions a physician may opt to prescribe in hypoxemic patients. It involves the delivery of heated and humidified oxygen at rates of up to 60L/min via large bore nasal cannulae in a controlled manner, with variables such as the fraction of inspired oxygen (FiO2) which may be controlled independently. Unlike low flow nasal oxygen, the FiO2 is not related to the flow rate, and there is the added advantage of less air leaks in HFNO. The set-up of HFNO consists of an oxygen generator, a flow meter, a humidifier and wide bore nasal cannulae.[1] In view of delivering the oxygen in a heated, humidified manner via nasal cannulae, as opposed to cold dry oxygen via a tight fitting mask, HFNO may be better tolerated by patients in comparison to long term oxygen therapy (LTOT) and non-invasive positive pressure ventilation (NIPPV).

Search criteria

The search for publications and abstracts was done electronically on PubMed, the Cochrane database of systematic reviews, using the search terms: 'high flow nasal oxygen in COPD'. The search was limited to articles available in English language, related to human subjects and published within the past five years. A total of fifty- five (55) articles were identified in this search. A single reviewer (myself) screened all potential references for inclusion, which brought the number of articles to thirty-one (31). The last update of the search was performed in May 2020.

Physiological mechanisms

There are 5 physiologic mechanisms that are believed to be responsible for the efficacy of HFNO. These include:

- Physiological dead space washout of waste gases including carbon dioxide (CO2)

- Decreased respiratory rate
- Positive end-expiratory pressure
- Increased tidal volume
- Increased end-expiratory volume

These mechanisms account for the multiple applications of HFNO in hypoxemic patients, both in the acute and chronic settings.

HFNO confers two advantages in relation to the washout of carbon dioxide from the physiological dead space, which is increased in conditions such as emphysema. Firstly, nasal cannulae do not increase the physiological dead space, as happens with masks used in other forms of oxygenation. Secondly, the high flow of oxygen washes out the carbon dioxide in the upper respiratory tract, as has been studied by measuring the CO2 elimination rate using a dynamic CO2 spectroscope with infrared radiation and a gamma camera.[2] The upper respiratory tract is one component of the physiological dead space, and thus the effect on HFNO on the other parts of this dead space, such as the bronchioles, is yet to be ascertained.

Decreased respiratory rate with the use of HFNO has been linked to the first mechanism. Clearance of carbon dioxide from the physiological dead space due to the positive end expiratory effect of HFNO results in better ventilation-perfusion matching, and this decreases the work of breathing and therefore respiratory rate.[2]

A decrease in the work of breathing may also be due to the positive end-expiratory pressure (PEEP) effect of HFNO. This arises from the high flow rate the nasal cannula achieves, which causes resistance against expiratory flow and increases airway pressure. The PEEP effect of HFNO has been compare to the pursed-lip breathing pattern COPD patients often adopt.[2] This effect is related to the size of the nasal prongs, whether the subject's mouth is open or closed, sex, body mass index and is directly proportional to the oxygen flow rate. [3]

Increased end-expiratory lung impedance has been reported with HFNO, suggesting increasing volumes and functional residual capacity which are more pronounced in patients with higher body mass index and not related to body position.[2] This effect was also reported in a small study specifically involving stable COPD patients whereby HFNO was compared to LTOT.[4] This same study reported an increase in tidal volume and a decrease in respiratory rate, thus supporting the above-mentioned mechanisms.

Furthermore, HFNO may improve lung epithelial mucociliary clearance as suggested by in vitro studies, and this was explored in patients with bronchiectasis and COPD with positive results including less acute exacerbations and fewer hospital admissions. However, these studies did not directly link the results to improved mucociliary clearance in COPD patients.[2]

Domiciliary HFNO / HFNO in chronic stable COPD

In 2017, HFNO was deemed safe to use in the short-term in stable COPD patients, where its effects were observed when use for one hour.[5] The Aalborg study in 2018 consisted of 200 COPD patients with chronic hypoxemic respiratory failure on LTOT, who were randomly assigned LTOT only or LTOT and HFNO. The use of HFNO for a daily average of 6-7hours resulted in a statistically significant reduction in acute exacerbations of COPD (AECOPD), as well as an improvement in mMRC grade from 3 months onwards. 138 patients completed the study at twelve months and

despite no significant difference in hospital admission rates, predicted hospital admission rates were lower for the HFNO group compared to the control group using amount of days on HFNO as an explanatory variable.[6] The post-hoc study involving 100 patients with COPD and chronic hypoxic failure confirmed this as there were reductions in the number of AECOPD, the number of hospitalisations and length of stay in patients treated with HFNO and LTOT, particularly in those with two or more exacerbations in the year prior to inclusion in the study. Thus it was concluded that dual treatment with HFNO and LTOT would be more beneficial to patients with frequent exacerbations.[7] Hypercapnic patients were included in this study, however, no correlation between paCO2 and number of exacerbations was identified.

On the other hand, Nagata et al's cross over trial in patients with stable hypercapnic COPD showed that six weeks of HFNO with LTOT did not improve dyspnoea, yet improved both quality of life and hypercapnia when compared to LTOT alone. The commonest adverse event with HFNO was nocturnal diaphoresis.[8]

Chronic hypercapnic COPD

In a randomised, multi-centre trial in COPD patients with daytime hypercapnia, it was observed that paCO2 decreased with the use of both HFNO and NIV, but decreased more with NIV, thus HFNO should be reserved for those intolerant to NIV.[9] This reduction in paCO2 is flow-dependent.[10]

HFNO in acute exacerbations of COPD

The first trial of HFNO in patients with hypercapnic AECOPD with pH <7.38 who had failed NIV was executed in 2018 by Braunlich et al. A significant improvement in pH and pCO2 was noted, more significantly in those with pH <7.35, and hence HFNO was deemed a promising alternative in the advent of NIV failure.[11] Besides the issue of NIV failure, a case of successful management of an AECOPD was reported in an acidotic, hypercapnic patient who benefitted from HFNO as his facial structure resulted in severe oxygen leaks when using NIV masks.[12]

In 2019, Pisani et al identified five trials about HFNO in relation to COPD exacerbations, which studied a total of 198 subjects with a male predominance and all aged over 70years.[13] Unfortunately, patient severity was not indicated in some trials, yet the FiO2 required to achieve target saturations of 88 to 92% (or 90 to 94% in one study) was accurately recorded. Two trials concerned COPD exacerbations post-extubation and concluded that HFNO, when compared with low flow oxygen therapy, significantly decreases the neuroventilatory drive and the work of breathing in patients with COPD recovering from an episode of acute respiratory failure after a planned extubation.[14] A lower mean arterial pressure was reported with NIV, yet no differences were identified with respect to arterial blood gas values, re-intubation rate, duration of invasive mechanical ventilation, length of stay at the intensive care unit and 28 day-mortality.[15]

The third trial conducted by Longhini et al assessed the effect of HFNO use in patients being weaned off NIV. It was found that whilst 36.7% failed NIV discontinuation, in those with successful discontinuation, NIV was re-started in a lower number of individuals who had received HFNO in comparison to those receiving controlled oxygen therapy (COT). The underlying mechanism for its success was a reduction in work of breathing without a rise in PaCO2, as previously explained.[13]

In patients presenting with severe AECOPD with moderate hypercapnic acute respiratory failure, 30 day intubation and mortality rates were not statistically different with the use of HFNO as opposed to NIV.[16] In this case, severe AECOPD was defined as sudden worsening of resting dyspnea, high respiratory rate (>30 breaths/min), decreased oxygen saturation (6.0 kPa) whilst moderate respiratory failure referred to pH levels between 7.25 and 7.35 on room air. In a similar cohort of patients, HFNO had an acceptable failure rate.[17] Another study noted a slight reduction in pCO2 levels measured transcutaneously when HFNO was used in AECOPD compared with standard nasal prongs, however, this was not statistically significant and there was no specification of the patient's acid-base status.[18]

Besides Pisani et al's analysis of these 5 trials, Sun et al enrolled 82 hypercapnic COPD patients in acute respiratory failure, and noted that HFNO had a lower failure rate than NIV despite this observation not reaching statistical significance. A significant difference was measured with regards to intolerance rate, which was higher for NIV. Despite this, no difference was detected between the two groups in terms of respiratory distress, hypoxemia and carbon dioxide retention. HFNO had less airway care interventions, less dermatological consequences but required a longer time of application compared to NIV. Another end-point that was measured was 28-day mortality, whereby no significant difference was observed between the two groups.[19]

Needless to say, in acute hypoxic respiratory failure it is essential to determine the cause, whilst keeping in mind the patient's co-morbidities, functional status and comfort, with regular evaluation of the clinical status and the need for intubation.[20]

HFNO AT THE EMERGENCY DEPARTMENT

HFNO causes less dyspnea and is more comfortable compared to COT in patients at the emergency department with acute dyspnea and hypoxemia, which may be attributed to COPD. However, there are currently no trials specific to COPD emergency presentations, and furthermore, this study did not measure FiO2 in COT subjects which is important to compare gas exchange especially in COPD patients.[21]

AEROSOL DELIVERY VIA HFNO

COPD management may involve the use of aerosolised treatment such as salbutamol. Inhalation of salbutamol/ipratropium bromide solutions via the oral route and HFNO route was studied in a population on separate days, and no significant post-inhalational differences were measured on spirometry.[22] However, HFNO confers the advantage of delivering medications without interruption of the oxygen supply. A comparison of the different modes of medication administration via HFNO cannulae at low flow rates of oxygen was drawn by measuring urinary salbutamol excretion. Vibrating mesh nebulisers were superior to jet nebulisers, and no additional benefit was derived from additionally using a spacer with the HFNO cannulae set-up.[23]

HFNO POST-EXTUBATION

Besides Jing and Di Mussi's observations explored above as AECOPD post- extubation, Zhang et al studied HFNO safety in COPD patients post-extubation. HFNO was deemed safe to use as it reduced length of stay at ITU, did not alter mortality and re-intubation rate, and had a similar side-effect incidence when compared to NIV. The only adverse finding was that of a higher oxygenation index in the

NIV group at twelve hours post-extubation, however, this observation did not hold at 24 and 72hours after extubation.[24]

HFNO DURING SLEEP

A small prospective study in 2017 assessed the effect of oxygen and HFNO on sleep in COPD patients with FEV1 >30% predicted and smokers as the control. HFNO was found to be advantageous in that it not only reduced the work of breathing, but also reduced paCO2, an effect not seen when using conventional oxygen.[25]

In 2018, the above findings were confirmed separately by directly measuring CO2 production using a metabolic hood and polysomnography. Two conclusions were derived, the first one being that responses in ventilation to HFNO during sleep were similar in COPD patients and controls. Secondly, the physiological mechanisms of HFNO were confirmed as the use of HFNO caused a substantial decline in minute ventilation due to a reduction in dead space ventilation without a major change in alveolar ventilation, CO2 production, energy expenditure or transcutaneous CO2.[26]

Later that year, the effect of HFNO on sympathetic activity during sleep was researched using finger pulse wave amplitude. HFNO reduced sympathetic activity in COPD patients especially during REM sleep, whilst supplemental oxygen did not. This effect was not observed in the control group, and was observed to a lesser degree in COPD patients with forced expiratory volume of greater than 1.65L.[27]

HFNO AND EXERCISE TOLERANCE

Exercise intolerance in COPD may be attributed to the dead space volume in the upper airways, and thus HFNO might play a role in this regard. In a small trial involving severe COPD patients with ventilatory limitation, the subjects experienced less dyspnoea during exercise when using HFNO. Other findings were those of increased oxygen partial pressure, however, the mechanism for these results was not studied.[28]

HFNO IN PALLIATIVE COPD PATIENTS

In his review of end-of-life respiratory support, Davies concludes that in spite of a wide evidence base for the use of NIV in this context, there is no evidence yet to support the use of HFNO, and this lack of evidence is not restricted to its use in COPD palliation, but also in other conditions.[29]

CONCLUSION

The use of HFNO in the management of COPD has risen along the years.[30] It plays a role in both acute and stable COPD patients, however, the present evidence is insufficient for HFNO to be utilised preferentially especially in the acute setting.[31] Larger scale studies are necessary to establish its role especially in these scenarios where NIV is currently recommended as the first line mode of oxygenation and HFNO is reserved for those unable to tolerate NIV.

FUTURE DEVELOPMENTS

Keeping in mind the body of evidence for the applications of HFNO in COPD patients which was explored in this article, there are still applications that need to be addressed or that necessitate larger trials to be conducted. One such query is posed by Mansfield regarding HFNO preceding the use of NIV in AECOPD, as well as its use when NIV is not tolerated.[32]

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REVIEW ARTICLE

Autism: the literature on gender differences

Catherine Dimech

Background

Literature on autism spectrum disorders over the years has documented a male-to-female ratio of approximately 4:1. Yet this gender-ratio is now being questioned with studies showing that this ratio may be lower. Factors underlying this male predominance are mostly unknown. Since the majority of published research on autism includes mostly, and in some cases, exclusively males, much less is known about females with autism.

In this literature review I examined the available published evidence over 7 years on the possible gender differences in autistic girls and boys.

Methods

A review of the literature was conducted using PubMed with the key words 'autism spectrum disorder' in combination with 'girls and boys' and 'gender differences'. Relevant articles were screened against eligibility criteria leading to 36 final articles which were analyzed in more depth.

Results

Seven key themes on gender differences between autistic girls and boys emerged. These themes include the female camouflage effect, genetic and hormonal mechanisms, autism diagnostic assessment tools which are being increasingly criticized, gender differences in the core diagnostic criteria of autism and differences in comorbidities between girls and boys on the spectrum.

Conclusion

Managing to understand gender differences better may lead to more accurate and earlier diagnosis of females on the spectrum. Future research should focus on including larger number of females and developing instruments which are better suited to diagnose the female phenotype of autism and to understand the specific needs of females on the spectrum.

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Introduction

Autism spectrum disorder (ASD) consists of a heterogeneous group of neurodevelopmental disorders,[1] which according to the latest edition of the *Diagnostic and Statistical Manual of Mental Disorders (DSM-5, 2013)* is characterized by 'persistent deficits in social communication and interaction as well as restricted and repetitive patterns of behaviors, interests and activities'. These symptoms need to be present from early childhood, particularly before the age of three years or, when demand outweighs capacity.[2]

The first attempts at identifying and describing autism were made as early as 1943 and 1944 by Leo Kanner and Hans Asperger respectively. Since then, definitions and criteria for diagnosis have been updated several times. Autism is being seen as a spectrum of conditions with different levels of severity.[1] Autism is a life-long condition and is known to affect 1% of the population[3-4] with a well-documented predominance in males, which is now being questioned.

Literature over the years has documented a male-to-female ratio of approximately 4:1.[3, 5-8] Even the DSM-5 states that 'ASD is diagnosed four times more often in males than in females'.[2] However this gender-ratio commonly reported in studies is being questioned.[9-10] In fact, according to Rynkiewicz and colleagues, studies conducted during recent years have shown that this ratio may be lower at the rate of 2.0-2.6 males: 1 female.[3] This was also reported by Beggiato and colleagues, where male to female ratio was found to be approximately 3:1. Despite these lower proportions, the diagnosis of autism still seems to be more common in males than in females. Factors underlying this male predominance are mostly unknown.[8]

Since the majority of published research on ASDs includes mostly, and in some cases, exclusively males, much less is known about females with autism.[11] For a long time it was assumed that females with autism had the same neurobiology and behaved in a similar way to males with autism. This probably may have led to a diagnostic bias 'towards a male stereotype of ASD',[12] leading to different professionals to unknowingly hold gender stereotypes and as a result are less sensitive to symptoms of autism when they occur in girls.[4]

Several studies have reported that early identification of autism is crucial since it is linked to early educational interventions, better communication skills, lower rates of problematic behaviors and less parental stress.[13] Misdiagnosis in females can also lead to similar problems since the young girl on the autism spectrum may be given treatment that she does not need and will not be given access to the necessary services and available support for school and employment.[14] Literature over the recent years has recounted stories of females on the autism spectrum who were not given a timely diagnosis, or no diagnosis at all, and as a result had issues with their identity, low self-esteem and felt as 'outsiders'. When eventually given a diagnosis, it 'was experienced as liberating and resolved a lifelong identity crisis'.[15]

In this literature review I examined the available published evidence over the past 7 years on possible gender differences in autistic girls and boys up to the age of eighteen years. Managing to understand gender differences better may lead to an earlier diagnosis and better support and treatment of ASD in girls and women.[16]

Materials and Methods

An electronic database search was done between April and July 2019 using PubMed. Articles relevant to this literature review published between January 2012 and July 2019 were searched.

