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Table of Contents

Never go to excess, but let moderation be your guide

Victor Grech

"Never go to excess, but let moderation be your guide" is a quote from Marcus Tullius Cicero (106-43 BC) who was a Roman statesman, orator, lawyer and philosopher. His statement is corroborated by medical science in that two recent studies have vividly demonstrated the wages of sin/excess.

A Lancet study has shown that even light-to-moderate drinking may cause hypertension, and thereby increase the chance of stroke. This was demonstrated in a genetic study that followed 500,000 Chinese for 10 years. However the findings are applicable to all populations and constitute the best extant evidence on the effects of alcohol. In summary:

- One to two units daily increased stroke risk by 10-15%.
- Four units daily increased stroke risk by by 35%.

The study failed to uncover evidence of a protective effect/s by light or moderate drinking. It appears that risk of stroke increases proportionally with the total amount of alcohol consumed.[1]

Yet another Lancet paper showed that poor diets have also been linked to 20% of all deaths worldwide. The review analyzed nearly 20 years of dietary data from 195 countries and estimated that poor diets killed 11 million people prematurely around the world in 2017, mostly by predisposing to cardiovascular disease and cancer. A poor diet has been described as an equal-opportunity killer. The solution is to eat less and to consume healthier options.

The excessive consumption of sodium (and the ensuing hypertension and cardiovascular morbidity) was found to be the highest contributor of diet-related death. Overall, the main problem appeared to be the low intake of healthy food (such as whole grains, nuts and seeds, fruits, vegetables, polyunsaturated fats and legumes) rather than excessive consumption of unhealthy food.[2]

Our patients, who depend on us for advice, should be soberly apprised with regard to these and other medical lifestyle studies.

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Cover Picture:
'Choosing Hope'
Acrylic on canvas
By Michael Farrugia

A Maltese Canadian management consultant with international experience. A wannabe artist who uses painting as a relaxation medium

Corinthia Group Prize in Paediatrics, 2019

The Corinthia Group Prize in Paediatrics for 2019 was awarded to Dr Daniel Lawrence Fiott, who obtained the highest aggregate mark over the combined examinations in Paediatrics in the fourth and final year of the undergraduate course. Whilst offering our congratulations to Dr Daniel Lawrence Fiott, we would also like to congratulate all those who performed admirably during the undergraduate course in Paediatrics. In the accompanying photograph, Dr Daniel Lawrence Fiott is seen receiving his prize of €232 from Professor Simon Attard Montalto, Head of Paediatrics, in the Medical School. Finally, the Academic Department of Paediatrics and Medical School remain indebted and are extremely grateful to the Corinthia Group for their ongoing support.

Professor Simon Attard Montalto

Original Article

Presentation and management of diabetic ketoacidosis in adults in Malta

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Abstract

Aim: The aim of this audit was to assess adherence to local guideline in the management of Diabetic Ketoacidosis (DKA).

Method: Patients admitted with DKA between April 2013 and March 2015 were identified and data was retrospectively collected from patients' confidential files and Isoft®. Data collected included initial parameters recorded and biochemical investigations taken (initial and subsequent assessment of pH, HCO^{3-}, blood glucose, potassium levels and urinary ketones), insulin regime started and intravenous fluid administered.

Results: During the established time period 40 cases of DKA were identified in 18 patients. Median age was 33 years with a female preponderance of 60%. Six patients had newly diagnosed diabetes mellitus while 8 patients had more than one admission of DKA. All cases had capillary blood glucose monitoring (BGM) and/or venous random blood (plasma) glucose (RBG) checked and pH and HCO^{3-} recorded on admission. 0.9% sodium chloride was the intravenous fluid started in all cases (as recommended by the guideline) and a median of 6.75L was prescribed during the first 24 hours. The median time spent on intravenous insulin infusion was 42.7 hours while the median time to pH >7.30, HCO^{3-} >15mmol/L and negligible urinary ketones were 6.88, 12.83 and 34.5 hours respectively. Subcutaneous insulin was started at a median time of 48.21 hours from initiation of DKA protocol.

Conclusion: This audit showed good adherence to local guideline. The great discrepancy between the time to pH >7.3 and the time to negligible urinary ketones highlights the need to introduce tools to measure systemic ketone production in the management of DKA with an update in the current local clinical practice guideline.

Keywords
Diabetes type 1, Diabetic Ketoacidosis, Complications, Mater Dei Hospital

Introduction

Diabetic ketoacidosis (DKA) is defined by the biochemical triad of ketone production, hyperglycaemia and acidaemia. Although not common, mortality from DKA is approximately 2%,[1] however, each death is potentially avoidable. Increasing patient and healthcare professional education and awareness of DKA and its management, has led to a decline in mortality over recent years.

The current audit aimed to assess the management of patients with DKA and compare these practices with the local DKA guideline issued in 2007.[3] Changes in current practice that could improve patient care and shorten hospital stay will be identified and instituted.

Methods

All adult patients (>16years of age) admitted with DKA to Mater Dei Hospital (MDH) over a two year period, between April 2013 and March 2015 were identified. These were identified from the Accident and Emergency (A&E) admission book and the Electronic Case Summary system. Patients' confidential files and Isoft® investigations were analysed in detail and predefined data sets obtained, in line with Data Protection Act. Only patients with parameters fulfilling the biochemical triad of DKA: 1) blood glucose > 11.0mmol/L or known to have diabetes mellitus, 2) metabolic acidosis with HCO_3^- <15.0mmol/L and/or venous pH < 7.3 and 3) significant ketonuria > 2+ on standard urine sticks, were included in the study.[4] The identified patients had their DKA management analysed in detail and compared to the current DKA guideline[3] available at MDH. All data was recorded on Microsoft Excel spreadsheet and analysis of data was then performed using IBM SPSS® version 22. Kolmogorov–Smirnov test was carried out to determine the normal distribution of the data and then either T-Test / ANOVA (for parametric data) or Mann-Whitney U / Kruskal–Wallis or $\chi 2$ (for non-parametric data) tests were used as appropriate. Correlation analyses were carried out using Spearman correlation.

Results

1. Demographics

Using the criteria above to define DKA, 40 cases (n = 40) were identified in a total of 18 different patients, during the study period. In the cases studied the median age was 33 years (IQR 24 – 52.25) with a female predominance of 60%. Six patients (33.3%) had newly diagnosed diabetes. 8 patients (44.4%) had more than one admission with DKA during the studied period.

2. Initial Assessment and investigations

Vital parameters (temperature (T), systolic blood pressure (SBP), Glasgow coma scale (GCS), oxygen saturation (SO_2%) and pulse (P)) at presentation, as documented in casualty were analysed (Table 1).

On admission all patients had recorded bedside capillary blood glucose monitoring (BGM). BGM was recorded as 'HI' in 7 cases, while the median reading in 32 cases was 25.7mmol/L (IQR 23.48 – 30). Venous random blood (plasma) glucose (RBG) was documented in 29 cases and the median was 33.6mmol/L (IQR 25.2 – 37.4). All 40 cases had pH and HCO_3^- levels checked, in 33 cases by an arterial blood gas (ABG) and 7 cases by a venous blood gas (VBG) analysis. The median pH of the study population at presentation was 7.18 (IQR 7.11 – 7.24) while the median value for HCO_3^- was 7.4 (IQR 5.4 – 11.45). A urine sample confirming ketonuria was obtained in 22 cases in the A&E Department.

Additional investigations recommended by the current DKA guideline[3] include a complete blood count (CBC), renal profile (U&E, Cr), arterial blood gases (ABG), urinalysis, pregnancy test in female patients, ECG and chest x-ray (CXR). An amylase level is recommended in patients with abdominal pain. The frequency and results of these tests in concordance to the local guideline is illustrated in Table 1.

All cases were admitted to Mater Dei Hospital, with 4 cases requiring admission to intensive therapy unit (ITU).

***Table 1**: Parameters and investigations with respective median results measured at admission*

Parameters and investigations on admission	Frequency (*n*)	Median (Interquartile Range)
Temperature (°C)	38	36.4 (36 - 36.8)
GCS	40	15
Oxygen saturation (%)	37	99 (98 - 99)
SBP (mmHg)	39	121 (107 - 134.5)
Pulse rate (/min)	39	103 (93 - 120)
White cell count (x10^9/L)	40	13.55 (8.78 - 19.98)
Creatinine (µmol/L)	40	104 (94.75 - 120.5)
eGFR (mls/min/1.73m^2)	40	60.5 (48.25 - 71.25)
Amylase (U/l)	24	39 (35 - 76.75)
ECG	39	n/a
CXR	33	n/a

Table 2: Frequency of ABG/VBG testing with median results for pH and HCO_3^-

Time of ABG/VBG (hrs from start of protocol)	Frequency (*n*)	Percentage (%)	Median pH (mmHg) (IQR)	Median HCO^{3-} (mmol/L) (IQR)
0	40	100	7.19 (7.11 - 7.25)	7.4 (5.4 - 11.45)
2	33	82.5	7.22 (7.18 - 7.27)	8.7 (5.4 - 13.2)
4	29	72.5	7.27 (7.22 - 7.31)	8.6 (7.2 - 13.7)
8	35	87.5	7.33 (7.28 - 7.37)	14 (12.2 - 16.6)
12	33	82.5	7.36 (7.34 - 7.40)	16.6 (15.4 - 19.0)
24	14	35	7.42 (7.36 - 7.43)	18 (16.6 - 20.5)

***Table 3**: Frequency of K level checked and median level at time interval 0, 2, 4, 8, 12 and 24 hours from start of DKA protocol*

Time of K (hrs from start of protocol)	Frequency of K level checked *n* (%)	Median K level (mmol/L) (IQR)
0	40 (100)	4.7 (4.2 – 5.1)
2	31 (78)	4 (3.4 - 4.4)
4	29 (73)	4.3 (3.9 - 4.5)
8	35 (88)	3.8 (3.5 - 4.4)
12	32 (80)	3.9 (3.5 - 4.1)
24	22 (55)	3.7 (3.2 - 4.1)

3. ABGs/VBGs

According to current local DKA guideline, pH and HCO_3^- should be measured at 2, 4, 8, 12 hours after starting the protocol or until normalisation of metabolic acidosis. All patients had ABGs/VBGs repeated until pH and HCO_3^- levels had normalised but not necessarily within the stipulated time intervals (see table 2).

4. Ketones

The current DKA guideline recommends measuring urinary ketones every 4 hours until clearance is achieved. Ketones were checked regularly in 38 cases (95%) during the first 24 hours, while 29 patients still required urinary ketone testing for more than 24 hours after starting DKA treatment protocol. In the initial 24 hours after starting treatment the median number of times urinalysis was performed was 4 times (IQR 3 – 5.75) with a median of 2 times (IQR 1 – 3) at 24 – 48 hours.

5. BGM

Hourly BGM checks are recommended in the current local DKA guideline, for patients on intravenous insulin infusion. The median number of BGM checked was 17.5 times (IQR 9.75 – 22.25) during the first 24 hours and 4 times (IQR 3 – 5.75) at 24 – 48 hours from admission.

6. Insulin administration

All cases studied were treated with a variable-rate insulin infusion (VRIII) of short-acting insulin (Actrapid®). Long-acting basal insulin together with intravenous Actrapid® was co-administered in 4 cases (10%). The median time spent on Actrapid® infusion was 42.7 hours (IQR 27.9 – 65.75). During this period of time the median number of units of insulin required was 89Units (IQR 65 – 114) in the first 24 hours of protocol and 66Units (IQR 54.5 – 83) at 24 – 48 hours. Total insulin dose in the first 24 hours was positively correlated with initial RBG (ρ=0.381, P= 0.024). In 7 cases (18%), a further increase in insulin was required to reach target BGM.

7. Intravenous fluids

All patients were started on 0.9% of sodium chloride in concordance with the local guideline. The patients received a median of 6.75L (IQR 6.11 – 7.45L) during the first 24 hours. 10 cases (25%) did not require intravenous fluid for more than 24 hours, while 30 cases (75%) received a median of 2L (IQR 0.5 – 2.72L) at 24 – 48 hours from starting DKA protocol.

Intravenous fluids are to be changed to 5% dextrose in normal saline if BGM is less than 11mmol/L and to 10% dextrose if BGM is less than 5mmol/L in the current local DKA guideline. Intravenous fluids were correctly changed in 36 cases when BGM fell below 11mmol/L. In 10 cases BGM fell less than 5mmol/L during the initial 24 hours and 9 of these cases had the intravenous fluid correctly changed to 10% dextrose.

Table 4: *Correlation between different parameters in DKA management*

		Initial pH	Initial RBG	Age	Systolic BP on admission	Initial Potassium	WCC on admission	eGFR on admission	Total Insulin given in 1st 24 hrs	Time Period till pH.>7.3	Time Period till HCO^{3-} >15	Time Period till urine Ketones -ve	Hours on Actrapid pump
HCO^{3-}	ρ	**0.560**	-0.323	-0.500	**-0.386**	0.070	**-0.630**	**0.487**	-0.296	**-0.396**	**-0.0630**	**-0.444**	**-0.497**
	P	**<0.001**	0.058	0.764	**0.017**	0.672	**<0.001**	**0.002**	0.071	**0.014**	**<0.001**	**0.023**	**0.001**
Initial pH	ρ		-0.041	0.304	-0.231	0.002	-0.253	0.200	0.072	**-0.579**	**-0.520**	-0.141	0.026
	P		0.814	.056	0.158	0.991	0.115	0.216	0.662	**<0.001**	**0.001**	0.483	0.872
Initial RBG	ρ			0.475	-0.309	**0.406**	**0.419**	**-0.747**	**0.381**	0.108	0.140	**0.409**	**0.544**
	P			0.003	0.066	**0.014**	**0.009**	**<0.001**	**0.024**	0.530	0.429	**0.038**	**0.001**
Age	ρ				0.074	**0.314**	0.194	**-0.325**	0.244	-0.046	-0.150	-0.090	**0.333**
	P				0.655	**0.049**	0.231	**0.041**	0.134	0.781	0.370	0.654	**0.036**
Systolic BP on admission	ρ					-0.236	0.028	0.181	-0.080	0.237	0.200	-0.302	0.020
	P					0.148	0.865	0.271	0.633	0.152	0.235	0.125	0.905
Initial Potassium	ρ						0.288	-0.191	-0.036	-0.127	0.017	-0.039	0.104
	P						0.072	0.238	0.825	0.441	0.919	0.849	0.523
WCC on admission	ρ							**-0.406**	**0.349**	0.224	**0.500**	**0.545**	**0.566**
	P							**0.009**	**0.029**	0.170	**0.001**	**0.003**	**<0.001**
eGFR on admission	ρ								**-0.328**	-0.264	-0.309	-0.325	**-0.589**
	P								**0.041**	0.105	0.059	0.098	**<0.001**
Total Insulin given in 1st 24 hrs	ρ									-0.050	0.182	0.091	**0.403**
	P									0.767	0.281	0.658	**0.011**
Time Period till pH.>7.3	ρ										**0.544**	0.015	0.165
	P										**0.001**	0.941	0.315
Time Period till HCO^{3-} >15	ρ									**0.544**		**0.494**	**0.390**
	P									**0.001**		**0.010**	**0.015**
Time Period till urine Ketones -ve	ρ									0.015	**0.494**		**0.436**
	P									0.941	**0.010**		**0.023**
Hours on Actrapid pump	ρ									0.165	**0.390**	**0.436**	
	P									0.315	**0.015**	**0.023**	

Results in bold are statically significant (P<0.05) p: Spearman rank-order correlation coefficient; P: Significance (two-tailed)

8. *Potassium supplementation*

The current guideline suggests checking potassium (K) levels at 2, 4, 8, and 12 hours and to add supplemental potassium chloride into the intravenous fluid solution according to results. Table 3 shows frequency and results of K level at the time intervals recommended. Correlation analysis showed K levels at presentation to be positively correlated with increasing age and RBG (ρ=0.314, P=0.049 and ρ=0.406, P=0.014 respectively). (Table 4)

9. *Additional management*

In 7 cases insulin was infused via pump at a higher rate than recommended by protocol while in 2 cases the intravenous fluids prescribed after admission differed by both rate (infused at a standard rate of 128mL/min) and type (Hartmann's solution) respectively from what is recommended in the guideline. Furthermore, 2 patients were prescribed sodium bicarbonate.