The following keywords were used in the search engine: 'autism spectrum disorder' in combination with 'girls and boys' and 'autism spectrum disorder' in combination with 'gender differences'. The initial database search using these keywords identified 824 articles. The titles and abstracts of these articles were screened against inclusion and exclusion criteria. Inclusion criteria included children and adolescents with a diagnosis of autism, up to the age of eighteen years, who were involved in research comparing girls on the spectrum versus boys on the spectrum. Prevalence studies, studies on participants with autism-like traits and studies on adults on the autism spectrum were excluded.

The above process resulted in 48 potentially relevant articles. Then, these 48 articles were read thoroughly to make sure that each article met all inclusion criteria discussed above. This resulted in a further 12 articles being excluded since when reading the whole articles it became evident that 3 studies were on infants with a high-risk of autism and not a diagnosis of autism, another 4 articles did not mention clearly the age of the participants, another 2 articles did not have clear data on the male and female cases who participated and another 3 articles were on neurogenetics. These were not evident when the titles and abstracts were read in the initial screening. This resulted in 36 final studies as seen in Figure 1 according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines.[17]

These final 36 articles were read in depth, and the topics and patterns which came up repeatedly during this process were highlighted and coded. This process of thematic analysis led to seven key themes on gender differences between girls and boys on the autism spectrum (Table 1).

Figure 1 Flow diagram of study selection according to PRISMA guidelines.

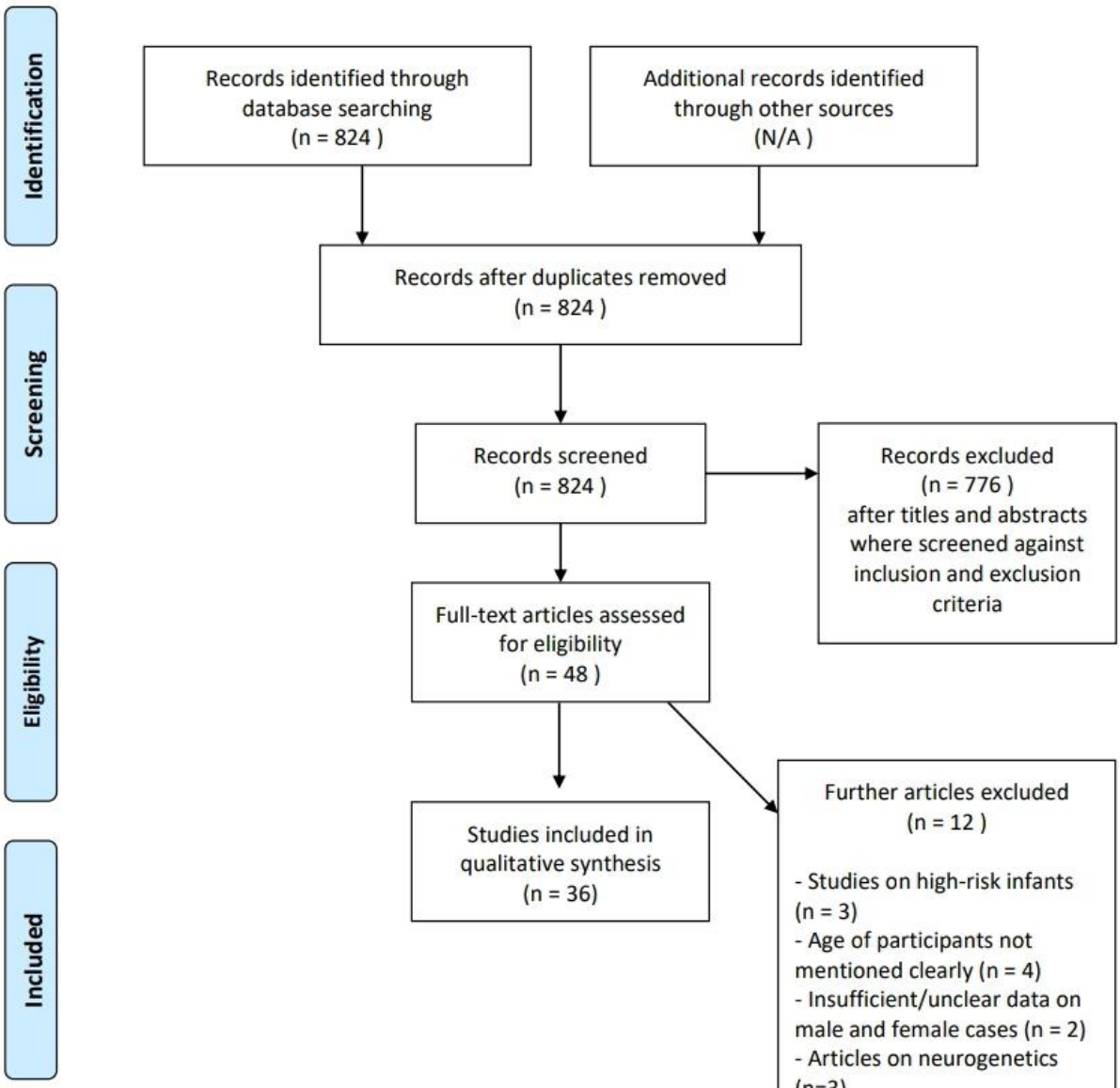

Table 1 The 7 Themes and the Articles addressing each theme

Theme 1 The Female Camouflage Effect	• Beggiato A et al. (2017) • Dean M et al. (2017) • Fulton AM et al. (2017) • Ratto AB et al. (2017) • Ormond S et al. (2018) • Matheis M et al. (2019)
Theme 2 Genetic and Hormonal Mechanisms and Theories	• Teatero ML et al. (2013) • Kreiser N et al. (2014) • Schaafsma SM et al. (2014) • Lai MC et al. (2015)
Theme 3 Diagnostic Assessments	• Kreiser N et al. (2014) • Tierney S et al. (2017) • Young H et al. (2018)
Theme 4 Core Diagnostic Criteria	• Hiller RM et al. (2014) • May T et al. (2014) • Supekar K et al. (2015) • Duvekot J et al. (2017) • Harrop C et al. (2018) • Antezana L et al. (2019) • Matheis M et al. (2019)
Theme 5 Social Interaction, Motivation and Interests	• Head A et al. (2014) • Sedgewick F et al. (2016) • Harrop C et al. (2017)
Theme 6 Social Communication	• Reinhardt VP et al. (2015) • Kauschke C et al. (2016) • Conlon O et al. (2019)
Theme 7 Behavioural and Emotional Problems	• Dean M et al. (2017) • Duvekot J et al. (2017) • Hull L et al. (2017) • Pisula E et al. (2017) • Margari L et al. (2019)

RESULTS

THE FEMALE CAMOUFLAGE EFFECT

Wing suggested the 'camouflage hypothesis' in 1981 as an explanation for the skewed gender ratio in autism. According to this hypothesis females on the spectrum are able to mask their autistic symptoms, mainly their social deficits, by managing to learn the rules of social situations.[5,18-19] This hypothesis contrasted strongly to the long-standing belief that females are only at a reduced risk of developing autism based on the lower prevalence rates among females over the years.

There is now growing evidence of this camouflaging effect among females on the spectrum, especially among those without intellectual disability.[20] A study by Dean and colleagues, examined and observed closely the social behaviors of 96 children (half autistic and half typically developing (TD) children), all with an IQ of 70 or more, during school recess. Gender differences in social behavior were clearly evident. Boys on the spectrum had more obvious social challenges than the girls on the spectrum. When observed from a distance, the latter were more similar in social behavior to the TD girls. On the other hand, the TD boys were playing structured games and the boys on the spectrum were more easily spotted wandering alone away from these games.[21]

Ormond and colleagues, state that girls are presented to professionals three and a half years after boys and a diagnosis of autism is given approximately five years later than boys.[22] This delay in diagnosis is of concern since it can negatively impact the life of these females.[19, 22] Fortunately, recently researchers are giving increasing attention to female self-advocates who are describing their difficult experiences to increase awareness both among the professionals and the general public.[20]

Delayed diagnosis occurs especially in girls on the high-functioning end of the autistic spectrum, one possible explanation being the higher intellectual quotient (IQ) scores and thus the increased ability to mask their deficits. In fact, there tends to be underrepresentation of females with a diagnosis of autism at the higher ends of the IQ distribution.[7]

GENETIC AND HORMONAL MECHANISMS AND THEORIES

Given that ASD is known to be genetic, multiple studies have been investigating genes that could be the cause of the male predominance in autism. Sex chromosomal genes which include the male-specific Y-linked genes and many X-linked genes have been found to be associated with autism however the mechanism by which they contribute to the male bias is still unknown.[6, 10]

High levels of prenatal testosterone have been found to activate and masculinize behavior of both boys and girls and seem 'to cause a shift on the ASD scale'. This shift however is not enough for the individual to meet the criteria for ASD. In fact, children who were exposed to the highest levels of testosterone did not meet criteria for diagnosis. Therefore, prenatal testosterone by itself is not able to explain the occurrence of ASD and so is seen as a contributing factor together with other genetic and environmental factors.[6]

Recent literature has shown that maternal stress can activate the maternal immune system and this together with early exposure to high levels of prenatal testosterone can

have a sex specific role in the cause of ASD. These studies are still in their infancy and more research is needed.[6]

Throughout the years, several models were proposed. The most widely studied model is the brain differences model (BDM) which includes the extreme male brain (EMB) hypothesis proposed by Simon Baron-Cohen in 2004.[14] In Baron-Cohen's view, males are better at systemizing by developing rules and guidelines whilst females tend to be better at showing empathy and identifying feelings. Since an extreme male pattern of cognition has been found in persons on the spectrum, males may be more susceptible to develop autism and so this hypothesis may explain the male predominance.[14, 23]

Wing proposed the greater variability model (GVM) which suggested that males are more vulnerable to develop ASD due to a greater genetic variability. A third model known as the liability/threshold model (LTM) proposed that males and females are equally at risk in developing autism, however females have a higher threshold for manifesting the symptoms and so need "more genes" to be affected by the condition. None of these mentioned models have been consistently supported by empirical evidence and they have been heavily criticized. Researchers are now investigating epigenetic mechanisms on the X-chromosome.[14]

DIAGNOSTIC ASSESSMENTS

The Autism Diagnostic Interview – Revised (ADI-R) and the Autism Diagnostic Observation Schedule (ADOS) are two assessment tools used in the diagnosis of autism. For a formal diagnosis to be reached the ADI-R and ADOS are most commonly used together in combination with direct observation of the child's behavior.[1]

Recent literature has shown researchers and professionals criticizing these diagnostic assessments. Main reason being that sex has not been taken into account during the development and validation of these tools.[9] In fact only 'one female for every four to seven males' were included during the validity of the ADI-R whilst an unequal sample size of eight females and seventy one males were included during the development of the ADOS.[14] Different studies have stressed the lack of sensitivity of the ADOS towards identifying girls on the spectrum.[9, 24] Apart from using predominantly male samples, further criticism was related to the fact that parental reports are used for the ADI-R and parents themselves can be unknowingly causing a bias due to gender stereotyping and expectations that more boys are on the autistic spectrum than girls. In addition, since the ADOS is based on observing the child for an average of forty minutes whilst administering the test, it is possible that girls go undiagnosed since their expression of autistic symptoms may be more subtle or different from those of boys.[1]

CORE DIAGNOSTIC CRITERIA

To date, research on gender differences in the core diagnostic criteria of autism still presents with inconsistent results. The most consistent finding shown in the literature is related to the restricted interests and repetitive behaviors domain.[25] Restricted Repetitive Behaviors (RRBs) consist of repetitive body movements and mannerisms [26] which are persistent, at an increased frequency and interfere with learning of children on the spectrum.[11]

Current literature suggests that girls on the spectrum show less repetitive use of objects and adherence to rituals when compared to boys on the spectrum.[5, 11, 25-28] Robust evidence for reduced levels of RRBs in girls with ASD

was found in a large study by Supekar and colleagues using the National Database for Autism Research (NDAR) dataset.[27] Nevertheless there are also several studies which have reported no significant gender differences in RRBs.[29-30] Certain studies showed that girls have interests which are less typical of ASD whilst on the other hand boys have more atypical movements, restricted interests and repetitive use of objects such as repetitive playing with wheels.[11, 25, 28]

SOCIAL INTERACTION, MOTIVATION AND INTERESTS

A persistent deficit in social communication and social interaction is one of the core diagnostic criteria. Individuals on the spectrum often experience difficulties in creating and maintaining friendships and understanding social relationships.[31]

A study by Head and colleagues found that girls on the spectrum scored higher on the Friendship Questionnaire (FQ) than boys on the spectrum, and similar to TD boys. Reports by parents showed that girls on the spectrum had better social skills and were more socially motivated than the boys.[32] A similar study was conducted by Sedgewick and colleagues focusing on the adolescents' motivation for social relationships and their experiences with friends. Again, this study showed that girls with ASD were more socially motivated than the boys as demonstrated by the higher scores on the Social Responsiveness Scale (SRS). Boys with ASD were less concerned with making and maintaining friendships.[31]

Many children with ASD may express themselves and connect with other people through play. Research was done to explore any gender differences during play by Harrop and colleagues. However, no significant differences were found in either play complexity or toy engagement between girls and boys on the spectrum between the ages of 2 years and 4 years 11 months participating in this study. Nonetheless it is possible that differences become apparent later on in development and so more research is needed.[33]

SOCIAL COMMUNICATION

Problems in communication have always been considered as one of the core features of individuals on the spectrum.

One way to assess pragmatic language is through storytelling or narratives measured by The Expression, Reception and Recall Narrative Instrument (ERRNI). Conlon and colleagues conducted a study to investigate possible gender differences in pragmatic communication in a closely-matched sample of 8-year-old boys and girls on the spectrum. Girls told stories which were richer in content and described more salient features of the story and the characters than the boys. Overall, this study suggested that some differences in social communication may exist between girls and boys with ASD and effective tools may be developed to measure these differences.[34]

A study by Kauschke and colleagues was conducted to investigate gender differences in narrative competence and internal state language (ISL) using stories elicited from a wordless picture book. Results showed no significant differences in narrative skills namely story length, coherence and cohesion between girls and boys with ASD and between the ASD group and the control group. However, a difference was found in ISL where girls on the spectrum verbalized characters' internal states and emotions more than the boys on the spectrum.[12]

Literature on gender differences in early social communication shows conflicting results. A study by Reinhardt and colleagues revealed no significant differences in developmental functioning and social communication skills between girls and boys with ASD. However it is possible that gender differences in communication and language become more apparent as children become older and acquire more language skills.[35]

BEHAVIOURAL AND EMOTIONAL PROBLEMS

Different comorbidities are often present in individuals on the autism spectrum and may obscure the clinical presentation.[36] There is literature which indicates that since boys on the spectrum are more likely than girls to show externalizing behaviours which include hyperactivity, aggressive and disruptive behaviours, boys are significantly more likely to be referred by teachers and parents.[21] Girls on the spectrum on the other hand are more likely to show internalizing and emotional problems including anxiety and depression. Nonetheless literature over the years shows inconsistent results about the presence of these behavioural and emotional problems in girls and boys.[28]

These inconsistencies in the literature may be linked with differences in the age and developmental levels of children participating in the study.[36] A meta-analysis by Hull and colleagues found age-related patterns for internalizing and externalizing problems. Therefore the levels of internalizing and externalizing problems in girls and boys became more similar as the children with ASD became older.[37]

Margari and colleagues found high rates of comorbidities in 159 high-functioning children and adolescents including Attention Deficit Hyperactivity Disorder, anxiety, depression, bipolar affective disorder, obsessive-compulsive disorder and anorexia nervosa. Anxiety was found at a high percentage in both sexes but there was no statistical significant difference. Also for the other comorbidities mentioned, except for anorexia nervosa, no statistical significant differences were found between girls and boys on the spectrum.[38]

DISCUSSION

Seven key themes on gender differences in autism emerged from this review of literature since 2012. These findings should be interpreted with caution and a number of limitations should be borne in mind. In this study only one database, PubMed, was used to identify potential eligible studies. Also most studies included have relied on the ADOS and ADI-R for diagnosis of autism, even though these instruments are thought to be male-biased themselves. Another limitation was that several of the studies included were underpowered in terms of number of female participants. Future studies should aim to include more females in order to draw stronger and more consistent conclusions.

The most common theme mentioned was the possibility that current diagnostic assessments are not sensitive enough to diagnose females on the spectrum. Since most of the research conducted on autism has included mostly or only male participants, this may have created a male-biased understanding of autism and assessment tools which are themselves gender biased.[5, 10, 14] It is also possible that the DSM diagnostic criteria we use describe symptoms mostly manifested in males but not in females. Even though females were included in the DSM-IV field trials, all participants had already been diagnosed with autism and were recruited from clinical settings. Therefore the

females in the samples may not be representative of females on the spectrum in general.[14]

Increasingly, literature is showing that girls may be missed diagnostically unless they present with additional problems, mainly behavioral or intellectual problems.[39] In fact females may need to exceed a higher threshold of severity than the males to receive a correct diagnosis of autism.[14, 20]

Early identification and accurate screening of autism is an essential clinical priority since early treatment and intervention are becoming increasingly linked to better outcomes for these children. Attwood et al. developed a Questionnaire for Autism Spectrum Conditions (Q-ASC) which includes characteristics which are potentially unique to females on the spectrum in the areas of play, friendships, social situations, interests and sensory profiles.[40] Ormond and colleagues piloted this questionnaire and results showed significant gender differences. Parents reported more sensory sensitivity, social masking, imitation skills, use of imagination and certain interests in girls when compared to boys.[22]

Another interesting theme which emerged from this review of literature is the female camouflage effect where females on the spectrum possibly try to mask certain autistic symptoms to try and fit better in social situations.[18] However this concept of 'masking' or 'camouflaging' was recently debated by Lawson and colleagues (in press) where they argue that these terms can be misleading since they can imply an intent to deceive and cheat deliberately. Their argument is that 'masking' may be a misleading term as it implies deliberate deception, when in reality trying to stay safe may mean the need for camouflage. This need is a strategy to survive which is nurtured over many years. In fact, individuals on the spectrum may cover up aspects of themselves which they want to keep hidden. Sometimes this may be done subconsciously and at other times intentionally, however the intent would not be to deceive. These strategies used by individuals on the spectrum to feel safe and adapt themselves to certain social situations can be compared to the behavior of chameleons which can change their color to match their surroundings. Like in chameleons, individuals with ASD make use of this state of 'adaptive morphing' in order to fit into social settings.[41]

Conclusion

Despite several inconsistencies in the literature, seven main themes on gender differences in autism were found in this descriptive review of literature since 2012.

Since the majority of research on autism includes mostly or exclusively males, not much is known about females with autism and as a result females may be missed or misdiagnosed. Many autistic female self-advocates talk about the importance of accurate and early diagnosis. As a result, future research should focus on including larger numbers of females in studies and developing instruments which are better adapted and fit to identify and diagnose the female phenotype of autism.[16] More research is needed to provide a comparison between girls and boys on the spectrum and typically developing children to improve services and resources available and better understand the specific needs of females on the spectrum.

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REVIEW ARTICLE

Medical observations on meteorological associations in the nineteenth century

Charles Savona-Ventura

At a time when disease aetiology was still unclear, the medical profession often assumed that climatic environment influenced both the onset and the progression of medical disorders. This encouraged physicians to collect climatic observations in attempts to relate illness to the environment providing a source of unrecognised information data relating to climate. Previously unreported nineteenth century medical sources detailing meteorological data for the Maltese Islands are reviewed in the light of known published sources of climate observations.

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Introduction

The Maltese Islands are a small group of very small islands sited in the Central Mediterranean. The official meteorological data for the Maltese Islands recorded by the Luqa Meteorological Office of the Department of Civil Aviation (1953-86) and the Water Works Department (1883-1953) covering a period of 130 years of rainfall data and 34 years of ambient temperature and other parameters has been collated and reviewed.[1] Earlier rainfall data for the period 1854-1953 collected by different observers or groups of observers from different sites in Valletta is also available. While the year 1841 serves as a landmark year in the process of scientific observations on ambient temperature data in Malta,[2] meteorological data for the late eighteenth century and earlier decades of the nineteenth century was collected and published by several interested workers, generally medical practitioners. This data is however not complete and gaps exist in the data record.

Medical practitioners during the late 18th and 19th century were preoccupied with the prevailing climate since it was commonly believed that climate conditions affected health and disease progression. Thus a late nineteenth century (1895) English medical textbook notes that "the number of births and deaths is more or less affected by the seasons of the year" and proceeds to classify the various infectious disease by their seasonal occurrence. A further section of the same textbook is devoted to meteorology.[3] It is therefore not surprising that medical practitioners practicing on the Maltese Islands were preoccupied with the ambient climate and themselves kept meteorological records in their attempts to understand the aetiology and progression of disease states.

Meteorological Data in the Late 18th Century

The earliest association of climate and health in the Maltese Islands dates to the turn of the eighteenth century (1798-1800), when the physician in charge of the French Troops, Dr. Claude Etienne Robert, discusses the disease prevalent in the Maltese Islands in the light of the local climate. Dr. Robert was a French military doctor who accompanied Napoleon Bonaparte to Malta in 1798 and remained on the Islands as Physician to the French troops until the expulsion of the French from the islands in 1800. Robert was familiar with the local meteorological situation and compares his observations to those of his compatriot D. Dolomeau who had published his work *Essai sur la temperature ou Memoire sur le climat de Malte* in 1783.[4] Dr. Robert gave serious regard to the type of winds prevailing during the seasons and kept daily temperature readings using the Reaumur thermometer available at the Public Library in Valletta. The daily records were not published, but meteorological details are given for the various seasons.[5] The mean seasonal temperature readings recorded by Robert are given in Table 1.

Table 1 Seasonal Climatic Observations 1798-1800

Season	Temperature [Centigrade]	Prevailing Winds
Spring	12-15°	N, NE
Summer	15-25°	E
Autumn	Nearly never rises above 28°	S, SE (scirocco)
Winter	7-10° above freezing point, rarely lower, but never down to 0°	N, NW, W, NE

Robert described the various winds which prevail on the Islands noting that "Les vents de la côte nord sont toujours froids; ceux du côté sud sont toujours chauds… Les vents du nord-ouest sont les plus froids et les plus purs, car ils traversent un long espace maritime; ceux de l'ouest sont moins froids et moins purs, car ils touchent un peu les côtes de l'Afrique. Le vent du nord est assez pur, car il traverse l'Italie et la Sicile, où la végétation est abondante; celle du nord-est et de l'est est pure, car elle traverse un espace maritime assez considérable. Le vent du sud et du sud-est est le pire et le moins pur, car il passe sur le continent africain, et que le canal qui sépare ce pays brûlant et aride de Malte est trop étroit pour qu'il puisse se purifier dans son voyage." [p.15-16].

METEOROLOGICAL DATA IN 1800-1820

Other writers published descriptions of the Maltese climate especially as this pertained to the suitability of the Maltese Islands towards convalescence. Thus the Physician to the Foreign Forces William Domeier who served in Malta during the period April 1806 and June 1808 published a general description on the climate of Malta however without giving any statistical analysis but quoting a mean annual temperature of 20°C and a mean annual rainfall of 15 inches.[6]

On the 28th March 1813, the Maltese ship San Nicola entered Marsamxett Harbour with plague cases on board. In spite of rigorous quarantine measures, the disease spread to the general population and was to cause the death of about 4468 individuals until the infection terminated in September 1813.[7] The aetiology of the disease was still unestablished and was variously attributed to contagion (infection through contact) or infection (communicated by the atmosphere). Meteorological data was collated for the period of the epidemic and these were subsequently published.[8] There were no correlations between the progress of the disease and the meteorological conditions to be noted (Table 2).

Table 2 Climatic Observations Apr-Nov 1813

Month	Max. Temperature [Fahrenheit]	Wind	Number of plague deaths registered
April	71°	*"Strong winds blew during part of the period, particularly in July"*	3
May	82°		111
June	84°		802
July	88°		1595
August	86°		1041
September	88°		674
October	83°		209
November	72°		33

METEOROLOGICAL DATA IN 1820-1850

The first valid scientific observations made in the Maltese Islands appear to be records of temperature data from the years 1820-40 published by S. Schembri in 1841. Unfortunately these data has not been traced.[1-2] Rainfall data started to be collected by C. Grech Delicata collected after 1840. These records form the first important group of meteorological data for the Maltese Islands.[1]

The British physician Sir James Clark who served as Queen Victoria's Physician-in-Ordinary from 1837-1860 wrote a thesis in 1841 describing the climate of Malta with reference to the eligibility of the island as a place of residence for invalids.[1,9] Further observations were published by the British doctor John Davy in 1842 who focused mainly on the prevailing winds and their origin. He also conducted a number of experiments to investigate alleged harmful effects of moonlight on health.[1,10] Other observations on climate data published in the local newspaper

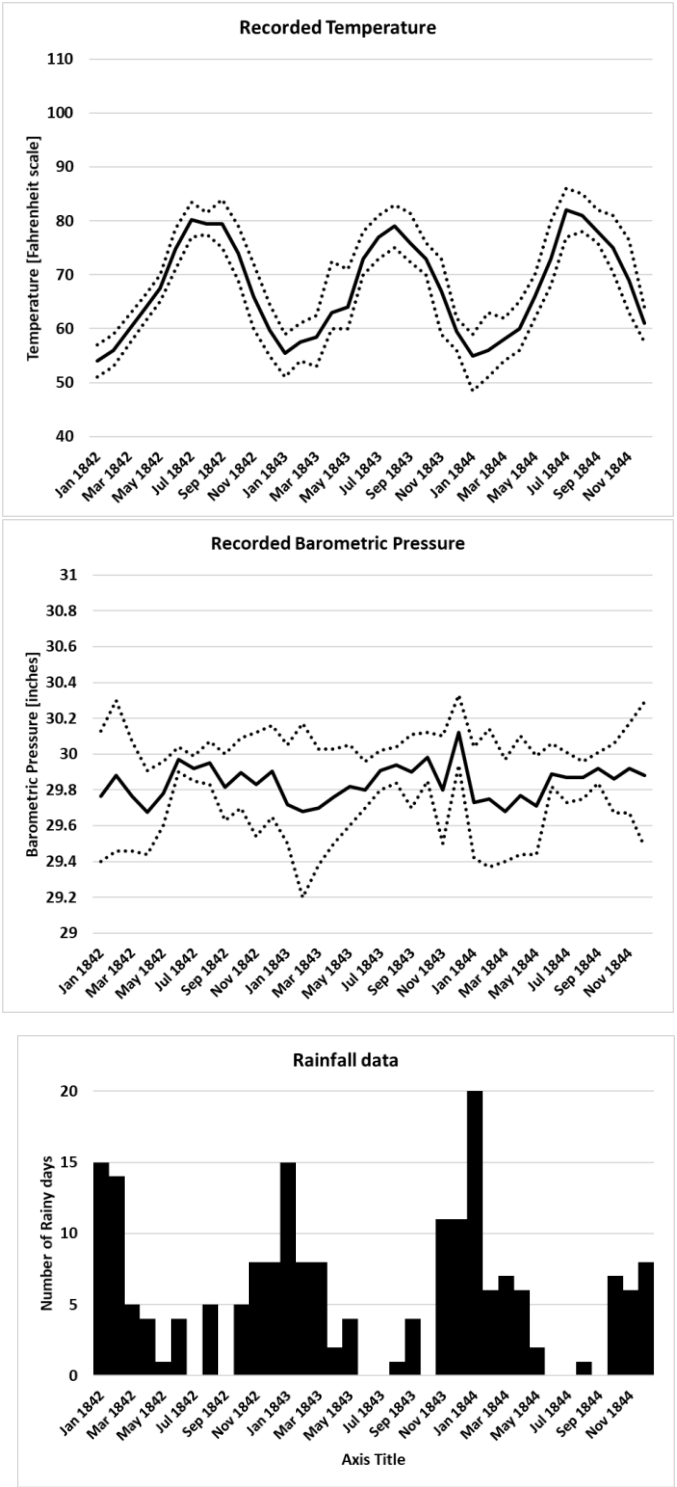
Portafoglio Maltese which gave daily rainfall data, while the *Societa Medica d'Incorragiamento di Malta* published the climate data including atmospheric pressure, mean temperature, wind direction and rainfall for the year 1843.[1,11]

Another British physician who published his meteorological observations during this period was Sir Thomas Spencer Wells. Thomas Spencer Wells was a British doctor who served as a surgeon for six years in the Bighi Naval hospital in Malta from 1841 to 1847. During his stay in Malta, Spencer Wells published several papers in international and local journals, and was influential in introducing surgical anaesthesia to the Islands. He was later to become one of the leading nineteenth century pioneers in abdominal surgery and a renowned leader of the British Surgical establishment.[12] Two of the papers published by Spencer Wells deal with the medical conditions he encountered during his stay in Malta. In these publications, he includes meteorological details for the period 1842-44.[13-14]

Spencer Wells kept accurate data on Maltese climate keeping observations on the minimum and maximum temperature and barometric monthly readings as read at mid-day with the instruments kept in a situation least exposed to local influences or changes. The prevailing winds and the number of rainy days during that month were also recorded. The climatic data recorded by Spencer Wells in Malta during 1842-44 are summarised in Figure 1. No relation between climate changes and the occurrence of disease states were reported, except that the death rate from phthisis (tuberculosis) was greater during or immediately after a prevalence of winds from the shores of Syria or Libya, i.e. the Scirocco and Liebeccio winds. It was remarked that the disease in common with all respiratory disorders ran a particularly rapid course when the Scirocco wind prevailed.[13,43]

The Maltese physician Nicola Zammit published the data on dewfall and evaporation for the period 1851-54. This data is presently unavailable.[1,11]

Figure 1 Meteorological Data for 1842-1844: Monthly Averages



METEOROLOGICAL DATA IN 1850-1910

During the latter part of the eighteenth century, meteorological observations started to be made by non-medical personnel. Monthly rainfall averages started to be published annually after 1851 in the Blue Books. The Royal Engineers set up and operated a full meteorological station. The Jesuit Fathers in 1883 set up two meteorological observatories, while rainfall data was regularly collected by the Water Works Department after 1888. The data after 1854 are published in the Annual Abstracts of Statistics.[1] Further meteorological data was collected by the Education Office during the late nineteenth century and published monthly in the Malta Government Gazette. This included information regarding the temperature, rainfall and general state of the atmosphere as noted at the University, the Public Library, and the Primary Schools in Malta and Gozo.[15]

In spite of the increasing interest in climate by non-medical bodies, the association of climate change to disease persisted in medical thought. The Maltese physician Nicola Zammit published the data on dewfall and evaporation for the period 1851-54. This data is however presently unavailable.[1,16] The Public Health Department published its first annual report for the year 1896. The report included an annual meteorological return based on monthly averages, and this continued to be reported regularly until the 1950s. The 19th century meteorological data was made available to the Chief Government Medical Officer by Rev. Fr. J. Dobson S.J. of St. Ignatius College. The data pertaining to wind direction and strength was made available by the Collector of Customs.[17] The St. Ignatius College meteorological readings for the period 1883 to 1902 were published in the Stonyhurst College Meteorological Reports. These published reports are not available locally,[1,18] but the data for the post-1896 years were published in the Department of Health reports and figuratively summarised in Figure 3.[17]

The 19th century Annual Public Health Reports also commented on the higher incidence of diseases of the digestive system during the summer months. It was believed that the essential cause for infantile enteritis resided in the soil and that under favourable meteorological conditions, particularly temperature, would gain access to the air, water and food causing the higher incidence of the infection during the summer months. By 1899, the Department of Health was undertaking investigations to attempt correlate the incidence of enteritis to soil temperature at various depths, the study being conducted at the Argotti Gardens at Floriana. The soil temperature data at a depths of 1-3 feet for the months of July-September were published for the period 1899-1900 (Figure 2).[19]

Figure 2 Mean [minimum-maximum] soil temperature data at 1 feet depth correlated to infant mortality from enteritis.