Antibiotics were prescribed in 23 patients. 10 patients had no documented source of infection, 5 patients had documented respiratory tract infection, 4 patients had a urinary tract infection, 2 patients had gastroenteritis while one patient had antibiotics started for pelvic inflammatory disease. White cell count on admission was found to be negatively correlated with initial HCO_3^- and eGFR (ρ=-0.630, P=<0.01 and ρ=-0.406, P=0.009 respectively), but positively correlated with initial RBG levels (ρ=0.419, P=0.009) and time to resolution of DKA (ρ=0.545, P=<0.01) (Table 4).

Urinary catheterisation was performed in 11 cases during admission. Reason for catheterisation was documented as haemodynamic instability in 5 cases, acute kidney injury in 4 cases and in 2 cases this was undocumented.

10. *Time to resolution of DKA*

According to our local guidelines, DKA is considered resolved and fixed doses of subcutaneous insulin are recommended to be restarted once pH and bicarbonate are normal, normoglycaemia is achieved, urine is free of ketones and patient is eating normally. Using these criteria time to resolution of DKA and time spent on DKA protocol (taken as the time to subcutaneous insulin) were determined. These results are shown in Figure 1. Most of the 4 variables which were taken as indicative of resolution of DKA correlated positively with each other as shown in Table 4.

Discussion

The main aim of this audit was to assess adherence of current practices to the local guidelines and identify areas for improvement in the management of DKA.

From the whole cohort, 8 patients had more than one admission. Seven patients had 2 admissions and one patient had 11 admissions. Recurrent admissions with DKA is associated with multiple factors including poor control, noncompliance and nonattendance to outpatient clinic, female gender, presence of co-morbidity and psychological problems.[2] From the cohort of patients with readmissions, 6 patients were females, 4 patients were non-compliant to treatment, 1 patient had underlying pancreatic tumour and 1 patient had steroid-induced DKA. The patient with 11 admissions with DKA had an underlying psychological disorder.

All patients had BGM checked on admission. Median RBG was noted to be significantly higher than median BGM (33.6mmol/L and 25.7mmol/L respectively). In 7 cases (17.5%) the BGM value was unrecordable as point of care machines are not able to give a numerical reading at very high levels. The median BGM was therefore underestimated as these 7 cases were excluded from the calculated BGM median.

Deviation from protocol was noted in some cases. All 40 cases had pH and bicarbonate levels measured. 33 cases (82.5%) had an ABG measurement, whilst 7 cases (17.5%) had a VBG measurement on admission. Current local guideline recommends taking ABGs until normalisation of pH and taking VBGs in difficult cases if general condition is improving.[3] Guidelines issued by the Joint British Diabetes Societies (JBDS) Inpatient Care Group[4] suggest measuring venous rather than arterial bicarbonate and pH as the difference between venous and arterial pH is 0.02 – 0.15 pH units and the difference between arterial and venous bicarbonate is 1.88mmol/L. This negligible difference will neither impact diagnosis nor management of DKA.[5]

In 18 cases (45%) a urine sample was not available for measuring urinary ketones at the A&E department for various reasons including inability of patients to pass urine, dehydration and low GCS.

According to the JBDS guidelines one of the criteria defining DKA is a serum ketonaemia of ≥ 3.0mmol/L or significant ketonuria of ≥ 2+ on standard urine sticks.[4] Locally ketone meters are not available yet and this may delay the detection of ketones in patients who are unable to provide a urine sample at A&E. Ketone meters detect β-hydroxybutyrate which is the main type of ketone produced in DKA as opposed to acetoacetate detected by the standard urine dipsticks. The latter also sometimes gives false positive results and the presence of acetoacetate in urine lags behind the actual systemic ketone production, therefore delaying both diagnosis and resolution of DKA.[6]

Local guideline recommends use of a VRII and in 7 cases (18%), a further increase in insulin treatment recommended. Updates in JBDS guideline suggest using a fixed-rate insulin infusion (FRII) rather than VRII. FRII consists of prescribing a fixed insulin regime according to weight, thus partially accommodating for the very obese patients[4] and enabling rapid ketone clearance. In 4 cases (10%) long-acting insulin (glargine) was continued together with intravenous short-acting insulin infusion. Continued use of background insulin avoids rebound hyperglycaemia when intravenous insulin is stopped and should also shorten duration of inpatient stay.[7]

Initial intravenous fluid recommended in current guideline is 0.9% NaCl, which is to be changed to 5% dextrose in 0.9% NaCl if BGM < 11mmol/L and to 10% dextrose if BGM <5mmol/L[3]. This recommendation was adhered to in 36 cases (90%). This represents a significant improvement from observations in a previous audit, in which correct change in intravenous fluids was observed in 71.4% of cases.[8] Patients in DKA often have mild to moderate hyperkalaemia at diagnosis, despite a total body deficit of potassium. The initiation of insulin further lowers circulating potassium as it shifts potassium intracellularly, potentially resulting in severe hypokalaemia.[9] Hence close attention needs to be given to potassium levels, in order to avoid complications associated with hypokalaemia, including cardiac arrhythmias, arrest and respiratory muscle weakness.[4] Data on potassium supplementation differs. The American Diabetes association guidelines suggest the addition of 20-30mmol of potassium in each litre of infusion fluid to maintain a potassium level between 4 and 5mmol/l,[10] whereas the JBDS guidelines[4] recommend replacing with a dose of 40mmol/L of potassium if serum level is less than 5.5mmol/l.

An elevated WCC was negatively correlated with HCO^{3-} and pH levels, although the latter did not reach statistical significance (p = <0.001 and p = 0.115 respectively). DKA is associated with an elevated level of proinflammatory cytokines, reactive oxygen species, and adhesion molecules which all contribute to the increased WCC.[11]

Assessment of resolution of DKA was based on normalisation of pH, HCO^{3-} and urinary ketones level. From our results, pH levels returned to normal at the shortest time interval, followed by HCO^{3-} and urinary ketones respectively (Fig. 1). From our data HCO_3^- correlated well with the 2 other variables measured for the resolution of DKA. However JBDS guidelines recommend not using HCO^{3-} as the only variable due to possible hyperchloraemia secondary to large volumes of 0.9% sodium chloride solution used as fluid replacement. Consequent hyperchloraemic acidosis may lower HCO^{3-} levels and lead to difficulty in assessing for resolution of ketosis.[4]

The limitations of this audit include missing data from files and observation charts. Unclear and incomplete documentation also limited extraction of relevant data for this audit. Nonetheless, the audit performed showed numerous strengths including correct diagnosis of patients on presentation to A&E, accurate assessment of fluid balance and BGM management, accurate documentation of time at which subcutaneous insulin was restarted and of resolution of DKA.

Conclusion

In the current local guideline the diagnosis and resolution of DKA is based on pH, bicarbonate and detection /lack of ketones in the urine. Results from our audit for resolution of DKA have highlighted the great discrepancy between the time taken to achieve a pH >7.3mmHg (7.38hrs) and the time taken to achieve negative ketones in the urine (26.25hrs). The difficulty in obtaining a urine sample to test for ketones early on presentation and the persistent detection of ketones in the urine after suppression of ketonaemia contribute to the delay in diagnosing DKA and in identifying resolution of DKA respectively. This might result in potentially harmful delays in initiating treatment of DKA and subsequent unnecessary prolonged treatment with

insulin infusion. The introduction of ketone meters to measure ketones in the blood would expedite DKA diagnosis, facilitate monitoring of the patient admitted with DKA and accurately identify resolution of DKA early while the administration of insulin infusion at a fixed rate, tailored to the individual patient according to the patient's weight, would contribute to rapid ketone clearance thus improving the overall management of the patient admitted with DKA.

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Original Article

Diabetes in pregnancy: diagnosis, management, outcome and complications

Maria Petra Agius, Mark Gruppetta, Josanne Vassallo

Abstract

Introduction: Numerous perinatal complications of diabetes in pregnancy have been recognised. Maternal post-partum complications can be equally devastating.

Method: In this study, a cohort of known type 1 and type 2 pregnant diabetics and newly diagnosed Gestational Diabetes Mellitus (GDM) patients were analysed. Data collected was analysed in terms of method of diagnosis, gestational age at diagnosis for GDM, relevant medical or obstetric history, subsequent management and follow up.

Results: Out of 79 viable pregnancies, 69.6% of patients were diagnosed with GDM, 13.9% with type 2 DM and 16.5% with type 1 DM. Mean gestational age for the GDM cohort was 37.9 (±1.6) weeks, 35.5 (±3.7) weeks in Type 2 and 37.1 (±0.7) weeks in the Type 1 cohort (p=0.010). 20.3% of all cohort and specifically 23.6% of GDM pregnancies had a fetus which was large for gestational age. 30% of GDM patients, 25.5% of Type 2 DM patients and 84.6% of Type 1 DM patients, had their blood glucose controlled by an insulin infusion pump peri-partum. Mean HbA1C in the third trimester was 6.0%, 6.3% and 7.1% in GDM, Type 2 and Type 1 diabetics respectively (p=0.004). A negative correlation was seen between HbA1C levels in third trimester and delivery gestational age (p<0.001).

Conclusion: Our findings emphasize the need for close follow up of these patients. Implementing a structured and holistic multidisciplinary team may have an impact on outcome, focusing on maternal education, in particular in GDM patients and their risk of developing type 2 DM in the future.

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Introduction

Diabetes mellitus (DM) is the most common medical condition complicating a pregnancy, affecting 16% of all life births[1]. Diabetes is the epidemic of the 21st century, with recorded increase in the incidence globally. Possibly, one may attribute this to an increased tendency for a sedentary lifestyle and a shift towards a western diet. The unmodifiable genetic predisposition is a major determinant which is quite relevant to the Maltese population. The prevalence of gestational diabetes in Malta was 15.5% in 2010 based on WHO criteria,[2] rising up to 16.5% when using the International Association of Diabetes and Pregnancy Study Groups (IADPSG) criteria.[3-4] A rise in obesity and delayed childbearing age have led to an increase incidence of gestational diabetes mellitus (GDM) and earlier onset of type 2 diabetes mellitus . The potential devastating effects of diabetes can affect both the mother and fetus with

the management and outcomes differing according to the aetiology of the condition.

This retrospective study conducted at Mater Dei Hospital in Malta, has analysed how pregnant mothers who had diabetes during pregnancy (GDM, type 1 & type 2 DM) are diagnosed and managed, further focusing on follow-up and subsequent maternal and fetal outcome.

Methods and Materials

A retrospective study consisting of a cohort of type 1, type 2 and newly diagnosed GDM patients, over a 5-year period. These patients consisted of all consecutive patients who presented to a single firm with any of the mentioned conditions in the study period. Our study comprised of 79 pregnancies, of which 69.6% were diagnosed with GDM, 16.5% were Type 1 DM patients and 13.9% Type 2 DM patients. The IADPSG criteria (Figure 1) was used for diagnosing GDM, based on an oral glucose tolerance test (OGTT) according to risk factors at booking and a fasting blood glucose level above 5.1 mmol/l. Risk factors for GDM include a high body mass index (BMI), strong first-degree family history of type 2 DM, severe polycystic ovarian syndrome (PCOS), previous unexplained stillbirth or macrosomia and macrosomia or polyhydramnios during the index pregnancy. However, two GDM cases were diagnosed during the third trimester of pregnancy secondary to clinical parameters such as polyhydramnios or increased fetal abdominal circumference.

The data collected included the method of diagnosis, gestational age at diagnosis, variations in HbA1c levels throughout pregnancy, management, gestational age and weight at delivery, any peri-natal maternal or fetal complications and long term follow up of the mother. Macrosomia was classified as birth weight above 4.5kg. Infants with weight above the 90th centile for gestational age were classified as large for gestational age. This was performed by ultrasound fetal measurements plotted on a growth chart. Data was collected on a proforma created using Microsoft Access.

Nonparametric assessments were used. Assessments between categorical variables were analysed using χ^2 test and Fisher's exact test. Associations between independent samples were analysed using the Mann-Whitney U or Kruskal-Wallis as appropriate. Correlation analyses were carried out using Spearman correlation. Statistical assessments were carried out using IBM SPSS® Statistics for Windows, Version 22.0, (IBM Corp. Armonk, NY, USA). A two-sided $P < 0.05$ was considered statistically significant.

Results

From a total of 79 pregnancies, 55 patients were diagnosed with GDM (69.6%), 13 patients had pre-existing type 1 DM (16.5%) and 11 patients had type 2DM (13.9%). The vast majority of GDM patients (50.9%) were started on oral hypoglycaemic agents specifically Metformin, while 32.7% required insulin mostly human insulin (Actrapid®) pre-prandially. About 63.6% of Type 2 DM patients were on insulin mostly combination regimes involving intermediate and short acting human insulins (Insulatard® and Actrapid®), 36.4% on both insulin and oral hypoglycaemic agents and 18.2% on oral hypoglycaemic agents only (Metformin). All our Type 1 patients were on insulin, the majority of which were on insulin analogues (insulin glargine and insulin aspart). The median gestational age at which a GDM diagnosis was made was 29 weeks (IQR: 28-32).

The mean fasting blood glucose in the GDM cohort was 6.31mmol/l (SD+/- 1.79), the mean blood glucose during the first hour of OGTT was 12.06 mmol/l (SD+/- 2.77) and the mean second hour blood glucose was 10.73 mmol/l (SD+/- 2.95).

The shortest mean gestational age of 35.5 weeks was in the Type 2 DM cohort compared to 37.1 and 37.9 weeks in the Type 1DM and GDM groups respectively (P=0.010). Type 1 DM mothers had generally a younger age (Mean +/- SD: 27.0 +/- 4.3 years) compared to GDM mothers (Mean +/- SD: 31.5 +/-6.8 years) and Type 2 DM mothers (Mean +/- SD: 32.4 +/-4.4 years) (P=0.031).

The mean gestational weight in the GDM group was 3.5kg (+/-0.7 Kg) and the mean neonatal weight in the type 1and type 2 cohort was 3.2kg (P=0.041). In 20.3% of patients, an antenatal scan showed a large for gestational age fetus, 23.6% of which were GDM pregnancies.

The median HbA1c in the pre-conception period was 7.8 (IQR: 7.25-9.35 %) and 7.6 (IQR: 6.65-8.18 %) in the Type 1 and Type 2 group respectively. In the Type 1DM cohort this went down to 7.4 in the first trimester and 7.2 and 7.1 in the second and third trimesters respectively. In the Type 2DM group, the HbA1c declined gradually from 7 to 6.8 and 6.3 in the first, second and third

trimesters respectively.

A statistically significant negative correlation (*P*=<0.001) was found between gestational age and HbA1c levels.

During the intra-partum period 30% of GDM and 25.5% of Type 2 DM patients required an insulin infusion pump. However, as expected, up to 84.6% of Type 1DM patients required an insulin infusion pump. No metabolic complications were reported during the intra-partum period. Apart from macrosomia, respiratory distress was common in babies of diabetic women, with a number of infants requiring neonatal intensive care admission for glucose monitoring. Two infants suffered a hypoglycaemia induced seizure at birth. Other neonatal complications reported include two intra-uterine deaths in the GDM group and a number of organ anomalies in 3 fetuses in the Type 1 and 2 group.

Six weeks post-partum, 52% of GDM patients attended for an OGTT, 21.8% of which had Type 2DM and 5.5% impaired glucose tolerance.

Discussion

Malta, an island in the Mediterranean Sea, has one of the highest rates of diabetes in Europe.[5] The estimated prevalence of diabetes in adults was 13.9% in 2015, according to the International Federation of Diabetes Atlas. Moreover, the prevalence of gestational diabetes is on the rise. A study conducted by Aganovic et al, in 1983 has shown that the prevalence of gestational diabetes was 11.5%, compared to a prevalence of 16.5% in 2010, according to IADPSG criteria.[6-7]

Diabetes in pregnancy has well been recognized as the commonest medical condition complicating a pregnancy. The effects of diabetes mellitus on the mother and her fetus can be described as diverse, complex and occasionally resulting in permanent end-organ damage. Albeit, in the vast majority of cases, complications can be avoided and prevented if the mother is followed-up closely and managed within a multi-disciplinary team. Maternal obstetric complications include a higher risk of pre-eclampsia, pregnancy-induced hypertension, higher risk of operative vaginal delivery and caesarean section wound infection.[7] The well-known medical complications associated with diabetes and micro-vascular disease tend to get worse during pregnancy. Diabetic nephropathy has a worse prognosis during pregnancy when compared to equivalent stages of chronic kidney disease outside pregnancy.[8] Pregnant Type 1 and 2 DM patients, should be screened for diabetic nephropathy throughout pregnancy, with albumin-creatinine ratio being a more accurate test.[9] Around 30 to 40% of diabetic patients suffer from chronic hypertension, however, during pregnancy 60 to 70% of diabetic patients develop hypertension thus exacerbating any pre-existing nephropathy. [10,8] The changes associated with diabetic retinopathy progress in around 50-70% of cases.[11] Screening should be done in the pre-conception period and in every trimester of pregnancy coupled with good blood pressure and glycaemic control.[12] On a positive note, despite the programmed routine screening in our cohort of type 1 and 2 patients, no cases of progressive nephropathy or retinopathy complications were reported. Fetal complications include, an increased risk of first trimester miscarriage, congenital anomalies, macrosomia, stillbirth, shoulder dystocia, neo-natal hypoglycaemia and respiratory distress syndrome.[13-14]

The IADPSG criteria were used for a diagnosis of gestational diabetes, in line with recent recommendations from the HAPO study.[15] Gestational diabetes can be defined as 'any degree of glucose intolerance with onset or first recognition during pregnancy'.[16-17] Our results show that the mean gestational age at delivery was highest in the GDM cohort compared to the Type 1 and Type 2 group. One can possibly explain these results by the fact that obstetric patients with pre-gestational diabetes are considered to be high risk patients and hence the obstetricians will have a lower threshold to deliver the fetus prior to the estimated date of delivery. Moreover, the lowest gestational age was recorded in the Type 2 DM group of patients. We also report that patients with Type 2 DM tend to be older and with a higher BMI, these results are in agreement with other authors.[18]

A strong positive correlation exists between percentage fetal body fat, fetal insulin levels and maternal glycaemia.[15] On average, patients with GDM had a fetus of a higher gestational weight, while mean gestational weight in Type1 and 2 DM patients was similar. This could possibly be explained by a relatively later diagnosis, monitoring and initiation of treatment in the GDM cohort as compared to patients with pre-existing diabetes mellitus.

The HbA1c during the pre-conception period in the pre-diabetic patients was sub-optimal in both groups. The median HbA1c level in both groups improved during the first trimester possibly due to the decreased insulin requirements in the first trimester. Nielsen et al have reported a decrease in HbA1c level, from 6.3% pre-pregnancy, to 5.6% in the third trimester in normal pregnant patients.[19] Moreover, the life span of erythrocytes during pregnancy shortens secondary to increased erythropoietin secretion.[20] Therefore, irrespective of glycaemic control, HbA1c will drop during the first and third trimester, and lowering the threshold by 0.4% in diabetic pregnancies will translate into better glycaemic monitoring during pregnancy.[21] The mean HbA1c levels remained highest in the Type 1DM group, throughout pregnancy. Adequate glycaemic control in Type 1DM during pregnancy is challenging mainly due to the risk of hypogylacemia coupled by peaks and troughs in insulin requirements which are not necessarily met by the insulin dosage regimen.

Women with GDM have a higher risk of developing Type 2DM, despite the fact that in most cases euglycaemia is achieved immediately after delivery.[21] All the GDM patients in our cohort were invited for a repeat OGTT 6 weeks after delivery. A low turnout of 52% was reported and 21.8% were diagnosed with Type 2DM. In a systemic review of 20 studies, patients with gestational diabetes have a 7-fold increased risk of developing Type 2DM when compared to patients with a euglyacemic pregnancy.[22]

Our study has shown a significant correlation between the different types of diabetes and pregnancy outcomes, emphasizing a known fact that pre-existing diabetes mellitus both Type 1 and 2, greatly determines obstetric outcomes. Our study has also confirmed the idea that women are at a higher risk of developing diabetes mellitus after a pregnancy affected by gestational diabetes. This underpins the importance of prevention of diabetes, and the emphasis on follow up once the condition has been diagnosed.

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Original Article

Socioeconomic status and its impact on the prevalence of severe ADHD in the Maltese Islands

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Abstract

Attention deficit hyperactivity disorder (ADHD) is a common disorder which presents in childhood. The core symptoms include; hyperactivity, impulsivity and reduced attention. If left untreated this may possibly lead to various impairments of function in other areas of one's life, such as lack of educational attainment, increased risk of accident-prone behaviour, substance misuse and antisocial behaviours. Although the exact aetiology is still not fully understood, various studies have demonstrated the presence of both a genetic and an environmental component. ADHD is highly hereditable, demonstrating a strong genetic component (0.75). Furthermore, increased rates of ADHD have been linked with a low socioeconomic status.

The islands of Malta have traditionally been divided for statistical purposes into 6 districts, with certain districts more often being associated with low socioeconomic demographics.

The main aim of this study was to assess whether higher prevalence rates of ADHD were present in the districts, which are classically associated with a low socioeconomic status. All persons aged 0 to 18 years attending the governmental clinics, having a documented diagnosis of severe ADHD and therefore being prescribed pharmacotherapy were identified and included in this study. Nine young people were living in institutional care and were therefore excluded from statistical analysis since this would skew that data in this study. A significant difference ($p<0.0001$) in the point prevalence of ADHD between the six Malta districts was found, with higher rates of ADHD occurring in the harbour districts. Though not statistically significant, a positive correlation was demonstrated between the ADHD prevalence and a number of socioeconomic variables, these included; the rate of smoking ($p=0.111$), number of people classified as at-risk-of-poverty per district ($p=0.397$), and number of people with no schooling per district ($p=0.156$). The overall point prevalence for ADHD in Malta obtained was 0.85, a value which is less than the average prevalence noted worldwide. The authors believe this value is an underestimation since the data collection in this study did not include ADHD cases off pharmacological treatment and any ADHD cases assessed and treated in the private sector.

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Keywords

ADHD, prevalence, Malta, low socioeconomic status c

Introduction

Attention deficit hyperactivity disorder (ADHD) is the commonest childhood-onset mental disorder which manifests itself with symptoms of inattention, hyperactivity and impulsivity, with males being affected more than females.[1] This condition can have serious effects on the overall

functioning of a child, since it can influence the child's education attainment together with his/her behaviour.[2] ADHD symptoms can persist in adulthood with prevalence rates as high as 4.4% in the community.[3] Evidence suggests that this condition is highly heritable [4], several studies in different countries have demonstrated that ADHD is more prevalent in socioeconomically disadvantaged groups.[5]

The Maltese archipelago consists of 3 main islands: Malta, Gozo and Comino. It is traditionally divided for statistical purposes into six districts, namely the Southern Harbour area, Northern Harbour area, the South-Eastern region, Western region, Northern region, and the 2 smaller islands Gozo & Comino being considered as one district. The harbour regions, are considered less affluent areas with greater social deprivation and poverty.[6] In published literature it was reported that people living in the harbour areas have higher rates of psychosis.[7]

The Government of Malta has set up two clinics that assess and treat children and adolescent with mental disorders. These are the Child and Young People's services (CYPS) located at St Luke's Hospital, Malta and the Gozo Psychiatry outpatient's clinic. A number of independent psychiatry clinics are also found throughout the Maltese islands. Government based child and adolescent clinics accept referrals for youngsters aged 0 till 18. Patients may be referred by any doctor working both in the private and government sector, including general practitioners, psychiatrists and paediatricians. After the age of 18, patients followed at these clinics are referred to mainstream adult psychiatry services.

The aims of this study included:

1. to retrospectively estimate the point prevalence of severe ADHD in children aged 0 to 18 years on treatment attending governmental clinics as per February, 2017, both in general and at district level
2. to assess whether a significant difference exists in the point prevalence of severe ADHD between the six districts in Malta.
3. to assess whether a correlation exists between rates of severe ADHD in those ages 0 to 18 years per district and a number of socioeconomic variables, including:

a. smoking
b. education
c. employment
d. population density
e. being classified at risk of poverty
f. being reared by a single mother
g. number of nights spent abroad as a measure of affluence

Methodology

Ethical approval and data collection

A retrospective study was designed with the aim of calculating the point prevalence of severe ADHD in every district in Malta respectively. Ethical approval was obtained from the Ethics board of the University of Malta and permission for data handling was obtained from the Data Protection Office for Mental Health Services of Malta, located at Mount Carmel Hospital.

This project did not involve any direct contact with patients, their carers nor their attending physicians. Data accessed throughout this project involved a retrospective case note review of the patents clinical files as well as clinic databases (where available). This demographic data collected, included; the name and identification number, age of the patient and address as well as diagnosis and treatment modality being used as per February 2017. All data were stored on a password protected private computer with confidential access throughout the whole project as per data protection law of the laws of Malta (DPA chapter 440).

Records of all patients under 18 years of age, who ever attended these clinics (included discharged patients), were studied. All patients who received a diagnosis of ADHD by a psychiatrist were highlighted for further analysis. Although these clinics do not have established written protocols for the diagnosis of ADHD, literature suggests that treatment should only be initiated in severe cases.[8] Hence, in order to aim for high specificity, only patients receiving treatment were selected implying the presence of severity of ADHD. Cases where a diagnosis of ADHD was done but was not sufficient enough to warrant a pharmacological intervention were excluded.

All data were imputed in a confidential Microsoft Excel® file, containing demographic data as well as diagnosis and treatment modality. In order to protect identification of patients all patients' names and identification numbers were converted to a generated personalised identification system, which was subsequently used throughout

the whole project. Patients' addresses were examined and every patent was allocated to one of the six districts, as per Census of Populations and Housing of 2011.[9]

Patients living in institutional care were excluded from the study in view of their current living address being unreflective of the original demographic address. It was acknowledged that a number of families do move home and change their address. However, following discussions with the medical statistician, in view that the number of inter-district translocations tends to be mutual and random it was deemed unnecessary to exclude patients whose family changed address before February 2017.

It was also acknowledged that a small number of children are reared in foster families. However, following discussions with the medical statistician since the number of fostered children in Malta and Gozo is very low, it was considered too small as to influence data collected. A number of foreign families decide to move to Malta for different reasons, including educational and employment opportunities. Foreign families tend to choose their accommodation according to their level of affluence. It was decided that foreign patients living permanently in Malta were not to be excluded from this study since these families will tend to distribute throughout the Maltese islands according to their social and economic status.

Data from the private / independent sector was not obtained for this research project. The extensive number of private clinics, together with non-uniformity in record keeping was a limitation in accessing this information and was considered beyond this project.

Socioeconomic variables

Previous studies have implied the existence of an association between ADHD and a number of socioeconomic variables, which include: low maternal and paternal education[10,4] being raised by a single parent[4], being born to a younger mother[11], and low family income.[4,5,12] The association of ADHD with parental occupation has also been studied with conflicting results.[13-14]

Higher smoking levels has been demonstrated to be associated with poverty and low socio-economic status. In a recent US publication, it has been demonstrated that the number of smokers in people considered below the poverty line is double the amount of people considered at or above the poverty line.[15] Hence smoking can be considered a factor associated with low socio-economic status.

Demographic data of the Maltese islands

Information related to the demographic data of the Maltese islands was obtained from the last National census carried out in 2011 with results published preliminarily in 2012 and with the final official report published in 2014.[9] These publications can be accessed freely on the internet from the National Statistics Office as well as purchased from the above-mentioned office itself. Data collected from the census included, total population according to the Maltese districts, including population per age group, population density per district, level of education and employment for individuals aged 15+. Further information was obtained about the lifestyle of the Maltese population, including number of smokers per district aged 18+, number of nights spent abroad aged 18+ (being assumed to be a level of affluence), and life satisfaction of all individuals aged 18+. This data was obtained freely from the Lifestyle survey 2007, with results being published by the National Statistics Office in 2009.[16]

Data were also obtained on the number of Maltese families at risk of poverty per district. This information was also accessed freely from the Statistics on income and living conditions 2010, published by the National statistics office in 2012.[17] Data regarding the number of single mothers per district was also extracted from a recent report on disadvantaged women in the Maltese islands.[18]

Results

Case population

As per Table 1, out of all patients attending the child psychiatry governmental clinics, till February 2018, 709 patients aged 0 to 18 years were diagnosed with severe ADHD by a psychiatrist and were receiving pharmacological treatment. Nine patients were residing in institutional care and were therefore excluded as per exclusion criteria mentioned above. The address of the selected 692 cases were analysed and allocated to the 6 districts. 179 patients were living in district 1, 194 patients were living in district 2, 94 were living in district 3, 93 were living in district 4, 83 in district 5 and 44 were living in district 6.

***Table 1**: Number of ADHD cases on treatment per district*

District number	Total number of ADHD patients on treatment per district
1	179
2	194
3	94
4	93
5	83
6	44

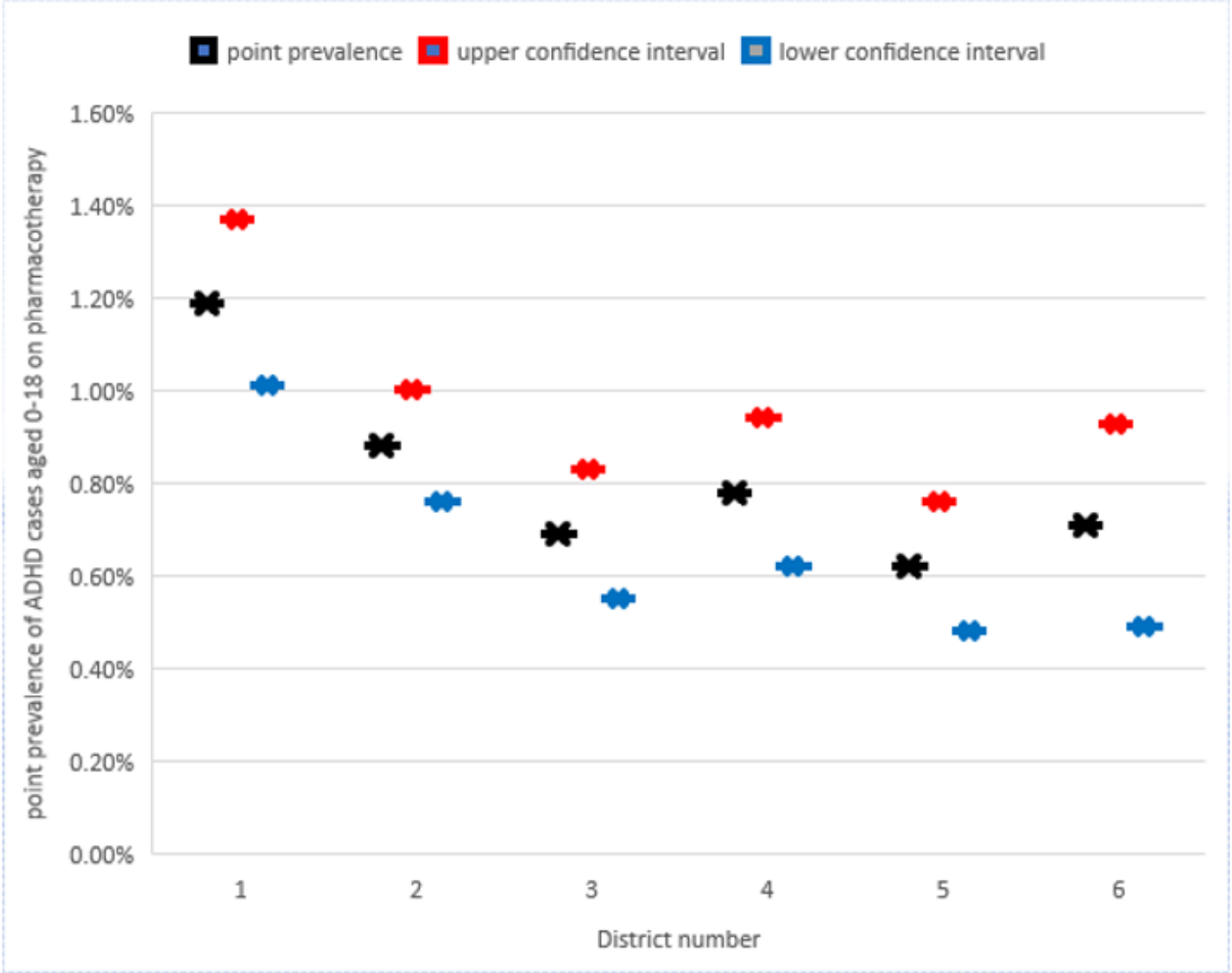
Data analysis

The chi-squared test was employed to assess whether there is significant difference between the prevalence of severe ADHD cases requiring medication. As per table 2 and figure 1, the highest point prevalence obtained was in the Northern Harbour District with a value of 1.19% (CI = 1.37% - 1.01%) followed in descending order by the Southern Harbour district (0.88%, CI = 1.0% - 0.76%), Western district (0.78%, CI = 0.94% - 0.62%) and the islands of Gozo and Comino (0.71%, CI = 0.93% - 0.49%). The two districts that demonstrated the lowest point prevalence were the South-Eastern district (0.69%, CI = 0.83 – 0.55%), and the Northern district (0.62%, CI = 0.76% - 0.48%). On comparing the six districts all together, the result obtained was statistically significant with *p* being less than 0.0001.