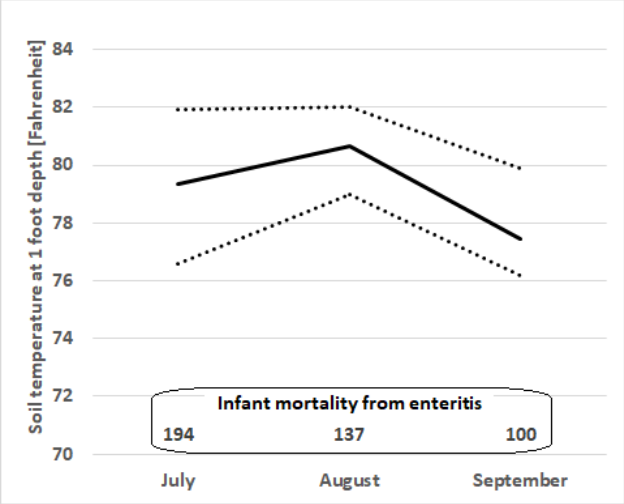
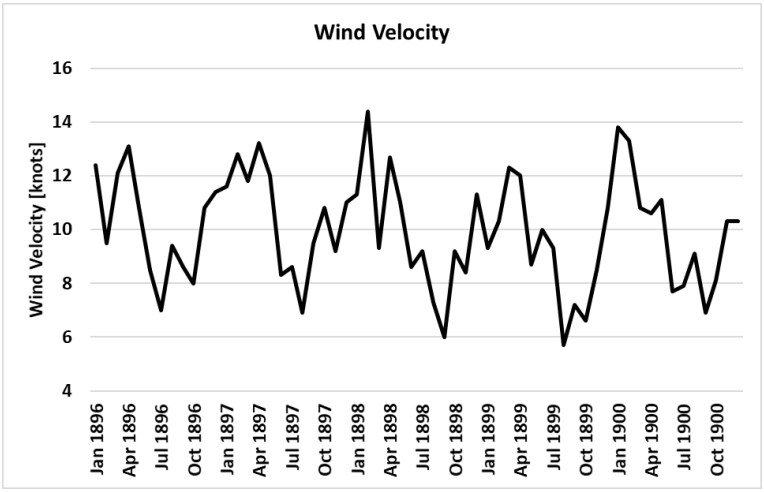
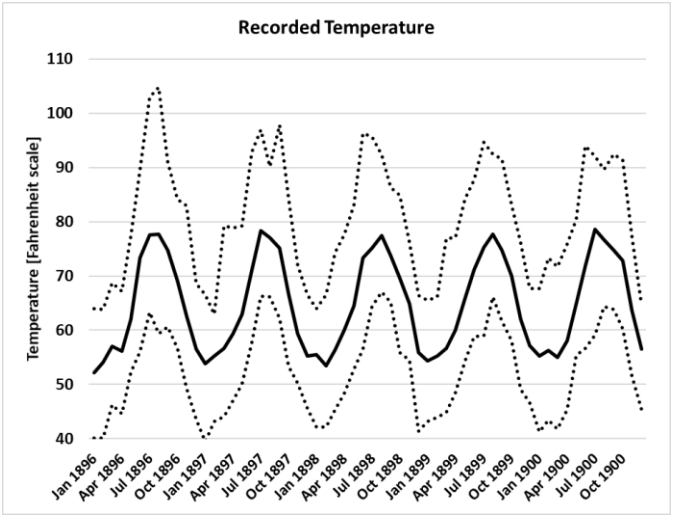
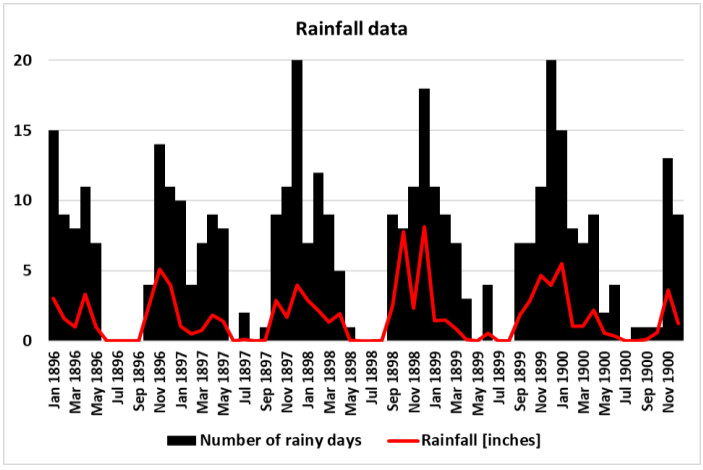
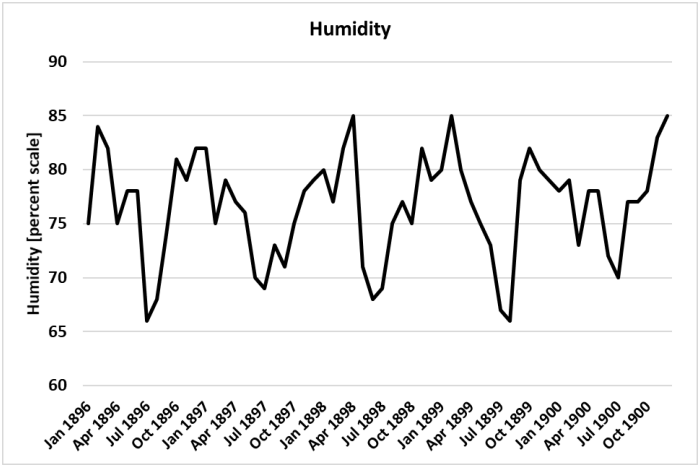


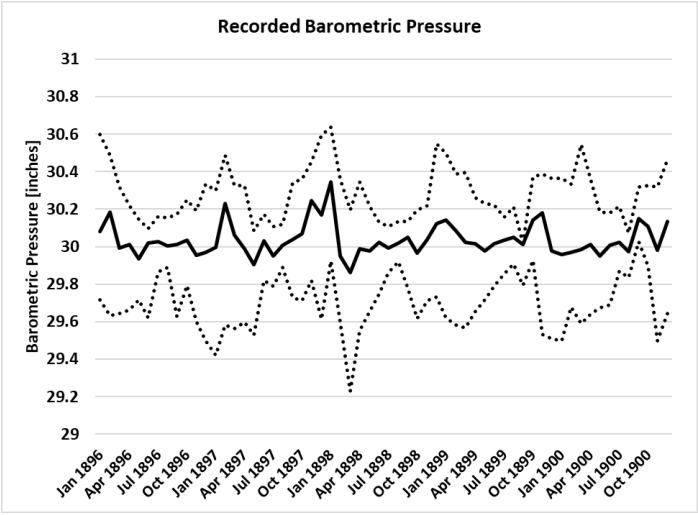
Figure 3 Meteorological Data for 1896-1900 – Monthly Averages











Meteorological studies were also carried out by the Mediterranean Fever Commission in relation to climate in the aetiology of Brucellosis. Dr. R.W. Johnstone correlated the mean monthly temperature and rainfall for the period 1894-1903 with the number of cases of Brucellosis occurring in the civil and military population and showed a correlation with ambient temperature. The reason for this correlation was not elucidated. Further results pertaining to the 1905-1906 period were published in 1907. [20]

Table 3 *Brucella* culture in soil after exposure to sun

Date & time of exposure to sun	Total exposure duration	Maximum temperature	Post-exposure culture
20th June 1904 12:15-13:00 hrs	45 minutes	53.3°C	Yes
+ 21st June 1904 08:50-11:50 hrs	225 minutes	57.2°C	Yes
+ 22nd June 1904 08:45-11:45 hrs	345 minutes	52.2°C	No
+ 1st July 1904 10:30-12:30 hrs	465 minutes	56.1°C	No

Studies were also conducted to assess whether the *Brucella melitensis* bacterium in soil was resistant to exposure to ambient temperature. A series of petri dishes containing white and red soils inoculated with *Brucella melitensis* were exposed for variable times to sunlight (Table 3). Further studies confirmed that heat derived from sunlight exposure with an ambient temperature of 63.3 – 67.2°C destroyed any *Brucella melitensis* bacteria in soil up to a depth of at least ½ inch.[19]

CONCLUSION

Meteorology in Malta became a science during the late 19th century when data pertaining to climate was collected and published on a regular basis. This data allows for statistical evaluation of climate conditions emphasising the secular trends. Early nineteenth century data collected by interested individuals is also available in scattered publications. The collation of this early 19th century data would help extend the available climate statistics for the Maltese Islands.

The association between disease and ambient climate is now accepted to be a indirect one with varying meteorological conditions determining the prevalence of disease-spreading vectors, e.g. insect vectors, and providing ideal conditions for microbial growth and/or survival. Climatic factors have also been postulated to directly or indirectly affect biological systems. A study on male-female ratios at birth had shown that the ratio of gender at birth in the European continent varied with latitude and a meteorological relationship was proposed to explain this relationship.[21] A subsequent study confirmed a possible relationship between gender ratio and climatic factors determined by seasonal fluctuations. However, the study was not strong enough to confirm a statistical significant relationship.[22]

The environmental stresses brought about by the excessive release of carbon dioxide and other greenhouse gases are affecting the global climate. These changes in the global climate are associated with a wide range of health risks, ranging from increased mortality to changing infectious diseases epidemiology increasing the likelihood of outbreaks of

waterborne and vector-borne diseases. Unless urgent action to reverse the global climate change is taken, an estimated 250 000 extra annual deaths will occur over the period 2030-2050.[23]

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REVIEW ARTICLE

Sexuality and intimacy in later life – hormonal determinants

Charles Savona-Ventura

The developed world has seen an increase in life expectancy and a general drop in fertility rates changing the population demographics in favour of a greater proportion of elderly individuals who retain an overall good health profile. The issue of sexuality in the elderly has unfortunately often been relegated to the backburner. The elderly, however, do have needs related to sexuality, and health professionals need to be tuned to the needs that often remained unspoken and unaddressed

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Introduction

Populations in the developed countries have gravitated towards an increasing proportion of elderly individuals. This shift has been engendered by a number of biological and social factors including the decreasing fertility rate caused by a tendency to have smaller families in these communities, and the increasing longevity. In the Maltese population, the mean life expectancy at birth in Malta has gone up from 78.20 years in 2000 to 81.95 years in 2015. The aim however is not simply to increase longevity but to have an increase in healthy longevity, i.e. an increase in life expectancy without activity limitation. The Health data for Malta for 2011 had shown that women and men aged 65 years were likely to enjoy a further 10.9 and 11.8 years of life respectively without activity limitation, and a further 6.0 and 3.7 years with only moderate activity limitation. In contrast, the EU27 average life expectancy at 65 years enjoying no activity limitation was 8.6 years for women and 8.6 years for men, and a further 7.7 and 5.9 years respectively with moderate activity limitation.[1] One aspect of "health living" that is often ignored completely or put on the backburner, is the issue of sexuality or the problems older people face related to sexual issues. There appears to be a general perception of an 'asexual' elderly population. Research has however shown that many older people enjoy an active sexual life.[2] The perception of an asexual elderly population is prevalent in the Maltese population. This myth defines the approach often taken by health care workers when dealing with the elderly where the issue is completely ignored unless directly addressed by the individual or couple themselves. This is very reminiscent of the 1971 British farce "No Sex, We're British" being translated into "No Sex, We're Elderly Maltese".

While the limited research suggests that many older people do enjoy an active sexual life, the available research however does suggest that increasing age is associated with a decreased interest in sex.[2-3] A study conducted in Italy also found significantly less interest in sex among the older individuals with all the 38 centenarians included in the study population admitting to having completely lost interest in sex.[4] The reasons for the apparent loss of interest in active sex with increasing age are multifactorial but include physiological alterations associated with aging and developing medical issues. This besides the psychological and social factors that potentially play an important determining role.

Endocrinological changes associated with aging

The body functions, particularly those related to sexuality and reproduction, can be said to be determined by a "puppet master" that drives the system through the effects of hormones. The biological aim of sexual activity is the need to reproduce the species, and the reproductive hormonal cascade is centred primarily for this aim – to drive the need for sexual activity during the fertile period and prepare the female's body to host the foetus. The reproductive biological age in females is determined by the follicular reserve in the ovaries, the follicles being essential to produce potential ova. Follicular reserve decreases dramatically with increasing age. A birth, the ovary is estimated to have about 1 million follicles. These decline to about a quarter of a million by the age of puberty. With increasing age, these primordial follicles undergo atresia. The follicles are supported by the granulose

cells that are responsible for ovarian hormone production. These granulosa cells similarly are depleted with increasing age along with the atresia occurring in the primordial follicles. Thus, once the ovarian follicles are depleted, ovarian hormone production also declines. In females, the reproductive hormonal cascade is determined by the cyclical interplay of the GnRH from the hypothalamus, the LH/FSH production by the pituitary, and oestrogen/progesterone from the ovaries (Figure 1).

While oestrogen and progesterone are essential for normal reproductive functions in females; testosterone, produced in the ovaries and adrenals, also affects sexual desire and function in women. The depletion of the ovarian follicles results in a gradual decline in the response to FSH stimulation and a decline in the levels of oestrogen. This is, in the perimenopausal period, initially mitigated for by a corresponding rise in FSH secretion that serves to whip the failing ovaries to continue functioning. The pituitary will at this stage fail to generate the mid-cycle LH surge resulting in anovulatory infertile cycles. Testosterone on the hand, because of the contribution from the adrenal glands, falls more slowly (Figure 2). The more gradual fall in testosterone suggests that while the hormonal drive for reproduction will decease after the menopause, sexual libido in women does not necessarily decrease at the same rate.[5]

Figure 1 The reproductive hormone cycle in males and females

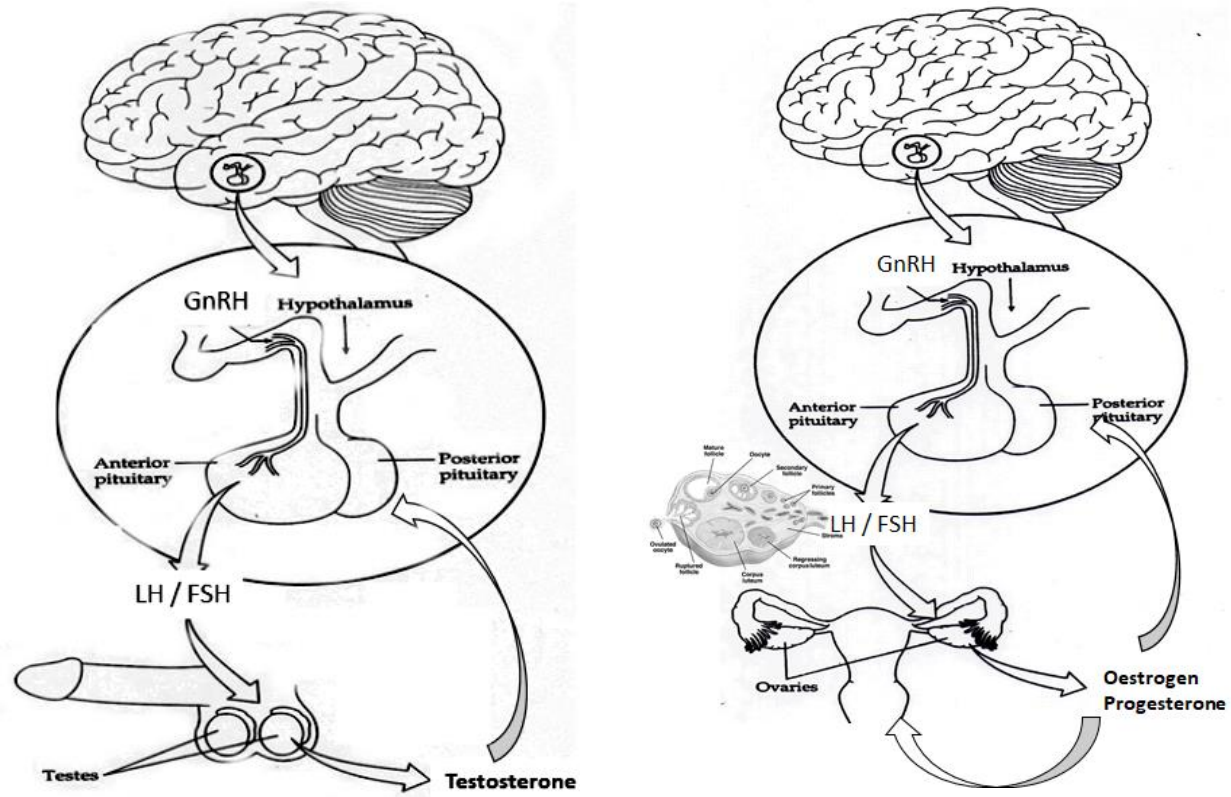
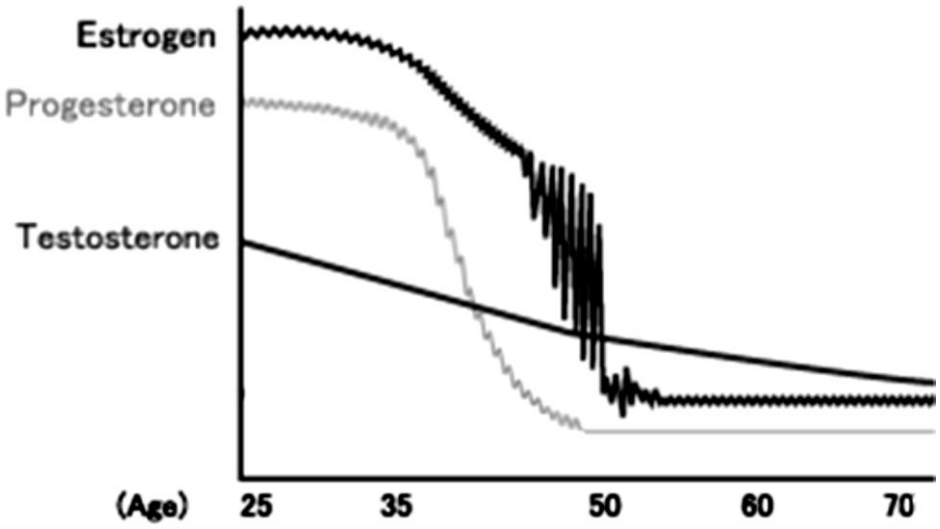


Figure 2 Hormone levels with age in women



While the reproductive endocrine system in females is characterised by a specific event that defines reproductive capability, the cessation of menstruation or menopause; no such dramatic event occurs in males. Here the changes are gradual and progressive so that one cannot truly identify the occurrence of a corresponding "andropause". In males, the reproductive hormonal cascade is determined by the interplay of the GnRH from the hypothalamus, the LH/FSH production by the pituitary, and testosterone from the testis (Figure 1). On average, male reproductive function remains normal or only slightly diminished until advanced old age (80+ years) when it then decreases. Subtle hormonal changes do however occur earlier, including a decrease in GnRH secretion, a decreased sensitivity to LH levels with a correspondingly decreased androgen secretion, and a decrease in the sensitivity of the negative feedback between the GnRH and LH hormones.[5-6] While testosterone levels do decrease with increasing age, following the same rate of decline as in females, the levels in males remain very much elevated in advanced old age (Figure 3).

These overall elevated levels maintain a relatively stable sexual libido. Testosterone levels, throughout life, are dependent on external factors that may deteriorate with increasing age. One such factor prevalent among Maltese men is adiposity with 76.28% of men falling in the overweight/obese classification. Adiposity tends to increase with advancing age.[7] An increasing BMI has been shown to be strongly associated with progressively low testosterone levels irrespective of age (Figure 4).[8]

Figure 3 Testosterone levels in females (above) and males (below) [conversion factor 100 ng/dL = 3.47 nmol/L]

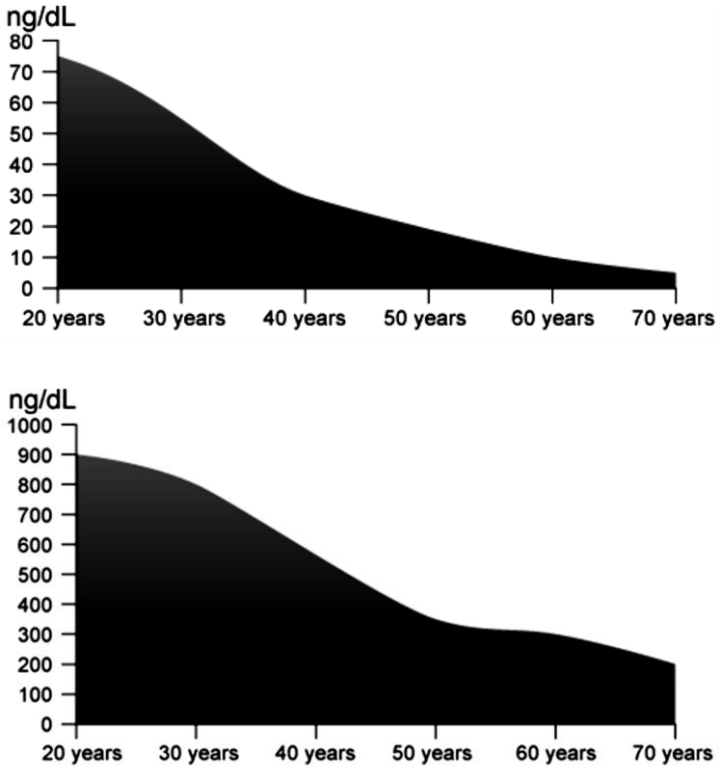
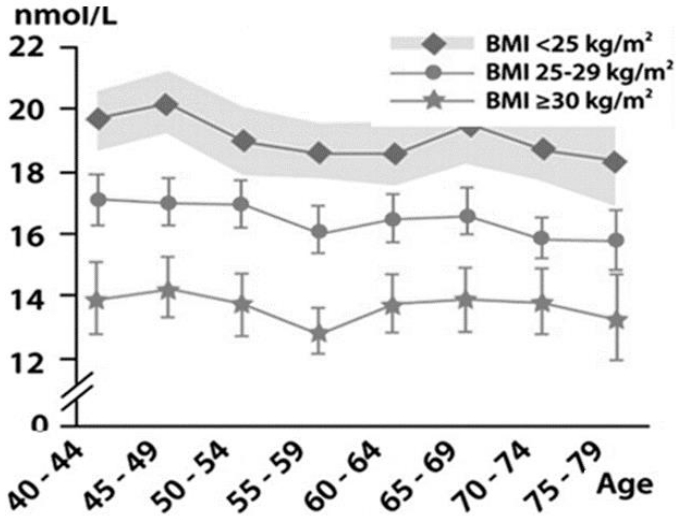


Figure 4 Testosterone levels by age and BMI [conversion factor 20 nmol/L = 576.4 ng/dL]



Physical changes associated with aging

The declining levels of oestrogen which occurs in females at menopause is associated with anatomical changes in the reproductive system. These changes include specific changes in the ovaries which become more fibrotic causing a significant decrease in size; in the uterus which exhibits a decrease in weight and volume due to a loss in the muscular component; in the vagina which exhibits a marked degree of atrophy, loss of elasticity, decreased vascularity and decreased secretions; and in the vulva which starts to show evidence of atrophy and loss of elasticity. Loss of lubrication and relative rigidity of tissue will predispose to dyspareunia; while the loss of the muscular component in the vagina predisposes to reduced orgasmic contractions. These factors, if unaddressed, will mitigate against enjoyable sexual activity irrespective of sexual libido.[9] Declining hormone levels also have systemic effects including thinning of the skin and atrophy of the sebaceous glands, atrophy of the bladder, decreased bone mass, and alteration in lipid metabolism.

The male continues to produce germ cells and testosterone well into old age, declining only with markedly advancing age. Physical changes do eventually take place because of advancing age and age-related fibrosis of blood vessels. The size and firmness of the testes decrease because of age-related fibrosis constricting the blood supply. This causes a gradual reduction in sperm production. Since erection is a purely vascular phenomenon, vascular fibrosis may also affect penile function. These anatomical changes can result in a delay in achieving an erection, while ejaculation decreases in force and volume.[10-11] Other general physical changes and medical conditions may directly or indirectly through medications administered effect penile function and contribute to erectile dysfunction.

Conclusions

The process of aging is a continuous process. While hormonal changes do occur at the end of reproductive life, these changes should not be allowed to directly influence sexual activity. Hormonal replacement therapy, systemic or local, are viable options for those elderly female individuals who wish to maintain an active sexual life. For males with erectile dysfunction, PDE5 inhibitors will help relax tight blood vessels allowing more blood to surge into the penis and facilitate an erection. Unfortunately, the social taboo about discussing sexuality especially in the elderly prevents those wishing to maintain an active sexual live from discussing the matter with their health professional. Health professionals should be more proactive regarding sexuality with their older patients and feel free to openly discuss these issues.

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CASE REPORT

Minimally invasive resection of a marijuana-associated giant bulla: a case report

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Background

Smoking is known to be a causative factor for emphysema. Literature also supports the possibility that marijuana abuse increases the probability of giant apical bullae in young individuals. Surgical resection is the only cure for giant bullae, whilst also having a prophylactic role. Video-assisted Thoracoscopic Surgery (VATS) bullectomy is the new gold standard replacing thoracotomy.

Case Presentation

We present a 31-year old marijuana smoker with a history of multiple pneumothoraces who was found to have a large emphysematous bulla in the left upper lobe accompanied by a smaller bulla in the superior lingular segment. Even though he was asymptomatic at the time, VATS bullectomy was carried out in view of his multiple previous pneumothoraces. The patient recovered well after surgery, and a follow-up chest x-ray 2 weeks post-operatively showed a fully inflated lung.

Conclusion

This is the first case of giant bulla being removed via minimally invasive VATS in Malta. Apart from continuing to show the effectiveness and suitability of VATS in the treatment of this condition, we highlight the important link between marijuana and giant emphysematous bullae.

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Introduction

The first case report on giant bullous emphysema was published by Burke in 1937.[1] It is a rare manifestation of emphysema.

According to the Global Initiative for Chronic Obstructive Lung Disease (GOLD), chronic obstructive pulmonary disease (COPD) is defined as a "common, preventable, and treatable disease that is characterized by persistent respiratory symptoms and airflow limitation that is due to airway and/or alveolar abnormalities usually caused by significant exposure to noxious particles or gases".[2] The report continues to elaborate that small airway disease and emphysema are the two main constituents of COPD.

Emphysema is a pathological term, which refers to the destruction of airspace walls distal to the terminal bronchioles, with the creation of permanently enlarged airspaces but without any fibrosis.[3] In some patients, this continues to advance to bullous emphysema, which consists of multiple bullae within emphysematous lung parenchyma. By definition, bullae are air spaces which are at least 1cm in size, encompassed by walls made of visceral pleura and remnants of alveolar and interlobular septae.[4] When bullae occupy more than a third of the hemithorax they are located in, they are labelled as giant bullae.[5-6] If no complications occur, the usual development of giant emphysematous bullae is gradual enlargement, which would ultimately impair breathing. However, rare spontaneous regression of giant emphysematous bullae have been reported, with symptomatic and radiological improvement.[7]

Nowadays, the international gold standard treatment for this disease is VATS-bullectomy, replacing open surgery. We describe here the first case of a giant bulla resected in this minimally invasive way in Malta.

Case

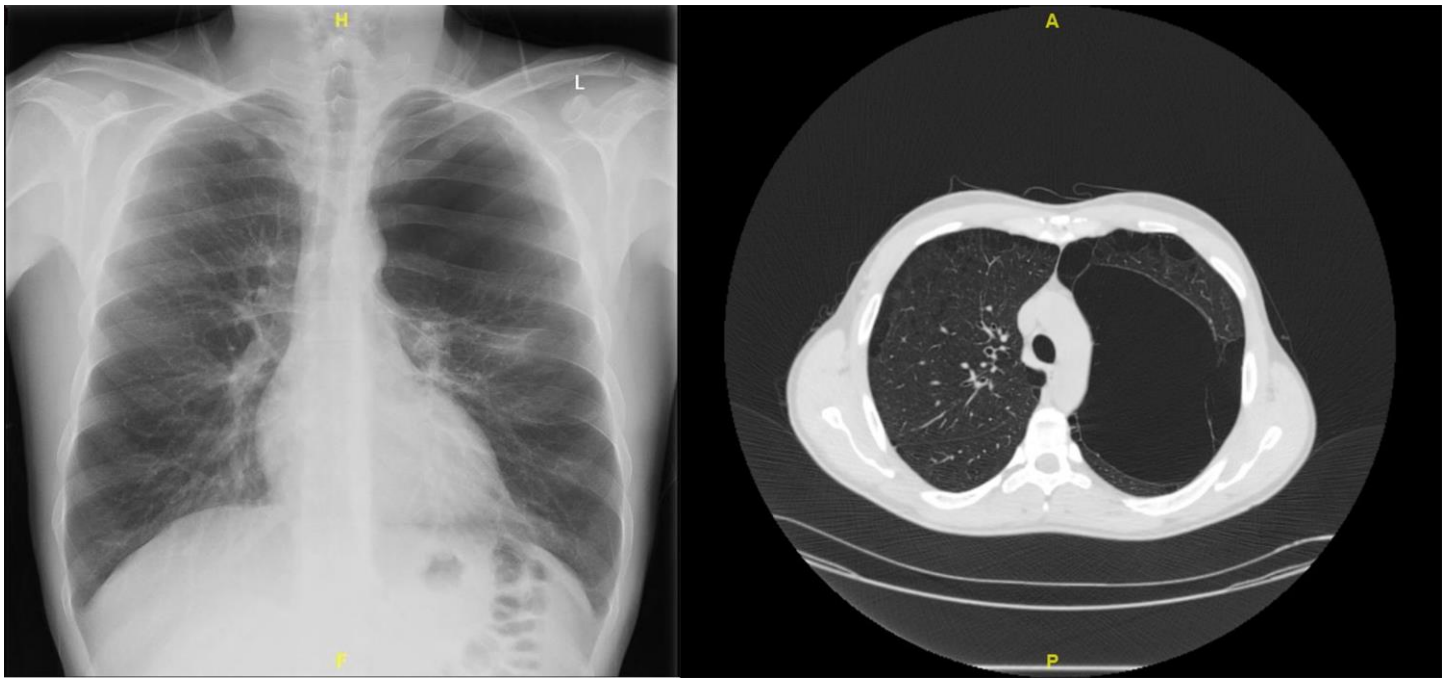
A 31-year-old patient, with a past history of right pneumothorax 3 years before, presented with a recurrent ipsilateral pneumothorax. This second pneumothorax was treated with a Seldinger insertion 12Fr intercostal chest drain for a few days. The lung re-inflated successfully, and the patient was referred electively to the cardiothoracic clinic.

His past medical history includes severe eczema requiring steroids and immunosuppressants. He is a cigarette smoker and has smoked approximately 1 packet a day for the past 17 years. He has also been smoking marijuana heavily, every day for the past 8 years. While being followed up 1 week later in the cardiothoracic clinic, he was not short of breath, and was otherwise asymptomatic. On examination, he had decreased air entry bilaterally, but was hyper-resonant over the upper 2/3 of his left lung. Pulse oximetry showed an oxygen saturation of 100% on air and his breathing rate was 12 breaths per minute. The rest of his parameters were stable.