***Table 2**: Prevalence of severe ADHD patients (age 0-18 on pharmacotherapy), standard error and confidence intervals for each district*

	District					
	1	2	3	4	5	6
Total population per district aged 0 – 18	15,046	21,986	13,719	11,869	13,473	6,232
No of patients diagnosed with ADHD requiring medication	179	194	94	93	83	44
Point prevalence of severe ADHD patients aged 0-18 on treatment	1.19%	0.88%	0.69%	0.78%	0.62%	0.71%
$SE = \sqrt{\frac{p(1-p)}{n}}$	0.0009	0.0006	0.0007	0.0008	0.0007	0.0011
CI = p ± 1.96 (SE)	1.37%	1.00%	0.83%	0.94%	0.76%	0.93%
	1.01%	0.76%	0.55%	0.62%	0.48%	0.49%

***Figure 1**: Point prevalence, upper confidence interval and lower confidence interval for each district*



The point prevalence rates of severe ADHD on treatment for every district were then compared with the confidence intervals of every district respectively as per table 3. Values that lied outside a confidence interval of another district were considered to be statistically significant. The Southern Harbour district obtained a significantly much higher point prevalence value compared to the other districts. In fact, the 1.19%-point prevalence obtained lied outside the confidence intervals of all the other five districts. The Northern Harbour district demonstrated a statistically significant difference when compared to district 3 and district 5. No statistical significance was noted when the point prevalence of district 2 was compared to the Western district as well as with Gozo and Comino Islands. No statistical significant difference was demonstrated when the point prevalence of district 3 was compared to districts 4, 5 and 6. On the contrary significant difference was obtained when the point prevalence of district 3 was compared to districts 1 and 2. The Western district, demonstrated a significant difference when compared to districts 1 and 5 but no statistical significance was noted in the difference between district 4 and districts 2, 3 and 6. The Northern district which demonstrated the lowest point prevalence rates of severe ADHD on treatment within the Maltese Islands, showed statistically significance difference to districts 1 and 2 but not to districts 3, 4 and 6. Similarly, Gozo and Comino, demonstrated significant difference to the Harbour districts but not to the other districts (districts 3, 4 and 5).

Table 3: *Table comparing prevalence of ADHD cases aged 0-18 on treatment per district with the confidence interval of every district respectively, prevalence values that lie outside a confidence interval of a given district are considered to be statistically different.*

			District confidence intervals									
			1		2		3		4		5		6	
			1.37%	1.01%	1.00%	0.76%	0.83%	0.55%	0.94%	0.62%	0.76%	0.48%	0.93%	0.49%
Point prevalence per district	1	1.19%			Significant difference		Significant difference		Significant difference		Significant difference		Significant difference	
	2	0.88%	Significant difference				Significant difference		No significant difference		Significant difference		No significant difference	
	3	0.69%	Significant difference		Significant difference				No significant difference		No significant difference		No significant difference	
	4	0.78%	Significant difference		No significant difference		No significant difference				Significant difference		No significant difference	
	5	0.62%	Significant difference		Significant difference		No significant difference		No significant difference				No significant difference	
	6	0.71%	Significant difference		Significant difference		No significant difference		No significant difference		No significant difference			

Correlation analysis with variables

It was further evaluated whether a correlation exists between the prevalence of severe ADHD in patients aged 0 to 18 years on treatment per district and the number of socioeconomic status variables specified below. These variables per district included population density, total number of people aged 0-18, smoking in individuals aged 18+, number of people with no schooling aged 15+, unemployment in people aged 15+, total number of people at risk of poverty, number of single mother families and number of individuals having experienced at least 1 holiday abroad during the previous 12 months. Data were analysed using the Spearman correlation test.

As per Table 4, although no correlation obtained displayed statistical significance, positive correlation was noted between the prevalence of ADHD cases on treatment aged 0 to 18 years and a number of variables, which included: number of smokers aged 18+ per district (p=0.111) and number of people with no schooling per district (p=0.156). A weaker positive correlation was noted between prevalence of severe ADHD on treatment per district with population density per district (p=0.329) and number of people classified as at-risk-of-poverty per district (p=0.397). The weakest correlation obtained was noted to occur between severe ADHD on treatment and the number of people unemployed (p=0.872). A negative correlation was obtained between prevalence of ADHD on treatment (population aged 0 to 18) and number of holidays spent abroad with p value of 0.787.

Table 4*: Correlations obtained using the Spearman's test between prevalence of ADHD patients on treatment aged 0-18 and factors: total population, population density, unemployment, tobacco consumption, no schooling, number of individuals at risk of poverty, number of single mother families and holidays abroad (at least 1 night) in the previous 12 months.*

			ADHD Prevalence
Spearman's rho	Average of smoking	Correlation Coefficient	.714
		Sig. (2-tailed)	.111
		N	6
	Average of Holiday abroad	Correlation Coefficient	-.143
		Sig. (2-tailed)	.787
		N	6
	Average of no schooling	Correlation Coefficient	.657
		Sig. (2-tailed)	.156
		N	6
	Average of population 0-18 total	Correlation Coefficient	.486
		Sig. (2-tailed)	.329
		N	6
	Average of unemployment	Correlation Coefficient	.086
		Sig. (2-tailed)	.872
		N	6
	Average of Population density per km2	Correlation Coefficient	.486
		Sig. (2-tailed)	.329
		N	6
	Average of at risk of poverty	Correlation Coefficient	.429
		Sig. (2-tailed)	.397
		N	6
	Average of single mother households	Correlation Coefficient	.429
		Sig. (2-tailed)	.397
		N	6
	Average of Total population per district	Correlation Coefficient	.486
		Sig. (2-tailed)	.329
		N	6

Discussion

Prevalence of severe ADHD in Maltese children

The overall calculated point prevalence of severe ADHD in children aged 0 to 18 years on treatment attending government-based clinics was 0.84% with values ranging from 0.57% in District 5 to 1.12% in District 1. However, this value could be an underestimation of the true point prevalence of ADHD in Maltese children, given that this study aimed for high specificity rather than high sensitivity and in view of a number of limiting factors, such as the unavailability of records for children attending private clinics.

Moreover, the prevalence of ADHD obtained in our study possibly includes referral bias, with potential cases being missed, either due to lack of awareness about ADHD both by professionals, as well as parents. Further psycho education about ADHD can enhance the pick up rate of cases and potentially a prevalence study of ADHD in Malta can be considered.

The above results only include children and adolescents who were severe enough to warrant pharmacological treatment, thus cases that were managed using other techniques such as behavioural therapy or in the case where parents refused medications were not included. Unfortunately, not all patients were under the care of the same psychiatrist, posing a further limitation in the way children were assessed and diagnosed

with mild, moderate or severe.

Data obtained from the Malta Health Regulation Authority for the authorisation of methylphenidate prescribing, indicates that there is a total of 1,244 people aged 0 to 18 years who had a permit for methylphenidate prescribing. This indicates, that a high proportion of people prefer to attend to psychiatrists privately without consulting governmental based clinics. This information suggests that further epidemiological research should be developed in order to estimate the true prevalence rate of ADHD in Malta.

Being small islands, both Malta and Gozo offer the advantage of increased availability and free access to clinics, therefore further promotion of services as well as further awareness can result in further detection of ADHD cases. Schools might be the optimal places where children could be observed and signs and symptoms of ADHD picked up. Hence, further education campaigns to both parents and teachers might increase awareness. In view that this study has demonstrated higher prevalence rates in the harbour districts, further resources might be offered in these districts so as to offer further support and potentially minimise behaviours associated with this disorder such as illicit substance misuse and crime.

Severe ADHD and low socioeconomic status in the Maltese islands

Rates of ADHD were noticed to be higher in districts that are classically associated with low socioeconomic status, that is primarily the Northern and Southern Harbour areas. Both Northern and Southern harbour areas are associated with high population numbers and density as well as lower levels of education compared to the other districts of Malta.[9] The northern harbour region is also associated with higher rates of smoking in those aged 18+ and also excluding Gozo (district 6), citizens of the Northern Harbour area were the least to have travelled and spent at least 1 night abroad in the previous 12 months.[16] The Harbour districts also demonstrate higher numbers of single mother families [18] as well as a larger number of individuals economically considered at risk of poverty.

Though not achieving a statistically significant result, positive correlations using the Spearman's test were demonstrated between prevalence of ADHD on treatment in those aged 0-18 and a number of socioeconomic variables as per below.

Smoking: A positive correlation was noted between number of smokers per districts aged 18+ and point prevalence of severe ADHD on treatment. Higher smoking levels has been demonstrated to be associated with poverty and low socio-economic status. In a recent US publication, it has been demonstrated that the number of smokers in people considered below the poverty line is double the amount of people considered at or above the poverty line.[15] Nigg, 2013 also reports that people suffering from ADHD are at a higher risk of developing addictions, including smoking.[19] This study suggests correlation, though not statistically significant between smoking and ADHD, although this does not necessarily imply causation, that is that smoking causes ADHD.

Education level: This study has demonstrated the existence of a positive correlation (though not statistically significant) between rates of severe ADHD on treatment per district and the number of people with no schooling (p=0.156). Several studies have demonstrated the association between parental education and the risk of ADHD in offspring.[10,4.]

Population density: A weaker positive correlation was demonstrated between the rates of severe ADHD on treatment and population density per district (p=0.329). Population density can be considered a marker of affluence, since richer people will tend to have bigger houses. As per Census of population and housing of 2011, higher population densities are located within the Northern (5,014 per kilometre squared) and Southern (3,035 per kilometre squared) harbour districts. These two districts are associated with smaller houses and a higher number of social housing.[9]

People considered 'at-risk-of-poverty': A positive correlation, though not statistically significant was also obtained between the number of people considered at risk of poverty per district and rates of severe ADHD on treatment (p=0.397). Several studies have demonstrated the association between poverty and risk of ADHD.[4, 5,12]

Unemployment: A weak positive correlation was obtained between rates of unemployment in people aged 15+ per district and rates of severe ADHD in those aged 0 to 18 on treatment (p=0.872). Ford et al 2004 found no associated between ADHD in off spring and parental occupation class.[13] Similarly, Al Hamed et al 2009, also demonstrated no association between paternal occupation and ADHD phenotype in offspring.

However, Al Hamed et al 2009, found that mothers who reported to be housewives had a higher prevalence of ADHD phenotype (OR2.85, 95% CI 2.02-4.03 $p<0.01$).[14] This finding suggests that further research could be performed in Malta so as to identify whether a similar association exists between ADHD and maternal occupation, specifically in mothers who are unemployed.

Single mothers: A positive correlation was obtained, though not statistically significant, between rates of ADHD and the number of single mother families per district (p=0.397). The relationship between single mothers and ADHD phenotype offspring has been already documented in previous studies.[4]

Number of nights spent abroad: A weak negative correlation was obtained (though not statistically significant) between number of nights spent abroad and prevalence of severe ADHD phenotype per district (p=0.787). This variable was selected as a measure of income, being postulated that richer families would tend to have more disposable income to spend on travelling. According to the Lifestyle survey 2007, compared to other districts, people living in the Northern district were the ones who mostly reported to have spent at least one night abroad.[16] One must still take into consideration that not all affluent families would consider travelling abroad as a means of recreation due to personal choice.

Low socioeconomic status: Although as expected rates of ADHD were significantly higher in the districts associated with a low socioeconomic status, it is also possible that more affluent families, particularly those residing in the Northern regions of Malta prefer to attend private clinics rather than make use of the governmental clinics. The correlation between increased rates of mental illness and low socioeconomic status has been widely described in literature.[20] Similarly, Camilleri et al. 2010, have reported a higher incidence of psychosis in the areas of Malta associated with a lower socioeconomic status, that is Southern and Northern harbour areas.[7] This study has also demonstrated the impact of socioeconomic status on the prevalence of ADHD in the Maltese islands and therefore further suggests the possibility of having more mental health resources allocated to these areas together with further education campaigns and improvement of socioeconomic factors such as good housing, education and employment opportunities.

Relatively high ADHD prevalence rates, though less than districts 1 and 2, were also obtained in district 4 which is associated with areas that are developing steadily such as the villages of Attard, Żebbug and Lija. Traditionally, district 4 is also associated with areas considered high class, example Mdina, being the old capital city of Malta, is considered the home town of nobility. People in this district might be more aware of ADHD symptoms and would therefore more readily seek professional advice.

Changing demographic trends

It is well recognised that certain regions of Malta that have classically been described as 'poor' are now becoming more affluent, particularly since rich foreigners are recently settling in old historic cities. Birgu (Citta Vittoriosa), for instance, though classically considered a poor area is now slowly being converted into an attractive place to settle in, with old historic buildings being converted into luxury homes. Moreover, investment by the local government is resulting in an increase of luxurious facilities such as yacht marinas etc.[21] On the other hand, St Paul's bay, which traditionally was considered to be a summer resort for the more affluent families is now becoming populated by socially deprived families, single mother families and immigrants.[22] These changes might eventually affect the prevalence rates of mental health conditions, therefore epidemiological studies must be dynamic and reflect the social trends.

Conclusions

This study has statistically demonstrated that there is a significant difference in the prevalence of severe ADHD cases in children aged 0-18 on treatment between the 6 districts of the Maltese islands, with higher values obtained in the districts that are traditionally known to be associated with a low socioeconomic status such as the Northern Harbour district and least in the Northern district of Malta. Such finding could be of assistance to the local policy makers in order to tailor the child psychiatry services better and possibly allocating more resources to districts that are associated with higher rates of ADHD.

Though not statistically significant, this study has also further implied an existence of a correlation between ADHD and a number of

socioeconomic factors, such as smoking, increased population density, poverty, lack of education and being raised by a single mother. though results obtained where not powerful enough to achieve statistical significance, these results can help policy makers in addressing a number of factors that potentially influence the development and maintaining of various psychiatric conditions, including ADHD.

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Original Article

The Outcome of the Follow-Up of Consolidations on Chest Radiographs in a Maltese Population, Presenting from the Community, Aged 50 or over – a Retrospective Study

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Abstract

Background: The British Thoracic Society (BTS) guidelines for community-acquired pneumonia (CAP) suggest a repeat chest radiograph 6 weeks after treatment for patients over the age of 50 to screen for lung malignancy. The benefit of this practice is not well determined.

Method: We conducted a retrospective study involving patients from the community over 50 years old with consolidations on chest radiography. These patients presented in Mater Dei Hospital, Gozo General Hospital and Maltese Health Centres during the months of January 2013-2017 and August 2013-2016.

The occurrence of follow-up imaging and subsequent diagnosis of lung malignancy was documented. All chest radiographs were reviewed by a radiologist.

Results: 402 patients met our inclusion criteria. Follow-up imaging was done in 214 patients (53.2%) within 12 weeks. There was no statistical significance in the follow-up rates when matched for the presenting month, whether radiologists recommended repeat imaging, whether patients were admitted to hospital, and for the patients' age and gender.

The diagnostic yield of lung malignancy was 1.74% (7 patients) within 12 weeks with all malignancies being at an advanced stage at diagnosis (lowest stage being IIIA) when detected. All seven patients had a smoking history.

Conclusion: 53.2% of community-acquired pneumonia patients over the age of 50 had follow-up imaging within 12 weeks. No clinical variables explaining this low rate could be identified.

This practice results in a low diagnostic yield. Moreover, the diagnosis of lung malignancy is achieved at an advanced stage, making it a poor screening tool.

Keywords

Community-acquired pneumonia, Follow-up imaging, Lung Malignancy, Screening

Abbreviations

CAP: Community-acquired pneumonia
BTS: British Thoracic Society
PACS: Picture Archiving and Communication System

Introduction

Scheduling repeat imaging in patients diagnosed with community acquired pneumonias (CAPs) with a consolidation on radiographs is routine practice for many a physician. Lung malignancies can have similar radiological features to that of a consolidation, while an airspace shadow caused by an infection can easily mask an underlying neoplasm. It is on this trail of thought that repeat imaging is routinely done within the first 2 to 3 months.

The 2009 British Thoracic Society (BTS) guidelines[1] on Community Acquired Pneumonias mention that repeat chest radiography should be performed 6 weeks after the initial chest X-ray in patients over the age of 50 or those with a smoking history. Similarly, the 2005 American College of Chest Physicians guidelines[2] suggest follow-up radiography after approximately 8 weeks.

On the other hand, the 2007 Infectious Disease Society of America and the American Thoracic Society consensus guidelines[3] do not mention any follow-up chest radiography in the management of CAPs.

More detailed guidelines on follow-up imaging are conspicuous by their absence. Consequently, physicians are left with their clinical judgment and patchy guidelines when they need to decide who the patients meriting future chest imaging are.

To address this void in the management of community acquired pneumonias, we have embarked on this retrospective study where our aims were twofold. Firstly, are patients over the age of 50 diagnosed with a community acquired pneumonia really being followed-up, as suggested by the BTS guidelines, and if not, why? Secondly, is this practice really feasible and efficient? Using this strategy, what is the diagnostic yield of lung malignancy and is the diagnosis being achieved early enough?

Methodology

In this retrospective study, we considered patients 50 years old or over who presented to Mater Dei Hospital, Gozo General Hospital and Maltese Health Centres with radiological findings of a pneumonia.

The age 50 was chosen since the The 2009 British Thoracic Society (BTS) guidelines[1] on Community Acquired Pneumonias actually consider patients over the age of 50 to be at high risk for lung malignancy when recommending repeat chest imaging.

Patients were recruited by searching for the keywords "consolidation", "pneumonia" and "opacification" in the radiologist reports for all the radiographs done in the months of January during the years 2013, 2014, 2015, 2016 and 2017 and the months of August in the years 2013, 2014, 2015 and 2016.

These reports were obtained using the local Picture Archiving and Communication System (PACS) software used in all Maltese state hospitals and health centres.

The patients whose reports had one or more of these keywords were then sieved through according to the inclusion and exclusion criteria as mentioned in **Tables 1 & 2**.

The consolidation must have been present only on chest radiographs. Thus, patients who had other modalities of chest imaging for up to one week after the presenting chest radiograph were excluded. Since this study focuses specifically on community acquired pneumonias, patients who were admitted for any reason in hospital during the three weeks prior to the chest radiograph were excluded. Patients with active malignancy were also excluded.

A radiologist higher specialist trainee reviewed all the chest radiographs which were reported to have a consolidation. This helped ensure that only chest radiographs with clear signs of consolidations were included in this study.

The final number of patients who satisfied all the aforementioned was 402 (*n*).

Table 1: *Inclusion criteria for patients to be eligible to form part of the study cohort*

Inclusion Criteria
Patients whose chest radiographs' reports contained the search words "consolidation", "opacification" and/or "pneumonia"
Age: 50 years or over
Consolidation must be seen on chest radiograph
Patients presenting in the months of January 2013-2017
Patients presenting in the months of August 2013-2016
Chest X-rays performed in Mater Dei Hospital, Gozo General Hospital and Maltese Health Centres

Table 2: *Exclusion criteria preventing patients from being eligible for the study cohort*

Exclusion Criteria
Patients under the age of 50
Patients who had chest imaging other than chest radiographs done in the first week after the initial chest X-ray
Patients deceased within 12 weeks of initial chest radiographs
Hospital Acquired Pneumonias, i.e. patients who had been admitted in hospital at any stage during the three weeks prior to presentation
Chest radiographs that were never formally reported
Lesion described on chest x-ray was already identified in previous imaging
Patients with pleural effusions that required drainage
Lung transplant patients
Patients with active pulmonary tuberculosis
Patients who did not have a fixed address in Malta (thus potentially making follow-up less likely)
Chest X-rays done over 24 hours after admission if no CXR was performed on admission
Presenting CXRs where the reporting radiologist recommended cross-sectional imaging and/or bronchoscopy and/or PET scans due to a high index of suspicion for a lung malignancy

The patients' demographics were documented along with the mortality and whether or not follow-up imaging was done or not. The initial chest radiograph reports were analysed to see whether the reporting radiologist had recommended follow-up imaging and consequently whether this affected the rate of follow-up or not. Other variables that may have affected rate of follow-up such as whether the patient was admitted and whether the consolidations were unilateral or bilateral were also documented.

All follow-up imaging done from one week until 12 weeks after the initial chest radiograph was scrutinized. The data collected was analysed using Statistical Package for Social Sciences (SPSS) software.

Where relevant, the histology, if available, and stage of the lung malignancy were noted. The 8th edition TNM classification[4] was used to assess staging.

Results

As mentioned previously, a total of 402 patients met our inclusion criteria. 207 were male (51.5%) and the age ranged from 50 till 99 years. The mean age was 74.18 years (S.D. ±11.8 years) with the median being 76 years.

Follow-up imaging was performed in 214 patients within 12 weeks after the initial chest radiograph. This implies that 214 patients had chest imaging done between 1 week and 12 weeks after initial presentation (as documented in **Table 3**). Chest radiographs done on admitted patients who were in hospital for at least 24 hours were excluded.

316 patients of the cohort of 402 patients (78.6%) required hospital admission after the initial chest radiograph. Repeat imaging after treatment of the pneumonia was suggested by a radiologist in 130 chest radiographs, i.e. in 32.3% of the CAP population. Refer to **Tables 3** and **4** for an overview of the data collected.

Different follow-up rates within 12 weeks were compared according to gender, the month of presentation and whether follow-up was recommended by radiologist or not (**Figure 1**), if the consolidations was bilateral and whether the patient required admission by using a chi square statistical test for each variable.

Taking a p-value of <0.05 as being statistically significant, it was noted that no significant difference was detected among the follow-up rates when comparing these different predictors **(Table 5)**. A paired t-test was done to compare age and follow-up rates. Once more, no statistical significance was noted **(Table 6)**.

Additionally, logistic regression testing was done to assess any interaction among all the aforementioned predictors that may affect the follow-up rate. Once again, no significant difference in follow-up rate was detected.

A total of 58 patients (i.e. 27.1% of all patients followed up) had non-resolving radiological findings on repeat imaging. 38 of these were eventually diagnosed with benign conditions while 13 did not have further imaging done.

The remaining 7 patients had non-resolving radiological findings that led to the diagnosis of lung malignancy. This means that 3.27% of patients followed up were diagnosed with lung malignancy, while the diagnostic yield (i.e. the number of patients diagnosed with lung cancer compared to the total number of patients with a community-acquired pneumonia) was 1.74%.

The diagnostic yield in the months of January was 1.48% while that in the months of August was similar at 2.27%. Using proportion testing, this difference was not significant **(p-value: 0.570)**.

Diagnosis of lung cancer was achieved at a relatively late stage in all cases; the most favourable stage was IIIA (as documented in **Table 7**).[4]

In addition to the aforementioned data, when including all radiology studies from one week after presentation up until 12 months after, a total of 320 patients had chest imaging done, i.e. 79.6% of the total cohort. In this scenario, 8 patients had unresolved lesions that led to a diagnosis of lung malignancy, i.e. only one patient was diagnosed with lung malignancy after not being followed up within 12 weeks. All 8 patients had a smoking history and their age ranged from 61 till 80 years (as shown in **Figure 2**). 7 of these patients were males. A cytology and/or histology confirmation of malignancy was achieved in 7 patients; one patient unfortunately passed away before this was achieved with his diagnosis only being done using radiological means. Three cases were adenocarcinoma, two squamous cell carcinoma and two small cell carcinoma. All were reported to be likely bronchial in origin. **Table 8** gives a detailed account of these 8 patients.

Moreover, similar to the rest of the cohort, repeat imaging had only been suggested in 4 of the 8 patients who were diagnosed with lung malignancy within one year.

Table 3: *Overview of the data gathered from all 402 patients with radiological signs of a lung consolidation and presenting with a community-acquired pneumonia from the months of January and August 2013-2016 and the month of January 2017*

Number of Patients (*n*)	402
Number of Males	207
Patients over 80 years old	143
Patients 50-80 years olds	259
Patients requiring admission	316
Follow-up imaging done (within 12 weeks)	214
% Follow-up done imaging within 12 weeks	53.2%
Follow-up Recommended by Radiologist	130
Follow-up done after Radiologist Recommendation (within 12 weeks)	76
% 12 week follow-up rate after Radiologist Recommendation	58.5%
12 week follow-up in patients over 80 years old	73
% 12-week follow up in patients over 80 years old	51.0%
12 week follow-up in patients 50-80 years old	141
% 12-week follow up in patients 50-80 years old	54.4%
Number of males with a follow-up chest imaging within 12 weeks	110
%12-week follow up in males	53.1%
Number of females with a follow-up chest imaging within 12 weeks	104
%12-week follow up in females	53.3%
Lung malignancy cases diagnosed on follow-up of non-resolving lesions	7
% diagnostic yield on follow-up (i.e. number of patients diagnosed with lung malignancy compared to total number - *n*)	1.74%
% of followed-up patients diagnosed with lung malignancy	3.27%
Chest imaging done within 12 months	320
% of cases having chest imaging done within 12 months	79.6%
Lung malignancy cases diagnosed within 12 months	8
% potential diagnostic yield (as identified by looking at all imaging done within 12 months)	1.99%

Table 4: *Comparing community-acquired pneumonias' follow-up in the months of August 2013-2016 with the months of January 2013-2017*

	Januaries 2013-2017	**Augusts 2013-2016**
Number of Patients (*n*)	270	132
Number of Males	133	74
Patients over 80 years old	96	47
Patients 50-80 years olds	174	85
Follow-up imaging done (within 12 weeks)	147	67
% Follow-up done imaging within 12 weeks	54.4%	50.8%
Patients requiring admission	215	101
Follow-up done in admitted patients (within 12 weeks)	114	53
% 12 week follow-up rate in admitted patients	53.0%	52.5%
Follow-up Recommended by Radiologist	98	32
Follow-up done after Radiologist Recommendation (within 12 weeks)	59	17
% 12 week follow-up rate after Radiologist Recommendation	60.2%	53.1%
12 week follow-up in patients over 80 years old	46	27
% 12-week follow up in patients over 80 years old	47.9%	57.4%
12 week follow-up in patients 50-80 years old	101	40
% 12-week follow up in patients 50-80 years old	58.0%	47.1%
Number of males with a follow-up chest imaging within 12 weeks	72	38
%12-week follow up in males	54.1%	51.4%
Number of females with a follow-up chest imaging within 12 weeks	75	29
%12-week follow up in females	54.7%	50.0%
Lung malignancy cases diagnosed on follow-up of non-resolving lesions	4	3
% diagnostic yield on follow-up (i.e. number of patients diagnosed with lung malignancy compared to total number - *n*)	1.48%	2.27%
% of followed-up patients diagnosed with lung malignancy	2.72%	4.48%
Chest imaging done within 12 months	217	103
% of cases having chest imaging done within 12 months	80.4%	78.0%
Lung malignancy cases diagnosed within 12 months	5	3
% potential diagnostic yield (as identified by looking at all imaging done within 12 months)	1.85%	2.27%

***Figure 1**: Pie Charts showing follow-up rates within 12 weeks of chest radiographs with signs of a community acquired pneumonia according to whether or not repeat imaging was suggested by the reporting radiologist*

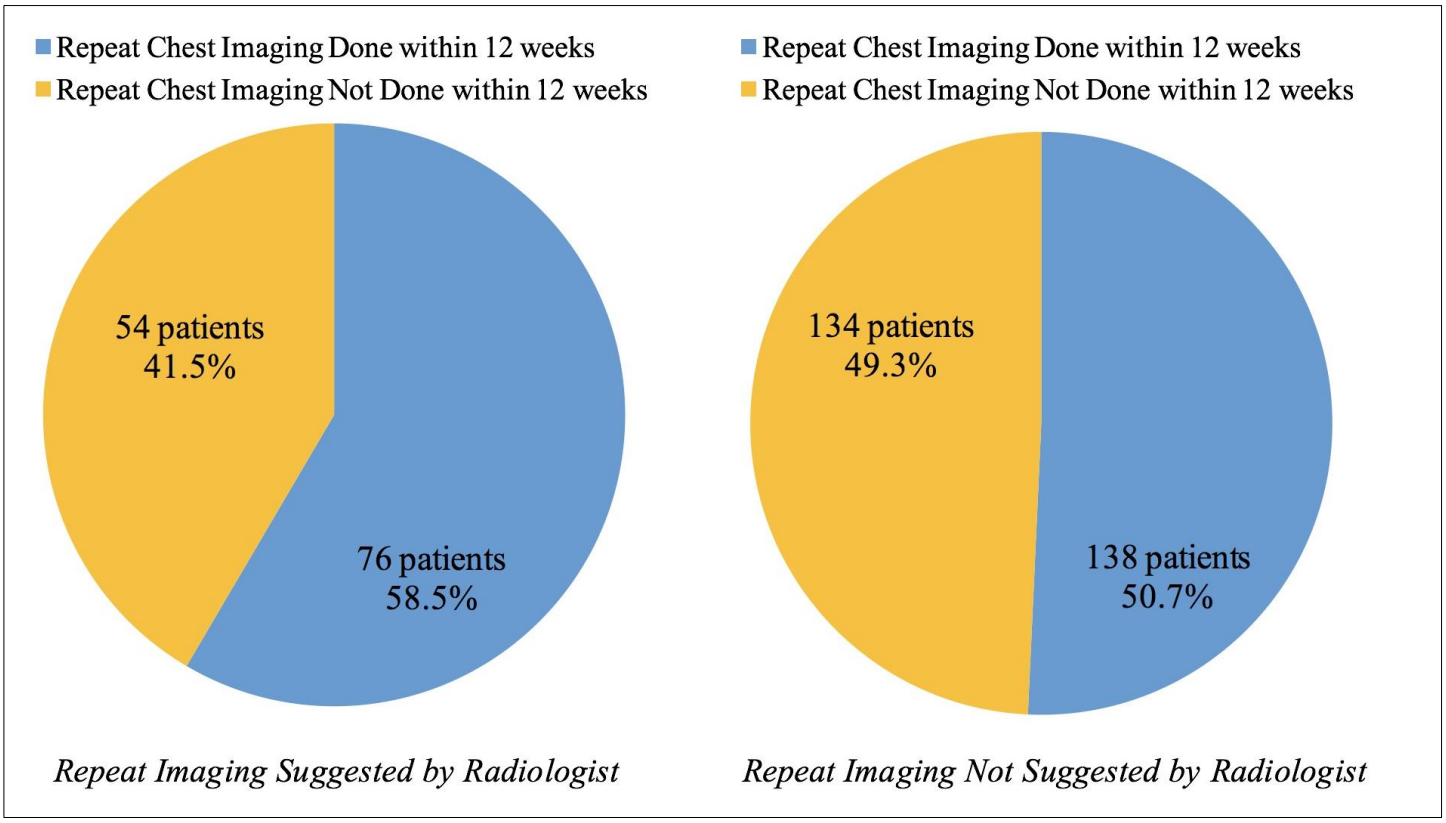

***Table 5:** Chi-Square Test (Pearson Chi-Square) to assess significance when comparing follow-up done within 12 weeks with the clinical predictors listed in the first column. None were statistically significant (i.e. p-values were all above 0.05)*