A chest X-ray showed decreased lung markings over the upper half of the left lung (Figure 1). A CT scan of the thorax was performed. This revealed a large emphysematous bulla in the left upper lobe, about 17 centimetres by 21 centimetres in size. Another bulla, measuring 7 centimetres by 6 centimetres, was also visualised in the superior lingular segment (Figure 1).

Figure 1 Left: Chest X-ray done on admission, showing decreased lung markings over the upper half of the left lung

Right: CT scan showing the giant bulla in the left upper lobe, and the smaller bulla in the superior lingular segment.



Accompanying this, there was also a very small pneumothorax of up to 9mm in depth around the left lung, and some para-septal emphysema in the right upper lobe.

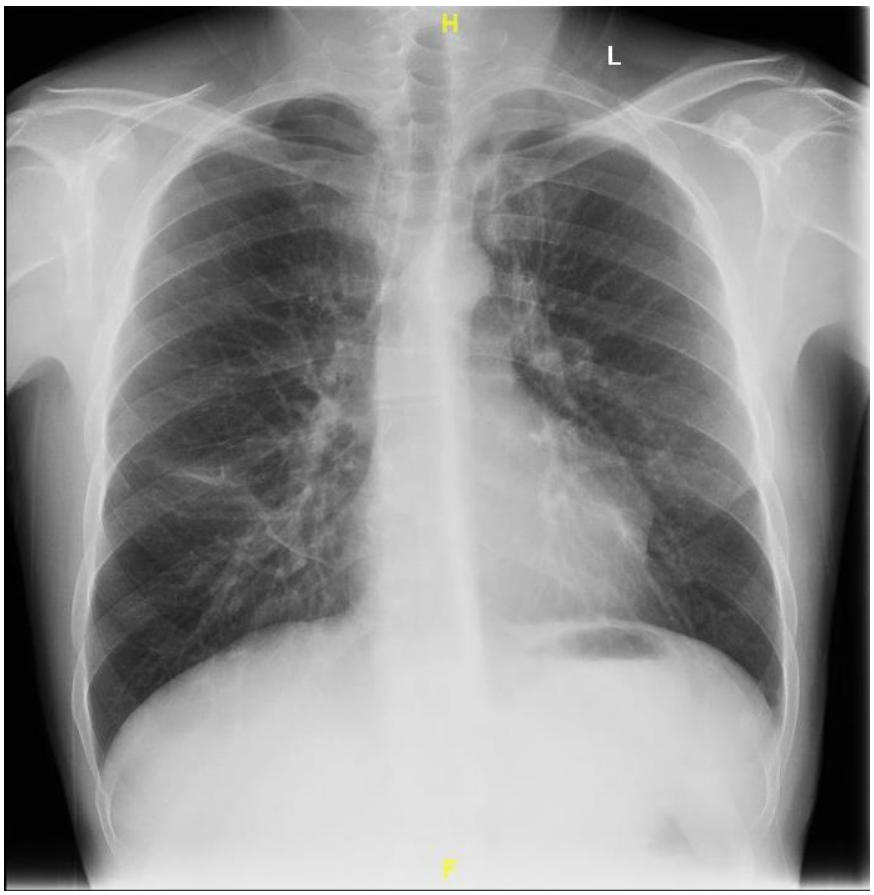
In view of his recent pneumothorax, no pulmonary function tests were done.

An elective VATS bullectomy was done, using single lung ventilation under general anaesthesia. Two port technique was used with adhesions removed between the giant bulla and the chest wall. The upper lobe giant bulla was resected using an Endo GIA™ (Covidien, Metronic, Minneapolis, Minnesota, USA) trilinear stapler. The resection was performed a centimetre beneath the origin of the bulla, to ensure that healthy lung seals well at the staple line. The second smaller bulla was resected in the same manner. A total pleurectomy was also performed to help prevent recurrence of the pneumothorax. One drain was placed but no suction was applied onto the drain, unlike routine pleurectomy operations for primary spontaneous pneumothorax. This was omitted to avoid sudden re-expansion of a chronically compressed lung with risk of staple line dehiscence. The patient mobilized the day after the procedure, his drain was removed 2 days post-operatively and he was discharged that same day.

The patient was reviewed two weeks after the surgery and all wounds were healing well (Figure 2). A repeat chest X-ray showed full re-expansion of the lung (Figure 3). The patient also stated that he was feeling quite well and was very happy with the care he had received.

Figure 2 The port through which the VATS bullectomy was carried out, 2 weeks post-surgery

Figure 3 Chest X-ray 2 weeks post-surgery, showing full re-expansion of the lung.



Discussion

Giant bullae are classified in many ways, such as; Reid[8], Wakabayashi[9], and DeVries & Wolfe's[10] practical classification into 4 groups. However, we favour the classification by Klingman which categorizes giant bullae according to the quality of the underlying lung.[11] Type 1 is where the giant bulla is surrounded by normal lung, type 2 by emphysematous lung and multiple other bullae and type 3 is that of vanishing lung syndrome (VLS).

VLS is the most extreme form of giant bullous disease where the bullae, with their low compliance, continue to be ventilated preferentially and the remaining lung involutes into nothing but a hilar bud. No lobes are discernible and unfortunately the condition is not amenable to surgical cure at this stage.

The indications for surgery in giant bullae include dyspnoeic patients with high residual volume and hyperinflation present, and the emergence of complications. Surgery is also indicated as a prophylactic measure in bullae occupying more than 50% of a hemithorax, and also if a longstanding bulla is occupying one third of the hemithorax, since this prolonged compression renders the remaining lung less likely to expand.

The commonest complications of giant bullae include infection, haemorrhage, and pneumothorax.[12-13] A rare complication that has been reported with giant bullous disease is superior vena cava obstruction, which unless treated early could lead to death.[14] Ischaemic stroke caused by air emboli from a ruptured giant bulla has been reported to occur although this is a very rare complication.[15] Interestingly, giant bullae are an emerging risk factor or even aetiological factor for lung cancer. Multiple cases of lung cancer associated with giant bulla and with differing histology have been reported.[16-17] More research about this association is needed, but this could potentially give another valid reason for preventative surgical treatment of giant bullae, especially in older patients, to improve the prognosis.

The case described here was a Klingman type 2 with the complication of recurrent pneumothorax. He had no other potential causes besides cigarette and cannabis smoking.

Marijuana abuse is highly linked with giant bullous disease of the lung. It is suggested that marijuana is more likely to cause giant emphysematous bullae when compared to tobacco smoking, which in contrast has a higher chance of causing emphysematous changes with smaller bullae.[18-20] This could potentially be due to the higher inspiratory pressures and prolonged breath-holding that are associated with marijuana smoking, accompanied by direct toxic damage to the lung parenchyma.[21] Studies indicate that bullous disease secondary to marijuana abuse tends to occur in a younger cohort of patients, and tends to be asymmetrical – as is the case in our patient.[22-23] It also seems to have a specific predilection for the lung apices.[18, 24]

Giant bullae affect gaseous exchange in a variety of ways. First of all, a ventilation-perfusion mismatch is created, since the destruction of alveolar walls creates a bulla which has minimal blood supply. Apart from that, the giant bulla compresses nearby parenchyma which has a better blood supply, therefore limiting ventilation in these airspaces.[4] Secondly, the destruction of the air space walls decreases the elastance hence increasing the compliance of the lung in that

hemithorax. This leads to air entering preferentially into the bulla on ventilation, down the pathway of least resistance resulting in a decrease in the ventilatory capacity of the lung, since gaseous exchange is minimal across the fibrous membrane of the giant bulla.

A study performed in 2005 by Palla et al showed that elective surgery is the treatment of choice for bullectomy. For the cases studied, the mortality rate in the first post-operative year was 7.3%, while the late mortality rate at 5 years post-op was 4.9%.[25] In our case, VATS-bullectomy was utilised, which has been proven to be a safe and effective treatment modality for giant bullae, with long-term symptomatic improvement.[26-27] In fact, VATS bullectomy results in a shorter hospital stay, quicker recovery, less post-operative pain and most importantly better ventilation with reduced chest infection rates, when compared to thoracotomy, and is therefore preferred.[6] Debate continues in the thoracic surgical community on the use of cellulose mesh and fibrin glue to reinforce the suture line[28] or use of BioGlue™ (Cryolife, Kennesaw, Georgia, USA) to reduce staple line dehiscence.[29] The technique described here relies on the presence of healthy lung to staple through at the margin of the bulla. If doubt exists on the strength of tissue one can lay open the bulla and staple the base from within, with the walls of the bulla acting as their own buttress.

Conclusion

There is a misconception that cannabis is less harmful to the lungs than cigarettes. This is not the case as we can see from numerous young people with very severe bullous lung disease. Cigarette smokers do not present so young and with such large bullae. Perhaps the fact that cigarettes are smoked through a filter for large particles plays a part in this difference.

Patients with giant bullae can undergo a novel minimally invasive operation, which carries less risk and a shorter recovery time than the conventional open operation. However, the long-term prognosis of the patient depends on their ability to stop smoking.

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CASE REPORT

Leprosy in Malta: not to be forgotten

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Leprosy is a granulomatous infection that was considered endemic in Malta up until being declared eradicated in 1999 thanks to the Malta Leprosy Eradication Programme. However, leprosy remains endemic in a number of low-to-middle income countries, and may be imported to non-endemic regions like Malta by migrants. We report a case of a man from the Philippines presenting with nodular lesions over the face, trunk and limbs and a hypoaesthetic patch over the arm. A skin biopsy supported the clinical suspicion of midline borderline/borderline lepromatous leprosy and triple therapy with clofazimine, dapsone and rifampicin was initiated. Despite having a wide clinical differential diagnosis, leprosy must always be kept in mind by clinicians, especially when treating nationals from endemic areas.

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Introduction

Leprosy is a chronic, progressive, granulomatous infection caused by *Mycobacterium leprae*. In Malta, this disease was once endemic but after the Leprosy Eradication Programme which started in 1972, no endemic cases have been reported since its termination in 1999.[1] However, in countries where the disease is still endemic the incidence remains relatively stable, possibly since many cases go unrecognised and therefore undiagnosed.[2] In view of its long incubation period, travelers from endemic countries may develop symptoms after migration. We present a case of a man from the Philippines residing in Malta, diagnosed with midline borderline/ borderline lepromatous leprosy.

Case Presentation

A 29-year-old man from the Philippines presented with a 4-year history of an enlarging erythematous patch over the outer aspect of the right arm (Figure 1) and a 6-month history of erythematous-to-brown nodular lesions over the face, trunk and limbs (Figures 2A and 2B). He reported numbness and reduced sweating over the right arm patch but all other lesions were asymptomatic. He was previously healthy, had moved to Malta from the Philippines 20 months previously and was residing with his partner who was asymptomatic. On examination there was a 12cm x 12cm annular erythematous patch with a hypopigmented centre on the right arm (Figure 1) The lesion had raised borders with palpable cord-like structures at one end and reduced sensation to cotton wool and pinprick. All other lesions appeared to have normal sensation. Incisional biopsies from the right arm, right cheek and left thigh showed granulomatous inflammation with sheets and nodules of foamy epithelioid histiocytes, lymphocytes and occasional plasma cells extending perineurally (Figures 3A and 3B). A Wade-Fite stain revealed moderate numbers of acid-fast bacilli within the cytoplasm of a minority of the histiocytes (Figure 3C). Based on the clinical and histological findings a diagnosis of tuberculoid/borderline tuberculoid leprosy recently downgrading to borderline lepromatous leprosy was made. Treatment with dapsone 100mg daily, rifampicin 600mg daily and clofazimine 50mg daily was started, for an expected duration of 24 months. A few weeks into treatment a widespread non-itchy, erythematous maculo-papular eruption, consistent with a Type 1 reversal reaction, appeared and was treated with one dose of intramuscular methylprednisolone acetate 80mg. Following improvement of these symptoms the patient decided to return to the Philippines. He was given written confirmation of his diagnosis and was strongly advised to seek medical attention and continue treatment on returning home.

Figure 1 Well-demarcated anaesthetic patch with an erythematous border and central clearing/resolution over the outer aspect of right arm

Figure 2A Multiple erythematous-to-brown nodular lesions over trunk (a) and lower limbs (b)

Figure 2A Multiple erythematous-to-brown nodular lesions lower limbs

Figure 3A Low power view showing perineural granulomatous inflammation. H&E stain. Original magnification: x100

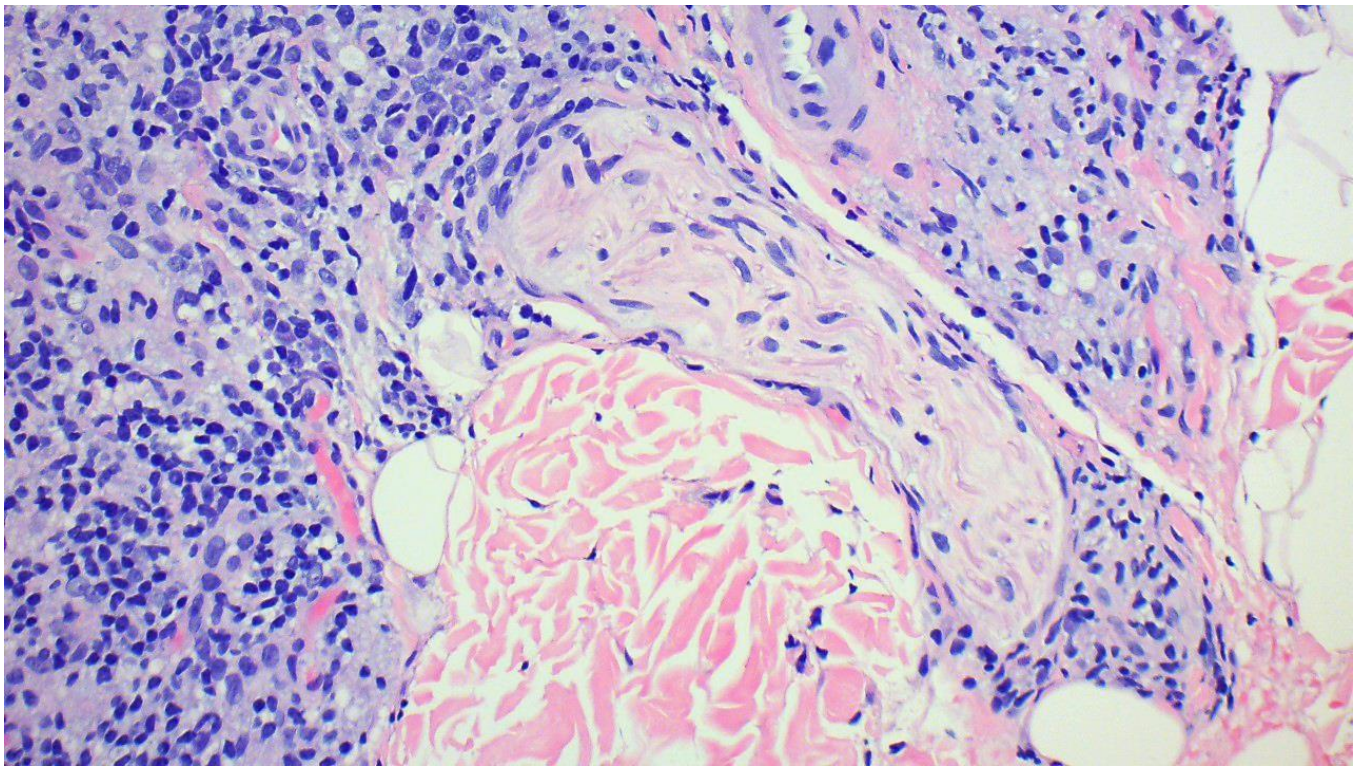


Figure 3B Medium power view showing non-necrotising granulomatous infiltrate composed of sheets of epithelioid histiocytes with abundant foamy cytoplasm and scattered lymphocytes. H&E stain. Original magnification: x200