Pearson Chi-Square Test comparing 12 week follow-up rates with different predictors	
	Asymptotic Significance (2-sided) *p*-value
Gender (Male vs Female)	0.969
Month (January vs August)	0.487
Admission to Hospital (Admitted to Hospital vs Not admitted)	0.766
Follow-up Recommended by Radiologist	0.215
Unilateral vs Bilateral Pneumonia	0.775

Table 6: *The results when comparing 12 week follow-up rates according to the age*

Follow-up done within 12 weeks	Number of Patients	Mean Age (in years)
Y	188	74.34
N	214	74.05

T-Test For Equality of Means				
Significance (2-tailed)	Mean Difference	Std. Error Difference	95% Confidence Interval of Difference	
			Lower	Upper
.810	.284	1.181	-2.039	2.606

Table 7: *Detailed overview of the seven patients who were diagnosed with lung malignancy on follow-up within 12 weeks*

Patient	Month when initial CXR was done	Gender	Age (years)	Imaging Modality used for first follow-up	Histology	Lung Malignancy Stage & TNM classification on diagnosis[4]
1	January 2013	Male	73	CXR	Squamous Cell Carcinoma	T2b N3 M1a Stage IV
2	August 2013	Male	75	CXR	Adenocarcinoma	T4 N3 M1c Stage IV
3	August 2013	Male	75	CXR	Small Cell Carcinoma	T2a N2 M1c Stage IV
4	January 2014	Male	79	CXR	Small Cell Carcinoma	T4 N3 M1a Stage IV
5	January 2015	Male	69	CXR	Adenocarcinoma	T3 N0 M1c Stage IV
6	August 2015	Male	61	CT	Not available *	T1c N2 M0 Stage IIIA
7	January 2017	Male	67	CXR	Adenocarcinoma	T2 N2 Mo Stage IIIA

**No histology was obtained in this case; diagnosis of lung malignancy was only radiological.*

Figure 2: *Simple column chart showing distribution of the age of the patients who were diagnosed with a lung malignancy within 12 months after presenting with a community-acquired pneumonia*

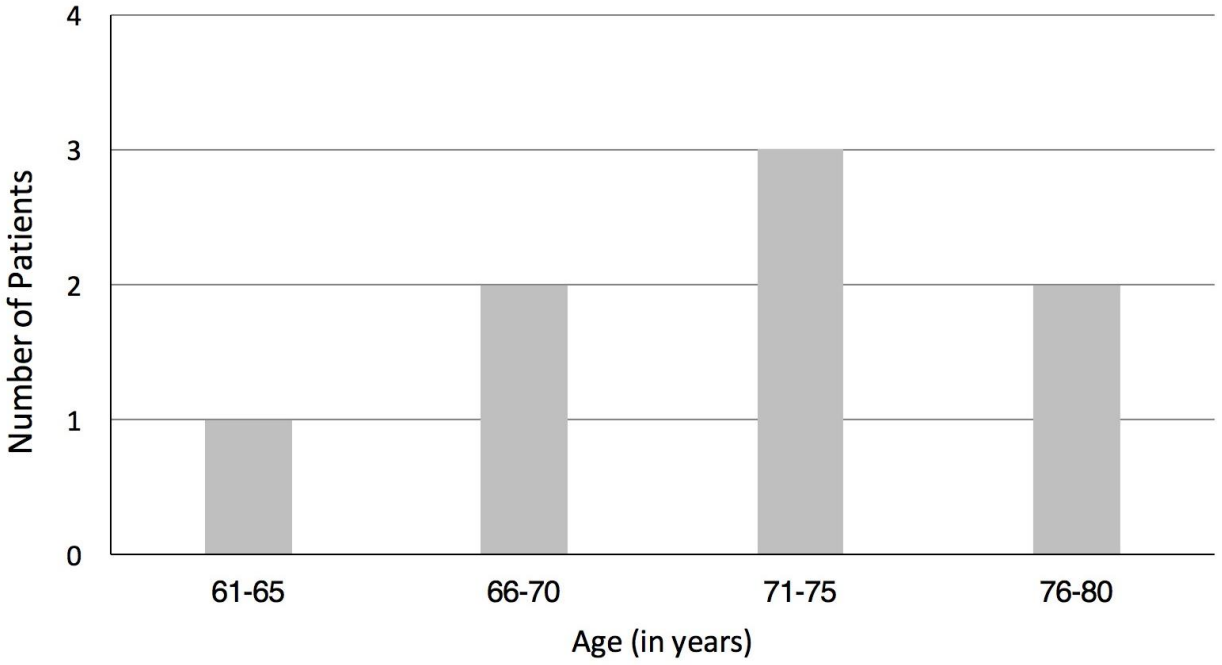

Table 8*: Detailed overview of the patients who were diagnosed with lung malignancy within 12 months after first chest radiograph. All patients had a smoking history*

Patient	Month when initial chest radiograph was done	Gender	Age (years)	Number of days after first chest radiograph when repeat chest imaging was done	Imaging Modality used for first follow-up	Histology
1	January 2013	Male	73	37 days	CXR	Squamous Cell Carcinoma
2	August 2013	Male	75	15 days	CXR	Adenocarcinoma
3	August 2013	Male	75	7 days	CXR	Small Cell Carcinoma
4	January 2014	Male	79	60 days	CXR	Small Cell Carcinoma
5	January 2015	Male	69	9 days	CXR	Adenocarcinoma
6	August 2015	Male	61	14 days	CT	Not available
7	January 2017	Male	67	25 days	CXR	Adenocarcinoma
8	January 2017	Female	80	283 days	CXR	Squamous Cell Carcinoma

Discussion

The most striking consideration from this study is that lung malignancy was diagnosed at a late stage during radiological follow-up of community acquired pneumonias. Using such a practice as a screening tool for lung malignancy is clearly inadequate from our data. None of the patients diagnosed with lung cancer on follow-up could reasonably be offered curative surgery as the most favourable lung cancer stage was IIIA. To our knowledge, no recent studies have been done delving into the actual stage of the lung cancer on diagnosis when following-up community acquired pneumonias.

Secondly, and equally as noteworthy, is the low diagnostic yield of lung malignancy on follow-up of community acquired pneumonias. Only 1.74% of patients who had follow-up chest imaging within 12 weeks were diagnosed with lung malignancy. This diagnostic yield did not vary significantly from the months of January to August.

53.2% of CAP patients were followed up with repeat imaging within 12 weeks, a figure that is similar to that in other studies.[5-7] This seems to suggest that multiple centres do not feel the need to adhere to guidelines such as those of the British Thoracic Society in each and every patient. The reason for this is likely multifactorial. Follow-up rate was however not affected by the presenting month, age and gender of the patients and neither by whether or not the patients were admitted, nor whether the radiologist suggested repeat imaging when reporting the first chest radiograph.

The fact that only one case of lung malignancy was diagnosed within one year in those patients who were followed-up within 12 weeks seems to suggest that physicians are picking up clinical clues that help choose which patients are most likely to benefit from repeat imaging. This study was unable to identify any such indicators.

Larger, prospective studies looking into multiple patient co-morbidities and demographics may help identify other, more specific clinical predictors that can better guide physicians to decide regarding follow-up imaging.

Limitations

This study had various limitations that one must point out. Firstly, the study was carried out retrospectively in a relatively small cohort. Similar studies have been carried out, however they are sporadic and thus, it was difficult to compare results. The clinical features on presentation, patient co-morbidities (apart from the presence of an active malignancy) and serology results that aid in the diagnosis of a pneumonia were not included in this study making it heavily reliant on radiologic findings.

Moreover, it was impossible to obtain proper smoking histories and detailed documentation from the patients' medical notes when they presented with the pneumonia. The reasons for this were several including the fact that a substantial cohort of patients have since passed away making access to their medical notes very difficult. Documentation outside Mater Dei Hospital, especially in the Health Centres, is also very sparse and not easily accessible.

Consolidations were identified only by three keywords on the radiograph report, thus the study was dependent on the report of the initial imaging. Only PACS software used in state-funded hospitals and health centres was analysed, meaning that follow-up imaging that could have potentially been done in the private sector or overseas was missed. This was mitigated to a certain extent by excluding patients without a Maltese fixed address.

Acknowledgments

We would like to particularly thank Prof Josef Lauri for his invaluable guidance during the statistical analysis of our data.

Conclusion

This study shows that, similar to other studies done in different centres, the follow-up rate locally of consolidations on chest radiographs in patients presenting from the community is low (53.2%). Why this is so is still unclear.

The diagnostic yield of lung malignancies on follow-up within 12 weeks in patients over 50 years of age is just 1.74%. When analysing all chest imaging done within one year in all the patients who fitted our inclusion and exclusion criteria, lung malignancy was diagnosed in 1.99%.

When lung malignancy *is* detected, the stage was always noted to be advanced, and hence inoperable and with a poor prognosis. Following up consolidations on chest radiographs in community acquired pneumonias is a poor screening tool.

Summary Box

1. The follow-up rate of chest radiographs in patients presenting with a community-acquired pneumonia is 53.2% within 12 weeks in state-run hospitals and health centres in the Maltese Islands.
2. Lung malignancy is diagnosed at a late stage when following up community-acquired pneumonias.
3. The diagnostic yield of lung malignancy when following up community-acquired pneumonias within 12 weeks is 1.74%.

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Original Article

The Maltese version of the DN4 Questionnaire. Initial Validation to Assess Neuropathic Pain in Patients with Chronic Spinal or Spinal-Radicular Pain.

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Abstract

Background: Neuropathic pain is frequently encountered in patients with spinal and spinal-related pain which needs specific treatment. Therefore, the objective of this study was to do an initial linguistic translation and validation of the Maltese DN4 questionnaire to diagnose neuropathic pain in this population.

Methods: The study was designed as a single-blinded, observational, prospective collected data and retrospective analysis. The English and French DN4 questionnaires underwent forward and backward translation, literal assessment and adaptation of the semantic equivalence into the Maltese language, followed by assessment of the Maltese DN4 during the initial patient assessment in patients who met the inclusion criteria.

Results: The total Maltese DN4 score obtained a Cronbach's alpha of 0.735 therefore having satisfactory internal consistency. Test-retest reliability yielded an intraclass correlation coefficient (95% CI) ranging from 0.975 to 0.991 (p<.001), while inter-rater reliability yielded an intraclass correlation coefficient (95% CI) ranging from 0.986 to 0.995 (p<0.001). Both the English and the Maltese DN4 questionnaires obtained the same sensitivity and specificity values of 0.422 and 0.941 respectively, and a positive likehood ratio of 7.153 and a negative likehood ratio of 0.614, at a cutoff score of 4.

Conclusion: The results of this study support the transcultural internal consistency, inter-rater, test-retest reliability, validity of the Maltese DN4 questionnaire to differentiate between neuropathic and nociceptive pain in patients with chronic spinal and spinal-radicular pain. Therefore, this simple tool can be used both in daily clinical practice but also in the clinical research setting to quickly screen for neuropathic pain.

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Keywords

Neuropathic pain, radiculopathy, validation studies, translations, back pain.

Introduction

The International Association for the Study of Pain (IASP) defined neuropathic pain (NP) as "pain caused by a lesion or disease affecting the somatosensory system."[1] According to the Douleur Neuropathique 4 questions (DN4)[2] and the Leeds Assessment of Neuropathic Symptoms and Signs (LANSS),[3] chronic NP was prevalent in 7–10% in the general population (van Hecke et al., 2014).[4] However, 40% of all patients attending German pain clinics had NP characteristics.[5] The bodily regions most affected by chronic NP were the neck and upper limbs, lower back, and lower limbs.[6]

NP tends to be refractory to pharmacological treatment including strong opioids[7] and it leads to a more reduced quality of life compared to nociceptive pain.[8] NP mechanisms are implicated in the etiology of leg pain caused by degenerative spinal changes since the compressed nerve roots show edema, fibrosis, demyelination and axonal degenerative changes in the affected neurons.[9] Therefore, diagnosing NP is crucial for the treatment of degenerative spinal disease. Classical questionnaires like the McGill Pain Questionnaire (MPQ)[10] and the Brief Pain inventory[11] are not sufficiently specific to diagnose NP, although the NP descriptors included in the MPQ may have a diagnostic value. This led to the formulation of NP-specific diagnostic tools, e.g., Neuropathic Pain Scale, LANSS, the Neuropathic Pain Questionnaire, the Pain Detect, ID-pain, and the DN4.

The DN4 questionnaire was developed by the French Group of Neuropathic Pain to diagnose NP. In their initial validation study subjects with spinal and spinal radicular pain were not included.[2] The DN4 was derived from a list of signs and symptoms associated with NP, and it includes a series of four groups of questions consisting of seven sensory descriptors and three signs related to sensory examination. Each of the ten questions has a nominal scale with two possible responses (yes or no) and the total score was generated by summing the binary scores of all the ten items. A cutoff score of 4 yielded a specificity of 89.9% and a sensitivity of 82.9, correctly identifying 86% of the patients with NP. However, the principal limitation of this study was that the gold standard diagnosis of NP was made by the investigators themselves.[2] Afterwards, the DN4 was validated in low back pain (LBP) patients due to herniated discs, spinal stenosis, degenerative disc disease, degenerative lumbar spine, and lumbar scoliosis. 23% of the subjects had a previous spinal surgery which included discectomy, chemonucleolysis, laminectomy, and lumbar arthrodesis. The DN4 obtained a sensitivity of 80% and a specificity of 92%, however the gold standard diagnosis of NP was made by the physicians.[12]

Another study compared the DN4, PainDETECT, LANSS, and the Neuropathic Pain Questionnaire and found that the DN4 was the most sensitive of the four questionnaires [13]. Similarly, a systematic review found that the DN4 and Neuropathic Pain Questionnaire were the most suitable for clinical use.[14] This systematic review stated that the DN4 is a simple and objective instrument with an easy scoring method which consists of a relatively small number of items but highly capable of discriminating between NP and nociceptive pain.

Therefore, the objective of this study was to do an initial linguistic translation and validation of the Maltese DN4 questionnaire to diagnose NP in chronic spinal and spinal-radicular pain. The Maltese DN4 is expected to have a similar diagnostic efficacy when compared to the English DN4 version.

Materials and Methods

Setting

The study was approved by the research and ethics board at the Rehabilitation Hospital Karen Grech, Malta. The authors of the DN4 Questionnaire authorized its validation to the Maltese language. The study was designed as a single-blinded, observational, prospective collected data and retrospective analysis. The principal interviewer (ES) knew the patient's diagnosis, but the patients were not aware that the objective of the questionnaire was to distinguish between NP and nociceptive pain, therefore obtaining a single blind. Data collection was performed within the Musculoskeletal Physiotherapy Outpatients Department at the Rehabilitation Hospital Karin Grech during the period September to December 2018. The DN4 questionnaire results were collected during the initial physiotherapy assessment for patients referred from Mater Dei Hospital due to chronic spinal or spinal-radicular pain. Signed informed consent was obtained from the patients.

Sample

The inclusion criteria were patients of both

sexes 1) above 18 years of age; 2) visiting the Musculoskeletal Physiotherapy Outpatient's facilities for chronic spinal and/or spinal-radicular pain; 3) with a pain duration of ≥3 months; 4) with moderate or severe pain intensity [scoring 4 or higher on the current pain Numeric Rating Scale (NRS) for spinal or spinal-radicular pain].

Patients were excluded if they had other severe musculoskeletal pain, major comorbidity (e.g., malignant disorders or sepsis), pain of unknown origin, fibromyalgia, complex regional pain syndrome, headache, visceral pain, severe alcoholism or substance abuse, cognitive impairment or intellectual disability, severe depression or psychosis and if unable to understand the questions.

Stages of validation

The validation process of the DN4 questionnaire to the Maltese language was instituted from the original French and English versions, and it consisted of 4 distinct stages: 1) Translation; 2) Retranslation; 3) Literal assessment and adaptation of the semantic equivalence; and 4) Assessment of the target population with the final instrument, according to the previously established methodology.[15]

First Stage- Translation

The first stage consisted of translating the original French DN4 questionnaire by a University Professor in French translations to the Maltese language. Separately, the English DN4 (Appendix 1) was translated by a University Professor in English translations to the Maltese language. The two versions obtained after the translations were simultaneously evaluated by the authors and resulted in one merged version that was submitted to the retranslation process.

Second Stage- Retranslation

The initial Maltese DN4 version was retranslated into the French and into the English language by the respective Professors who carried out the initial translation. Alterations in the initial Maltese DN4 version were conducted at this stage.

Third Stage- Literal assessment and semantic equivalence

The literal assessment and adaptation of semantic equivalence was performed by the authors, all of whom had complete mastery of the Maltese language and understanding of the terms related to this area. The Maltese DN4 version obtained by the retranslation process was compared with the original French and English versions, considering whether the questions were rewritten with the same words (literal assessment) or whether the original meaning had been retained (semantic equivalence). This initial Maltese DN4 questionnaire was pilot tested in a sample of 10 patients with chronic spinal and/or spinal-radicular pain from different social classes and from various educational backgrounds. They answered the first seven questions of the Maltese DN4, inquiring about their understanding of each item. The last three questions of the Maltese DN4 tool, regarding the sensory examination, were not tested at this point. The same was carried out with a group of 5 health professionals at university level, who deal with pain patients. In addition to answering the questions about the degree of understanding, these professionals suggested the use of better terms that could have been applied.

Fourth Stage- Maltese DN4 testing and the 2016 International Association for the Study of Pain NP grading system in the target population

The linguistic validation of the Maltese DN4 questionnaire (Appendix 2) was performed on a sample of 62 patients who met the inclusion and exclusion criteria in order to assess the capacity of the instrument to distinguish nociceptive from NP in chronic spinal and spinal-radicular pain. At this stage a verbal NRS, ranging from zero (no pain) to 10 (maximum pain) and a body chart to document pain location were used.

In the initial physiotherapy assessment, the investigator (ES) asked each patient to describe his/her pain according to the seven NP descriptors using the Maltese DN4 questionnaire. Afterward, the same investigator carried out the sensory examination using a SENSELab Brush-05 (Somedic SenseLab AB, Sösdala, Sweden) to assess for hypoesthesia to brushing and brush allodynia while a 5.1g Semmes-Weinstein monofilament (Baseline Tactile Monofilaments, New York, USA) was used to assess hypoesthesia to fine tactile stimuli, as carried out in the original DN4 validation study.[2] Two repetitions of each of the three sensory tests were performed in the most painful area and compared to the corresponding contralateral aspect. In case of an inconsistent result

between the two test repetitions, the result for the specific testing modality was scored as a normal response.

At the end of the assessment, the investigator (ES) asked the patient to describe his/her pain using the first seven NP descriptors of the English DN4. This approach has been chosen because although a 1-2-day gap would have been ideal to reduce memory bias, however calling the patient back in 1-2 days for the purpose of this study was not feasible within the departmental setting. On the other hand, if the English DN4 examination was carried out 1-2 weeks after the Maltese DN4 exam, there was the possibility that the pain could have changed as a consequence of the physiotherapy treatment or analgesics, thus introducing a bias. For inter-rater reliability, the Maltese DN4 questionnaire was re-administered after the English DN4 exam in all of the subjects (n=62) by a research assistant, blinded to the diagnosis proposed by the principal investigator (ES). To assess test retest reliability, the Maltese DN4 questionnaire was re-administered in all of the subjects (n=62), 2 weeks after the first assessment by the principal investigator. Between the two visits, patients were allowed to take analgesic medications as prescribed by their medical consultant. A score for each positive (1) or negative item (0) was set for all the Maltese and the English DN4 items and the diagnosis of NP was made for a total score equal or larger than 4.

The gold standard diagnosis of NP was based on the medical history, physical exam, electromyography and/or imaging exams as advocated by the IASP NP grading system and each patient was graded as "unlikely NP", "possible NP", "probable NP" and "definite NP".[16] The methodology adopted by Hasvik et al.,[17] specific to using the IASP NP grading system in spinal and spinal-radicular pain was adopted for the purpose of this study.

Statistical analysis

The Cronbach's alpha was used to assess internal consistency thereby examining the contribution of each individual item measured by the Maltese DN4. Cronbach's alpha was first assessed for the complete questionnaire; then, each item was removed to assess the independent contribution of each item to the measurement error of the instrument. Moreover, to verify the validity of the DN4 items, factor analysis was used where principal component analysis was used for the extraction method and Varimax with Kaiser Normalization was used for the rotation method. The Kaiser-Meyer-Olkin (KMO) Measure and Bartlett's Test of Sphericity were conducted to determine whether the data had factorial validity. To verify the agreement between each individual item of the Maltese DN4 and the English DN4 questionnaires, the Cohen Kappa was used because these items had a nominal scale (yes or no). Since the scores had a metric scale, the Intraclass correlation coefficient (ICC) was used to assess inter-rater reliability and measure the agreement of the results obtained by two different raters for each item and for the total score of the DN4 questionnaire in all of the subjects (n=62). The test-retest reliability was assessed by comparing the initial and the second Maltese DN4 examination by the same investigator (ES) at two weeks in all of the subjects (n=62), by using the ICC. Receiver-operator characteristics (ROCs) analysis was carried out to assess the sensitivity and specificity of both the English and Maltese DN4 total scores in distinguishing patients who had NP defined by the IASP gold standard diagnosis. All statistical analyses were performed by using the SPSS version 25 statistics package (SPSS Inc., Chicago, IL, USA). In all statistical analysis, a 0.05 level of significance was adopted, where p-values less than 0.05 criterion indicated statistical significance. Item 10 of both the Maltese and the English DN4 was removed from the statistical analysis since no subject reported positive to this item.

Results

Sample description

Figure 1. provides a flow diagram of the participants. The baseline demographic and descriptive data of the 62 participants who took part in the study is presented in table 1. Overall, the subjects were composed of 51.61% males and 48.39% females. The completion rate was 53.9%. Patients with NP showed a significant higher mean current NRS (p<0.001) and highest NRS score (p<0.016) compared to the subjects with nociceptive pain. The most common causes for NP were spinal stenosis and spinal surgery, whilst a degenerative spine was the most common cause for nociceptive pain.

***Figure 1**: Flow diagram of the participants in the study*

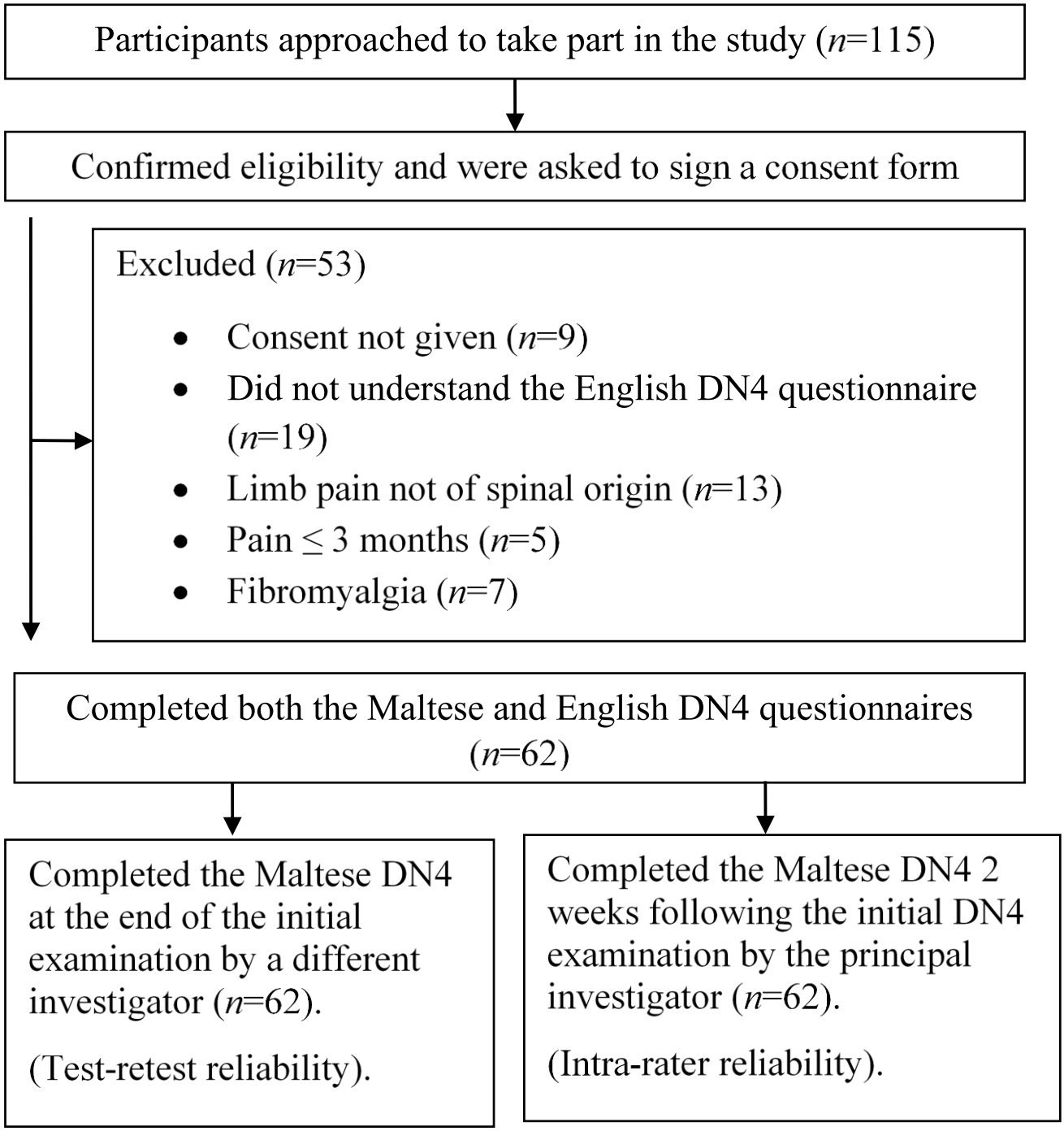


***Table 1**: Descriptive statistics of the subjects in the study*

	Neuropathic pain according to the DN4 (score > 4) (*n*=20)	**Nociceptive pain according to the DN4 (score < 4) (*n*=42)**	***P*-value (p <0.05)**
Number of subjects with lumbar related pain	18	36	
Number of subjects with cervical related pain	2	6	
Number of subjects who had undergone previous spinal surgery	6	4	
Mean age (years) (range)	56.5 (18-81)	60.0 (35-83)	0.338
% female	60%	54%	
Current number of analgesic drug classes consumed (range)	0.90 (0-3)	0.93 (0-3)	0.914
Mean lowest NRS (range)	3.20 (0-8)	2.02 (0-9)	0.073
Mean current NRS (range)	7.40 (4-10)	5.43 (4-10)	<0.001
Mean highest NRS (range)	9.20 (8-10)	8.19 (5-10)	0.016
Mean years with spinal pain	5.88 (3months-17years)	5.81 (3 months-50 years)	0.978
Mean Maltese DN4 interview score (score out of 7)	3.80 (3-7)	0.93 (0-3)	<0.001
Mean total Maltese DN4 score (score out of 10)	5.10 (4-8)	1.27 (0-3)	<0.001
Spinal pathologies on MRI	Stenosis *n*=6 Spinal surgery *n*=6 Disc herniation *n*=5 Degenerative spine *n*=3	Degenerative spine *n*=10 Disc herniation *n*=9 Stenosis *n*=9 Spondylolisthesis *n*=6 Spinal surgery *n*=4 Myofascial origin *n*=3 Modic changes *n*=1	
Two-tailed tests were carried out assuming a 0.05 level of significance.			

In addition, both the mean Maltese DN4 interview score and the total Maltese DN4 score were significantly higher (p<0.001) in the NP population. The predominant presenting symptom in the nociceptive pain group as graded by the Maltese DN4 was axial LBP, while in the NP group it was leg pain. The two most commonly mentioned Maltese DN4 NP descriptors for spinal and spinal-radicular pain were items 1. Ħruq (75%) and 5. Tingiż (75%) (table 2). No adverse events occurred due to the administration of both the English and the Maltese DN4 questionnaires.

Validity of the items in the instrument

Factor analysis

The data has factorial validity if the Kaiser Meyer Olkin (KMO) value exceeds the 0.5 threshold value, and the Bartlett's p- value is less than the 0.05 level of significance. In this data set, both criteria are satisfied indicating that factor analysis is essential. The scree plot (figure 2) can be used to identify the number of dimensions (factors) in a data set. In this particular data set, the scree elbow occurs at the third component indicating that the first two dimensions (factors) should be retained, where their eigenvalues (2.937 and 1.485) both exceed the threshold value 1. Moreover, these dimensions explain 49.134% of the total variation in the data (table 3). The vast majority of the Correlation Coefficients are positive indicating that participants scoring high in one item tend to score high on the others (table 4).

Factor loadings

The factor loadings (table 5) show that the first seven items are loading heavily on dimension 2, while items 8 and 9 are loading heavily on dimension 1.

Internal consistency, inter-rater reliability and test-retest reliability

The Cronbach's alpha measures the internal consistency between the related items, and it ranges from 0 to 1. A Cronbach's alpha above 0.7 indicates satisfactory internal consistency between the items. The Maltese DN4 questionnaire obtained a Cronbach's alpha of 0.735 exceeding the 0.7 threshold value indicating satisfactory internal consistency between the items and the vast majority of the inter item correlations are positive. Moreover, the Cronbach's alpha decreases when an item is removed, particularly item 4. Tnemnin, item 5. Tingiż and item 6. Stat imtarrax (table 6). This indicates that these three items contribute most to the internal consistency of the items and have the largest impact when measuring NP in spinal and spinal-radicular pain. On the other hand, the Cronbach's alpha increases slightly when removing item 2. Kesħa li tweġġa', indicating that this item contributes least to the internal consistency of the items and has lowest impact when measuring NP of spinal origin.