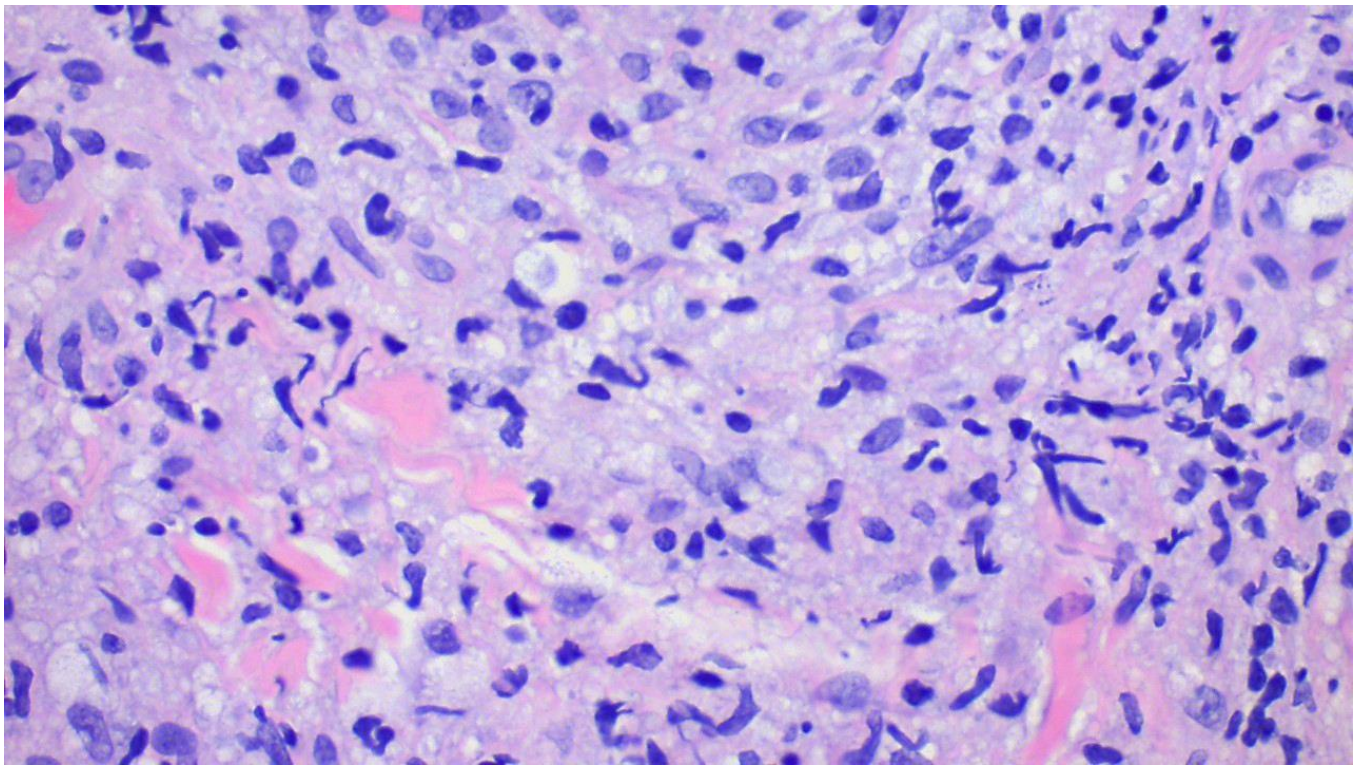
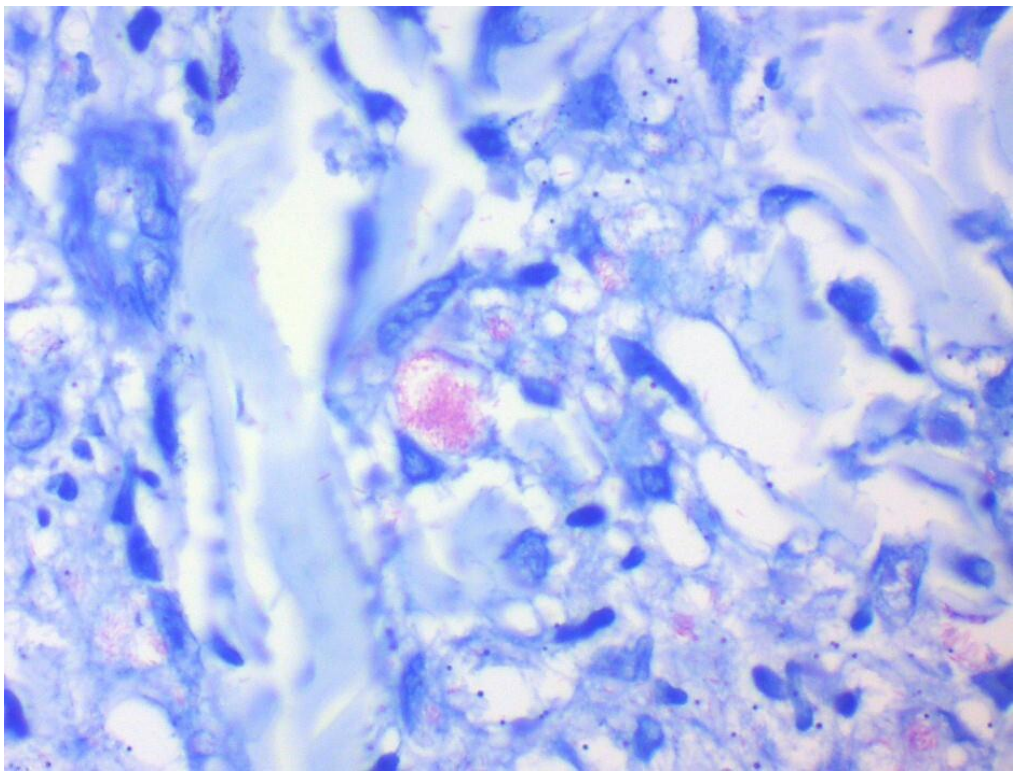


Figure 3C High Power view showing occasional clusters of acid-fast bacilli. Wade-Fite stain. Original magnification: x400



Discussion

Leprosy is a chronic and still-feared infectious disease. Early diagnosis and treatment are essential to help prevent the physical disability and psychological sequalae associated with this disfiguring disease.[3]

The clinical manifestations are varied and can include hypopigmented, erythematous or scaly macules, patches, plaques and nodules. These features depend on the host's cellular immune response to the causative organism and predominantly affect the skin and peripheral nerves. Because of its varied clinical presentation leprosy can mimic several skin conditions including granuloma annulare, tinea corporis, annular psoriasis, lupus erythematosus, cutaneous leishmaniasis and mycosis fungoides. Diagnosis of leprosy may be particularly challenging in pigmented skin and a key distinguishing feature of lesions is impaired sensation.[4]

There are two main classifications of leprosy (Tables 1 and 2).[5-6] The Ridley-Jopling classification categorises leprosy in five groups, based on cutaneous, neurological, histopathological and immunological features.[5] The World Health Organisation (WHO) classification is simpler and is based on the number of skin lesions and bacilli on skin smear.[7]

Table 1 Ridley-Jopling classification.[4,6]

	Ridley-Jopling classification				
Observation / Test	**Type of leprosy**				
	TT	**BT**	**BB**	**BL**	**LL**
No. of lesions	Single usually	Single or few	Numerous (+)	Numerous (++)	Numerous (+++)
Size of lesions	Variable	Variable	Variable	Variable	Small
Surface of lesions	Very dry, sometimes scaly	Dry	Slightly shiny	Shiny	Shiny
Sensation in lesions (not face)	Absent	Moderately or markedly diminished	Slightly or moderately diminished	Slightly diminished	Not affected or minimally affected
Hair growth in lesions	Absent	Markedly diminished	Moderately diminished	Slightly diminished	Not affected
AFB in lesions	Nil	Nil or scanty	Moderate numbers	Numerous (+)	Numerous with globi (++)
AFB in nasal scraping or in blows	Nil	Nil	Nil	Usually nil	Numerous with globi (++)
Lepromin test	Strongly positive (+++)	Weakly positive (+/++)	Negative	Negative	Negative

AFB: Acid fast bacilli, TT: polar tuberculoid, BT: Borderline tuberculoid, BB: Mid-borderline, BL: Borderline lepromatous, LL: Polar lepromatous

Table 2 WHO Classification.[5]

WHO Classification	
Paucibacillary Leprosy	**Multibacillary Leprosy**
5 or fewer skin lesions without detectable bacilli on skin smear	6 or more skin lesions and may have detectable bacilli on skin smear

Our patient had a single long-standing hypoaesthetic lesion on his right arm suggestive of tuberculoid/borderline tuberculoid leprosy. The new infiltrated lesions on the face, trunk and limbs were in keeping with progression to borderline lepromatous disease, supported by the presence of numerous acid-fast bacilli within the cytoplasm of the histiocytes on histology.

Current recommended treatment of tuberculoid leprosy is dapsone (100mg daily) and rifampicin (600mg daily) for 12 months whilst for patients with leprosy at the lepromatous end of the spectrum dapsone (100mg daily), rifampicin (600mg daily) and clofazimine (50mg daily) for 24 months is recommended.[4] Accordingly, our patient was treated with the latter regimen.

Possible immunologic reactions in leprosy patients include type 1, reversal reaction (RR) and type 2, erythema nodosum leprosum (ENL) and can affect up to half of patients during or after completion of treatment.[4] RR, as seen in this case, manifests as oedema and erythema of existing skin lesions in association with fever, ulceration and nerve involvement. ENL typically presents with acute tender red skin nodules, fever and sometimes multiorgan involvement including neuritis, uveitis, arthritis, orchitis and hepatosplenomegaly. [4]

In 1972, Malta became the first country worldwide to institute a leprosy eradication programme with a multidrug therapy regime. This consisted of 2 tablets of rifampicin 300mg and 2 tablets of isoprodian taken 6 days a week for at least 5 months, depending on the clinical and bacteriological status of the patient. Each isoprodian tablet consisted of 75mg isoniazid, 75mg prothionamide and 50mg dapsone.[1, 8] Prior to this, standard leprosy treatment involved lifelong dapsone monotherapy. In the 5-year period 1967-1971 prior to initiation of this programme the mean annual incidence of new cases of Leprosy was 2.7 cases per 100,000 per year.[9] In the programme all known leprosy patients (irrespective of their bacteriological status) and new patients subsequently diagnosed were treated and subsequently monitored closely for possible relapse.

The success of this programme led to its methodology being implemented by the WHO in the mid-1980s in an attempt to eradicate the disease on a global scale and multidrug therapy has since then become accepted worldwide as the standard treatment for leprosy. The global prevalence of the disease has since diminished drastically from 5.4 million to a few hundred thousand.[10]

Presently the overwhelming majority of leprosy cases are in the developing countries of Southeast Asia, South America, Africa, Western Pacific and the Eastern Mediterranean.[10] According to the WHO global leprosy update (2019), South-East Asia region (SEAR) has contributed to 71% of the new leprosy cases worldwide.[11] Migration, however, can result in patients with leprosy presenting anywhere. In the past few years Malta has seen an increasing influx of migrants and workers from countries where leprosy is endemic. For example the number of migrants residing in Malta, originating from SEAR countries such as the Philippines and India has increased by fourfold and ninefold respectively between 2014 and 2018.[12]

Whereas the Malta Leprosy Eradication Project was formally concluded in December 1999 and Public Health Department records show no new cases of leprosy diagnosed in the indigenous Maltese population from the year 2000, new cases have been diagnosed in migrants in 2008, 2011 and 2019 (the current case).[13-14]

Thus, physicians must be aware of the increasing possibility of encountering leprosy, and the potential for leprosy to mimic a number of conditions. Moreover, although infectivity of leprosy is considered to be low, it is higher in patients at the lepromatous end of the spectrum and thus it is important that patients are diagnosed and treated as soon as possible.

Conclusion

This case highlights the importance for clinicians in Malta to maintain an index of suspicion for non-endemic diseases such as leprosy, particularly given the recent rise in immigration and ever changing population dynamics.

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Clinical photographs (Figures 1 and 2) courtesy of Dr Brian Cassar, Medical Illustration Unit, Mater Dei Hospital.

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CASE REPORT

Antidepressant discontinuation syndrome – a case report

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Antidepressant discontinuation syndrome (ADDS) is often an under-recognised cause of multiple unpleasant symptoms upon stopping antidepressant. It requires a high index of suspicion to not miss this elusive diagnosis. This case will look at a common scenario of a nursing home resident forgetting to refill his antidepressant prescription which lead to the above syndrome. This will lead to discussion on how to treat this syndrome and subsequently allow the patient to carry on their daily life.

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Introduction

Antidepressant discontinuation syndrome usually occur within a few days of stopping the causative drug.[1] It is usually short-lived and mild but in certain severe cases, it can lead to many unpleasant symptoms and incorrectly diagnosed as other condition, thereby leading to more non adherence by the patient.[1]

The symptoms vary and can include different systems and can be rather vague and general such as flu-like illness, headache and lethargy making it unique as it is not directly related to the treating psychiatric illness. Therefore, the condition can be mistaken as other neurological conditions, infectious diseases or adverse effects of other medications taken by the patient.[2]

All antidepressant groups including monoamine oxidase inhibitors (MAOI), selective serotonin reuptake inhibitors (SSRI) and tricyclic antidepressant (TCA), have the potential to cause this syndrome.[1,3] As compared to longer acting antidepressant such as fluoxetine, shorter acting antidepressant such as paroxetine and venlafaxine have higher potential to cause antidepressant discontinuation syndrome.[3]

Case Report

Mr. K is a 49-years-old Chinese man who presented with history of crying spells for the past 3 days. He was accompanied by his caretaker in the nursing home. He claimed he has been crying without any apparent reason or control. It was associated with nightmares and insomnia. There was also increase in salivation, rhinorrhoea, nausea and dizziness. There was no blurring of vision or syncope. There is no suicidal ideation or aggressive behaviour.

Premorbid, he has hypertension, type 2 diabetes mellitus and suffered 2 episodes of right middle cerebral infarct in 2005 and 2013. As a consequent of his recurrent stroke which left him dependant on wheelchair, he developed depression a year later and was started on paroxetine 10mg daily which managed to control most of his depressive symptoms which included low mood, feeling of worthlessness, anxiety and irritability with the absence of crying spells. He is on 8 types of medications for his hypertension, diabetes, stroke and depression.

Physical examination showed an alert middle-aged man who was crying in between the consultation. He maintained good eye contact and had slurred speech. His vital signs were stable. He is orientated to time, place and person. Neurological examination revealed hypersalivation with presence of gag reflex. The power over his left upper and lower limbs was 3/5 with normal power on the opposite limb.

Mr K is a divorcee with no children and no contact with his former wife. He has been in the nursing home since his second episode of stroke. He has no siblings. His parents are his only close relative who kept regular contact with him. On further history, patient has not been taking his antidepressant for the past one week as the medicine has finished and he missed his last hospital appointment. He also complains of feeling irritated by his friends in the nursing home as they keep asking him the reason for his persistent crying.

He was treated as a case of antidepressant discontinuation syndrome. His differential diagnosis was relapse of his previous depression. As paroxetine was not available in the clinic, he was started on another selective serotonin reuptake inhibitor (SSRI), sertraline.

He was given an appointment in 2 weeks in which he reported to be well and cheerful with no more crying spells and insomnia. His salivation and flu-like symptoms also had resolved. He, along with his caretaker were advised to not stop his antidepressant without prior consultation with the treating physician and to be more adherent to his hospital appointments.

Discussion

Antidepressant Discontinuation Syndrome (ADDS) occurs after abrupt discontinuation of medications that has been taken for a minimum of six weeks. The symptoms last for one to two weeks and is rapidly halted by the re-initiation of the drug taken. There is limited data on the prevalence or burden of this condition due to several factors including issues with diagnosis, and its transient nature. It is said around 20% of patients will develop this syndrome if the use is abruptly stopped.[1]

There are also classifications according to the type of treatment used, for example the SSRI discontinuation syndrome which is caused by the halt of SSRI usage.[4]

As many as 50 symptoms have been reported to occur in ADDS.[5] SSRI and TCA usually share the symptoms shown in Table 1:[5]

Table 1 Common symptoms related to ADDS.[5] SSRI and TCA

Symptom group	Example of specific symptoms	Common in SSRI	Common in TCA
Sensory	Paraesthesia, numbness, visual trails	Yes	No
Disequilibrium	Dizziness, light-headedness, vertigo	Yes	No
General somatic	Lethargy, headache, sweating, tremor, anorexia	Yes	Yes
Affective	Irritability, anxiety, low mood, tearfulness	Yes	Yes
Gastrointestinal	Nausea, diarrhoea, vomiting	Yes	Yes
Sleep related	Insomnia, excessive dreaming, nightmares	Yes	Yes

This includes general somatic, gastrointestinal, affective and sleep-related symptoms.[5] Sensory and disequilibrium symptoms are however more with the use of SSRI.[5]

However, reactions to MAOI discontinuation seems to be the most severe with worsening of even baseline depressive symptoms, manifestations of acute confusional state with paranoid delusions and hallucinations, and anxiety symptoms including hyperacusis and depersonalization.[5]

In order to rapidly remember these symptoms, the mnemonic FINISH is used; **F**lulike symptoms, **I**nsomnia, **N**ausea, Imbalance, **S**ensory disturbance and **H**yperarousal (anxiety/agitation), which are the six core symptoms. It has been reported to be experienced by up to 40% of patients who have abruptly stopped their treatment.[1,6-7]

There has been other suggestions to identify symptoms and use it for the basis of diagnosis, in order to help with management of these patients. For example, in 2000, a range of symptoms were suggested for the SSRI discontinuation syndrome which involves two or more of the following symptoms:[4]

Dizziness, light-headedness, vertigo or feeling faint; shock-like sensations or paraesthesia; anxiety; diarrhoea; fatigue; gait instability; headache; insomnia; irritability; nausea or emesis; tremor; and visual disturbances.

Also taking into consideration is the symptom developing within 1-7 days of stopping or reduction of medication after 1 month of use, the symptoms cause significant distress and not cause by other medical conditions.

However, to our knowledge these criteria has not been formally validated.[1,4,6]

Diagnosis is usually established based on history of stopping the antidepressant. This will usually require a high index of suspicion to look out for discontinuation symptoms.[1]

Management mainly involve restarting treatment and symptomatic management of troubling symptoms. As is well said, "prevention is better than cure". Therefore, pre-emptive advice and education for both treating clinicians and patients before starting antidepressant about the possibility of discontinuation symptoms on suddenly stopping antidepressant should be emphasised.[1,5]

However, this step alone, still does not solve the problem. Hence there has been several proposed methods in the literature regarding this issue. One of which suggests to slowly taper down the dose. The rate would depend on the medication, so for example those with a shorter half- life such as venlafaxine and paroxetine should be tapered down more gradually within weeks to months.[3,8] Sometimes switching to a longer half-life antidepressant; fluoxetine may be warranted.[8] However, switching antidepressants needs to be done with caution.[3]

Other methods of management have suggested alternative management which may include a short course of benzodiazepines for symptomatic treatment, antimuscarinic agents that may help with gastrointestinal symptoms and cholinergic rebound in TCA withdrawals, and also antipsychotic treatment with patients experiencing withdrawal mania.[1,8]

Depression is a common presentation in primary care and part of the management is stopping the treatment once the patient is cured, hence primary care physicians should be made aware of ADDS and its management. The repercussions of the treating clinician not familiar with this condition can lead to heavy consequences such as medical and psychiatric misdiagnosis, and may lead to patient unwilling to use psychotropic medications and lead to difficult treatment of such patients.[1]

Although the symptoms of ADDS was related to the non-compliance of this patient, it has taught both the authors and patient a valuable lesson on this syndrome. This patient is more likely to experience ADDS, when trying to taper down his antidepressants. Therefore, better preparation can be made should this decision be agreed upon later on in his course of treatment.

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CASE REPORT

Dipeptidyl Peptidase-4 Inhibitor-Associated Bullous Pemphigoid in Malta: A case report and clinical series

Monique Cachia, Stephanie Pullicino, Alexandra Betts, Susan Aquilina

Bullous pemphigoid (BP) is an autoimmune blistering disease associated with a number of predisposing factors including age, neurological disease, diabetes mellitus and drugs. Over the past few years, dipeptidyl peptidase-4 inhibitors (DPP4-Is), referred to as gliptins, have been increasingly associated with the development of this blistering disease.

Locally, since the introduction of gliptins into the national formulary, we have noted a surge in the number of cases of presumed gliptin-induced BP. We present a local case report, followed by a short case series which highlights the typical characteristics of patients with gliptin-induced BP and shows the surge in the number of local cases.

Patients with drug-induced BP, as opposed to conventional BP, tend to respond quicker upon cessation of the culprit drug. Therefore physicians should be aware of this association and have a low threshold for investigating diabetics who present with unexplained pruritus, erythema and bullae, especially if these patients are on DPP4-Is.

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Introduction

Bullous pemphigoid (BP) is a sub-epidermal blistering skin disease mediated by autoantibodies to hemidesmosome proteins BP180 and BP230, which are crucial for stable adhesions between the epidermis and dermis.[1]

Risk factors associated with this disease include age, neurologic disease, diabetes mellitus and various drugs. Over 60 different drugs have been associated with BP in the literature. However, in a recent systematic review only aldosterone antagonists, dopaminergic drugs, anticholinergics and dipeptidyl peptidase-4 inhibitors (DPP4-Is), have been shown to be statistically associated with BP.[2]

DPP4-Is, widely referred to as gliptins, are oral hypoglycaemic agents used in type 2 diabetes. They were first introduced into the market in 2006 and since then there has been evidence to suggest an association between the use of DPP4-Is and development of BP.[1,3]

We report a case of an elderly diabetic man with presumed gliptin-induced BP. Moreover, we report a surge in the number of cases of BP in diabetic patients at our outpatient clinic a few months following the introduction of DDP4-Is into the national formulary.

Case Presentation

An 85-year old male presented with a one-month history of large, pruritic, tense bullae on the lower aspect of both legs. The patient's medical history included type 2 diabetes, hypertension and ischaemic heart disease, for which he was on a number of drugs which included vildagliptin, metformin, gliclazide, perindopril, aspirin, simvastatin, isosorbide dinitrate and omeprazole. Amlodipine had been stopped a few weeks prior to presentation in view of worsening of lower limb oedema.

On examination, oedematous legs with bullae and some excoriation marks were visible. Initially the differential diagnosis included bullae associated with lower limb oedema, bullous diabeticorum and bullous pemphigoid. The former diagnosis was favoured at the outset in view of the incidental worsening of the lower limb oedema and the fact that the bullae only affected the legs. Thus the patient was commenced on a loop diuretic.

A few days later the patient re-presented to clinic, this time having new bullae on the forearms. A punch biopsy was taken from the forearm and this revealed a subepidermal blister. Direct immunofluorescence showed linear deposits of IgG and C3 in the basement membrane zone which was consistent with a diagnosis of BP. He was treated with clobetasol propionate ointment applied onto the blisters, nicotinamide 500mg t.i.d and doxycycline 500mg b.i.d. The bullae initially healed without formation of new blisters but the patient complained of persistent pruritus. Eight months from the initial presentation, the patient presented urgently to clinic complaining of worsening pruritus, erythema and desquamation (Figure 1). After ensuring compliance to current treatment of BP a review of other possible triggers was done. Of note, the patient was on vildagliptin for diabetes which was the most recent drug added to his list. This had been started two years prior to this presentation. Keeping in mind the association of BP with DPP4-Is, vildagliptin was omitted following liaison with his diabetologist for alternative management. In the meantime, topical clobetasol propionate ointment was continued. There was complete resolution of his symptoms within three months from discontinuing vildagliptin,

suggesting a final diagnosis of BP that was triggered by DPP4-I use.

Figure 1 Legs showing erythema and desquamation

Discussion

Drug-induced BP very often has the same clinical and histological features as classical BP. In its established form patients typically present with pruritus and formation of bullae. However, in the pre-bullous phase, the clinical picture of BP may be misleading and may only include pruritus with possibly vague erythematous and urticated areas. In drug-induced BP patients very often respond well after the drug is stopped and have little or no relapses while patients with classical BP tend to have a more chronic course and very often require long term systemic therapy. Nevertheless, a small cohort of patients with drug-induced Bullous Pemphigoid who initially respond to stopping the culprit drug later on develop classical BP.

Our patient had many risk factors for BP including age, DM and was taking a statin, ACE-I and DPP4-I, all of which have been associated. Initially he was thought to have classic BP. However, as the patient complained of persistent pruritus and worsening erythema despite systemic therapy, a thorough review of his drug history confirmed that the most

recently added medication was Vildagliptin prompting us to a possible association.

In classical BP, autoantibodies typically target specific portions of the hemidesmosomal proteins of the basement membrane, BP180 and BP230, which are normally crucial for maintaining adhesion between the epidermis and dermis. In 85% of cases these antibodies target the non-collagenous region 16A (NC16A) of BP180 (collagen XVII). Antibodies to BP230 are also found but to a lesser extent.[4]

In drug-induced BP, the antibody target is similarly BP180 but the portion targeted may be different.[4] In DPP4I-associated BP, the gliptin is thought to alter the antigenicity of BP180 making it more amenable to attack by antibodies. In this case they tend to target the mid-portion of BP180 rather than the NC16A domain as in classical BP[5].

DPP4-Is are a relatively new class of drugs which have been introduced into the market in 2006. These drugs are used to treat type 2 diabetes mellitus and act by competitively inhibiting the enzyme DPP4 which is normally found in various organs including the skin. DPP4 normally inactivates glucagon like peptide (GLP-1) and glucose-dependant insulinotropic polypeptide (GIP). DPP4-Is thus prevent inactivation of these incretins thereby increasing insulin levels and inhibiting glucagon production.[6]

The first licensed gliptin was sitagliptin in 2006 and this was followed by vildagliptin, saxagliptin, linagliptin and alogliptin.[7] Since their introduction into the market there have been various case-reports, case-control trials and pharmacovigilance database studies which have confirmed an association between the use of gliptins and the development of BP. Moreover, a systematic review and adjusted meta-analysis by Phan et al. has positively suggested a significant association between DPP4-I use and development of BP. The strongest association was found with vildagliptin while sitagliptin did not seem to be associated with development of BP.[3]

Locally, the DPP4-I vildagliptin was introduced into the national formulary in April 2016. Between 2017 and 2019 we have seen a surge in bullous pemphigoid amongst the diabetic community with a good proportion of these patients taking gliptins. We therefore retrospectively analysed the data of patients presenting to the department of dermatology at Sir Paul Boffa Hospital between 2017 and 2019 with a known diagnosis of gliptin-induced BP (Table 1).

The above findings are similar to the published data on the subject, which confirm that patients developing gliptin-induced BP were more likely to be male and elderly. The latency period between drug initiation and the development of symptoms also appeared to be quite variable in our findings (6-28 months) when compared to various pharmacovigilance reports which report a mean latency period that can vary between 6 to 19 months.[3] Clinical symptoms appeared to resolve in a number of weeks to months, and 13 out of the 15 patients have remained symptom-free. The gliptin associated in all but one of the cases was vildagliptin, which is the only DPP4-I in the government formulary.

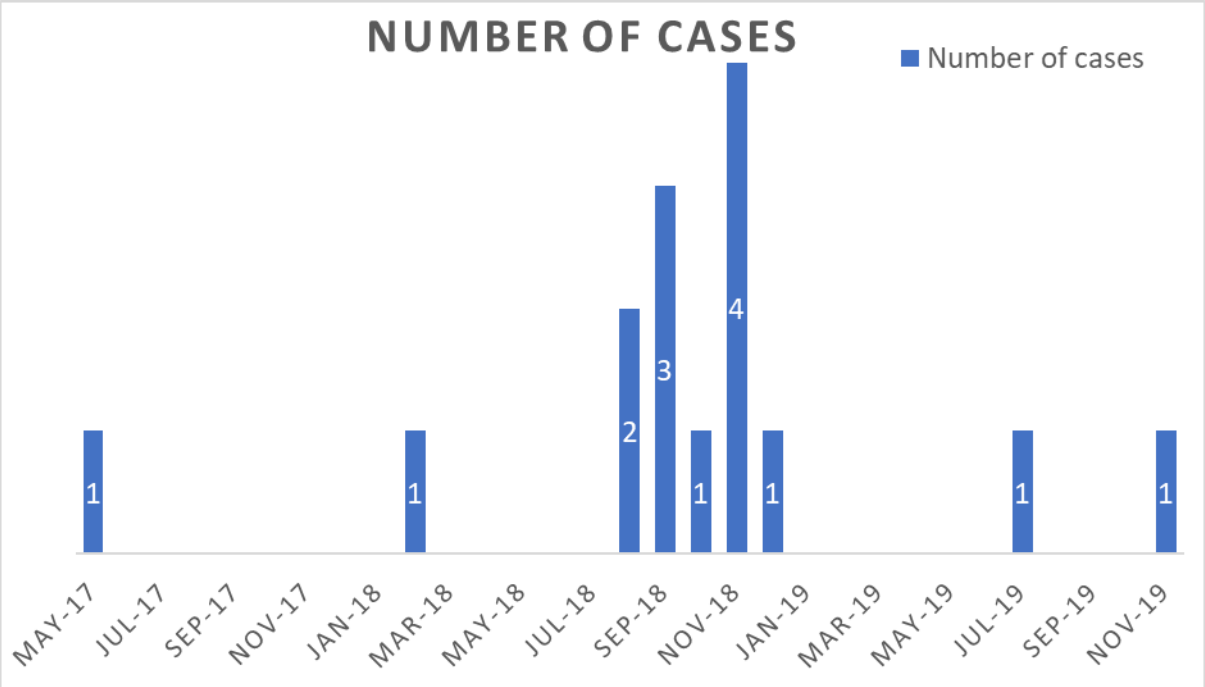
Table 1 Summary of data

Number of Patients	15 (1 patient deceased)
DPP-IV inhibitor	93% Vildagliptin (14/15) 7% Linagliptin (1/15)
Sex (M/F)	60% M (8/15) 40% F (6/15)
Average age (yrs)	76 (59-87)
Latency period before onset of bullous pemphigoid (in months)	Mean 14 months (range: 6-28 months)
Symptoms	Pruritus and bullae13/15 Pruritus without bullae 2/15
Treatment (topical vs oral vs other)	Topical steroids alone: 6/15 Oral agents added: 9/15
Outcome (sustained or not)	Sustained:13/15 Refractory: 2
Gliptin Stopped **Gliptin not stopped**	14/15 0/15

Stopping the drug in conjunction with short term application of topical steroids is usually sufficient to treat DPP4I-associated BP. However, few cases have been reported where, due to a phenomenon referred to as 'epitope spreading' after cessation of the drug and initial improvement, patients may then develop conventional BP.[5] Two of our patients had initially responded to treatment and later started complaining of re-emerging symptoms, possibly due to development of classical BP. These have been started on systemic drugs.

Locally, the numbers of cases of presumed gliptin-induced BP have been notably high when compared to the current literature.[3] Between 2017-2019 we had 15 patients presenting with this diagnosis with 11 of these patients presenting in the second half of 2018 (Figure 2). These findings could be explained by the initiation of gliptins in a large cohort of diabetic patients once introduced into the formulary in 2016. The surge in 2018, could be explained by the long latency period and reflects the bulk of patients that were started. Moreover, some patients might have been misdiagnosed as gliptin-induced BP rather than classical BP due to the increasing awareness of this association. Confirmation of drug-induced BP can only be done upon re-challenge of the drug, which is not ethically correct.

Figure 2 Bar graph showing the number of new cases presenting with a diagnosis of gliptin-induced bullous pemphigoid between May 2017 and November 2019.



Conclusion

This case highlights the importance of keeping drugs in mind as potential culprits for skin disease. Many drugs may have a long latency period, so a thorough drug history including the time when the drugs were started is relevant. Physicians should be aware of the association between BP and DPP4-I and have a low threshold for investigating patients on gliptins who present with non-specific pruritus with or without the presence of bullae.

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