Table 2: *Maltese DN4 responses: Pain descriptors and the sensory examination*

Maltese DN4 item	Number of times mentioned (% of those who were diagnosed with NP by the Maltese DN4) (n=20)
1. Ħruq	15 (75%)
2. Kesħa li tweġġa'	2 (10%)
3. Xokkijiet	11 (55%)
4. Tnemnim	14 (70%)
5. Tingiż	15 (75%)
6. Stat imtarrax	14 (70%)
7. Ħakk	5 (25%)
8. Hypoesthesia malli tmissha	12 (60%)
9. Hypoesthesia mat-tingiz	14 (70%)
10. Ibbraxxjar	0 (0%)

Figure 2: *Scree plot*

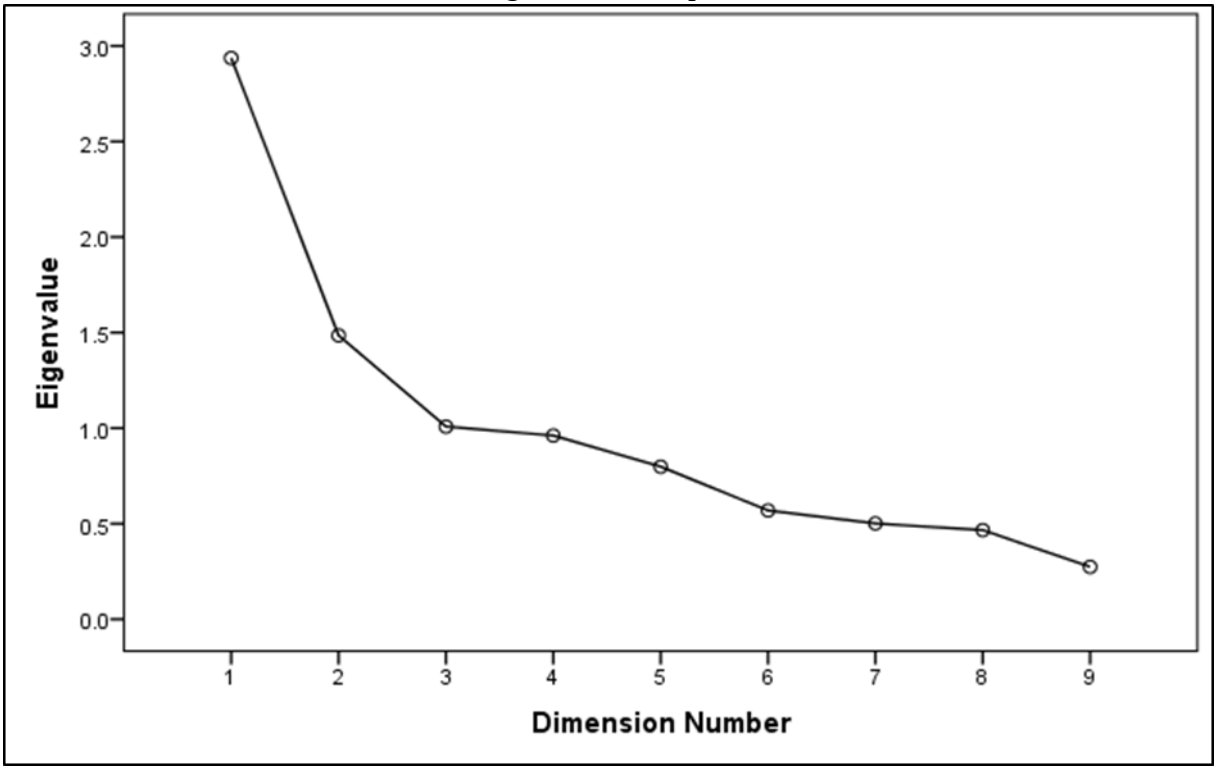


Table 3: *Total Variance Explained*

Dimension	Initial Eigenvalues			Rotation Sums of Squared Loadings		
	Total	% of Variance	Cumulative %	Total	% of Variance	Cumulative %
1	2.937	32.633	32.633	2.272	25.246	25.246
2	1.485	16.501	49.134	2.150	23.888	49.134

Table 4: *Inter-Item Correlation Matrix*

	Ħruq	Kesħa li tweġġa’	Xokkijiet	Tnemnin	Tingiż	Stat imtarrax	Ħakk	Hypoesthesia malli tmissha	Hypoesthesia mat-tingiż
Ħruq	1.000	0.043	0.245	0.197	0.393	0.168	0.176	0.357	0.121
Kesħa li tweġġa’	0.043	1.000	0.015	0.061	0.266	0.186	0.198	-0.032	-0.058
Xokkijiet	0.245	0.015	1.000	0.363	0.249	0.421	0.172	0.227	0.083
Tnemnin	0.197	0.061	0.363	1.000	0.367	0.427	0.330	0.190	0.380
Tingiż	0.393	0.266	0.249	0.367	1.000	0.343	0.411	0.191	0.268
Stat imtarrax	0.168	0.186	0.421	0.427	0.343	1.000	0.319	0.238	0.352
Ħakk	0.176	0.198	0.172	0.330	0.411	0.319	1.000	-0.032	-0.058
Hypoesthesia malli tmissha	0.357	-0.032	0.227	0.190	0.191	0.238	-0.032	1.000	0.531
Hypoesthesia mat-tingiż	0.121	-0.058	0.083	0.380	0.268	0.352	-0.058	0.531	1.000

Table 5: *Factor Loadings*

	Dimension	
	1	2
Ħruq		0.303
Kesħa li tweġġa’		0.547
Xokkijiet		0.407
Tnemnin		0.493
Tingiż		0.667
Stat imtarrax		0.538
Ħakk		0.774
Hypoesthesia malli tmissha	0.806	
Hypoesthesia mat-tingiż	0.807	

Table 6: *Cronbach`s Alpha to the items of the instrument*

	Item-Total Statistics
	Cronbach's Alpha if the Item is Deleted
1. Ħruq	0.719
2. Kesħa li tweġġa’	0.745
3. Xokkijiet	0.712
4. Tnemnin	0.689
5. Tingiż	0.687
6. Stat imtarrax	0.685
7. Ħakk	0.727
8. Hypoesthesia malli tmissha	0.711
9. Hypoesthesia mat- tingiż	0.713

Table 7*: Cohen Kappa values for each item of the Maltese DN4*

Item	**Kappa Value**	***P*-Value**
1. Ħruq	1.00	<0.001
2. Kesħa li tweġġa’	1.00	<0.001
3. Xokkijiet	1.00	<0.001
4. Tnemnin	0.756	<0.001
5. Tingiż	0.633	<0.001
6. Stat imtarrax	0.796	<0.001
7. Ħakk	0.880	<0.001
8. Hypoesthesia malli tmissha	1.00	<0.001
9. Hypoesthesia mat- tingiż	1.00	<0.001
10. Ibbraxxjar	1.00	<0.001

Table 8*: Inter-rater agreement of the Maltese DN4*

		Rater 2		
		Positive	Negative	Total
Rater 1	Positive	20	0	20
	Negative	0	42	42
Total		20	42	62

Table 9: *Test-retest of the Maltese DN4*

		Rater 1 (retest)		
		Positive	Negative	Total
Rater 1 (test)	Positive	20	0	20
	Negative	1	41	42
Total		21	41	62

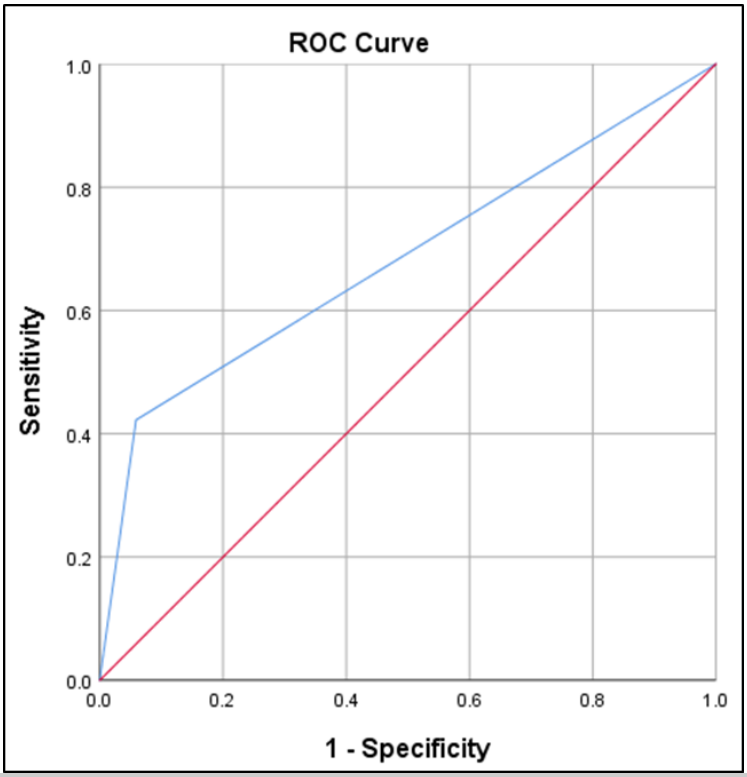
Table 10: *Agreement in the diagnosis of NP between the Maltese DN4 and the English DN4 total score*

		DN4 (English version)		
		Positive	Negative	Total
DN4 (Maltese version)	Positive	20	0	20
	Negative	0	42	42
Total		20	42	62

Table 11*: Agreement between the Maltese DN4 and the clinical classification based on the International Association for the Study of Pain (IASP) grading system*

		IASP NP Grading System		
		Positive	Negative	Total
DN4 (For both the Maltese and English versions)	Positive	19	1	20
	Negative	26	16	42
Total		45	17	62

Figure 3*: Receiver operating characteristic (ROC) curve and area under curve (AUC) for the total score of the English/Maltese DN4 questionnaire. Either tools obtained a sensitivity of 0.422 and a specificity of 0.941 at a cut off score of ≥4. Both the Maltese and the English DN4 obtained a positive likehood ratio of 7.153 and a negative likehood ratio of 0.614.*



The Cohen Kappa was used to measure the reliability between each item of the Maltese and the English DN4 questionnaires. There was satisfactory agreement between each individual item of the Maltese and the English DN4 tools, ranging from 0.633 to 1.00 (p<0.001), with six out of the ten Maltese DN4 items obtaining a Kappa score of 1.00 (p<0.001) (table 7).

Inter-rater agreement for the total Maltese DN4 score (table 8) was very good, having an ICC (95% CI) ranging from 0.986 to 0.995 (p<0.001) (n=62). At an interval of 2 weeks, the test-retest ICC (95% CI) for the total Maltese DN4 score ranged from 0.975 to 0.991 (p<0.001) (n=62) (table 9).

Psychometric validation

According to the IASP grading system of the 62 cases assessed, 22 (35.5%) were classified as having "definite" NP, 23 (37.1%) were classified as having "probable" NP, 9 (14.5%) were classified as having "possible" NP, and 8 (12.9%) who did not have NP according to the IASP NP grading system. The current study adopted the methodology of Abdallah et al.,[18] were a DN4 score of ≥4 was comparable to a IASP NP grading of "probable" and "definite" NP, while a DN4 score of ≤3 was comparable to a IASP grading of "possible" or the "absence" of NP. Therefore the 4 categories of the IASP grading system were grouped into 2 sections.

There was perfect agreement between the English and the Maltese DN4 questionnaires in classifying subjects with either NP or nociceptive pain (table 10). Therefore, when compared to the gold standard IASP NP grading system, both the English and the Maltese DN4 questionnaires obtained the same sensitivity and specificity values of 0.422 and 0.941 respectively, at a cutoff point of 4 (table 11) (figure 3). The area under the ROC curve (0.682) was significantly larger than the 0.5 threshold value since the p-value (0.028) is less than the 0.05 level of significance. Moreover, the 95% CI of the area under the ROC curve ranges between 0.546 and 0.818, which excludes the 0.5 threshold value (figure 3). Both the Maltese and the English DN4 obtained a positive likehood ratio of 7.153 and a negative likehood ratio of 0.614.

Discussion

This study provided the initial validation of the Maltese DN4 questionnaire for assessing NP of chronic spinal and spinal-radicular pain and it also found that the English and the Maltese DN4 possess a similar diagnostic power. In fact, there was perfect agreement between the final score between of the English and Maltese DN4 questionnaires in diagnosing patients with NP.

Until the present day there was no specific pain questionnaire in the Maltese language that was capable of distinguishing between NP and nociceptive pain. On the other hand, Dr. Gatt should be accredited with performing the translation of the MPQ, a first for the Maltese language.[19] The NP descriptors in the original MPQ can have a diagnostic value for NP, however more specific questionnaires like the DN4 thanks to its sensory examination can diagnose NP better. There are several similarities and differences in comparing the Maltese DN4 to the Maltese MPQ by Dr. Gatt. Items 1. Ħruq, 3. Xokkijiet and 4. Tnemnin of the Maltese DN4 are also present in the Maltese MPQ. Interestingly, item 6. Numbness of the English DN4 was translated to 6. Stat imtarrax in the Maltese DN4 and to "Torqodlok" in the Maltese MPQ. This portrays the similarity in meaning of certain Maltese words. Item 5. Tingiż of the Maltese DN4 was not mentioned in the Maltese MPQ, while item 2. Kesħa li tweġġa' was referred to as "kiesah silg" in the Maltese MPQ. Even though these have a similar meaning in Maltese, the former adds a painful dimension, while the wording in the MPQ does not imply pain, but rather an intense cold.

In the analysis of internal consistency, each of the seven Maltese NP descriptors obtained very good Cohen Kappa values (range 1.00-0.633, p<0.001) compared to the English DN4 indicating similarity in meaning between the individual terms whilst underlying the importance of each item of the questionnaire. The bilingual aspect of the Maltese population probably contributed for the Maltese DN4 questionnaire to obtain the excellent Cohen Kappa values in this translation. In addition, both the Maltese and the English DN4 versions categorized the subjects in an identical way. The test-retest and the intra-rater reliabilities of the Maltese DN4 were satisfactory. Therefore, the DN4 is considered stable over time and between different examiners. In the analysis of the reproducibility of the instrument, it was observed that the group of health professionals had a greater understanding of the Maltese DN4 questionnaire, which is justified by their knowledge and familiarity with the terms used in the DN4. A number of the patients

presented with difficulties in understanding some of the items, which is reasonable considering the lower educational background of this population compared to the health professionals.

The sensitivity of both the English and Maltese versions was low compared to the original DN4 validation study, while the specificity was higher. The low sensitivity for both English and Maltese DN4 versions could be due to linguistic specificities, cultural differences, the methodology of the study and the pathology under investigation. However, most importantly, contrary to previous DN4 translations which used the physician's or the examiner's NP diagnosis, this study adopted the objective IASP NP grading system as the gold standard to diagnose NP, therefore altering the sensitivity and the specificity of the DN4 compared to its initial validation study. Also, in the original developmental study of the DN4 patients with spinal and spinal-radicular pain were excluded. Nonetheless the high specificity and a positive likehood ratio of 7.153 of both tools, makes the DN4 as a valid and quick screening tool for diagnosing NP.

Furthermore, there is a growing body of evidence showing that the sensitivity of the DN4 varies with the underlying condition. In subjects with failed back surgery syndrome the sensitivity of the DN4 was 62%[20], in cervical or lumbar radiculopathy it was 76%[21] and 80% in subjects with LBP radiating to the lower limbs.[12]

Recently, VanDenKerkhof et al.,[22] found that the sensitivity of the DN4 was 72.1% in lumbosacral radiculopathy. However, in this study the gold standard diagnosis of NP was not explicitly provided but the terms used in the IASP grading system including "no", "possible", "probable" and "definite" were used. However, a limitation of this study is that all the study subjects had a previous diagnosis of NP thus increasing the sensitivity compared to what would be obtained in a sample of patients with heterogeneous pain, like in our study. According to VanDenKerkhof et al.,[22] the most commonly mentioned NP descriptors for lumbosacral radiculopathy were item 6. Numbness (88%), item 1. Burning (70%) and item 4. Tingling (70%). In the general, the three most common NP descriptors were ongoing burning pain (65.4%), paroxysmal electric shock-like pain (57.0%) and brush-evoked pain (54.9%)[23], with most patients reporting a coexistence of heterogeneous sensory signs and symptoms.[24] In the current Maltese sample, item 1. Ħruq (75%) and item 5. Tingiż (75%) of the Maltese DN4 were the most prevalent NP descriptors used in cases of subjects with NP.

Weakness and strength of the study

The current study included only patients with chronic spinal or spinal-radicular pain for the validation of the Maltese DN4 questionnaire This unique feature, however, poses certain limitations on the generalizability to other NP conditions which can be assessed using the DN4. Thus, this is one of the main limitations of this study.

One of the strengths of this study compared to previous DN4 translations into other languages is the adoption of the IASP NP grading system as the gold standard. Previous translations have adopted either the physicians´ or an expert or the investigators´ NP diagnosis as the gold standard, therefore introducing a subjective bias and potentially overestimating the diagnostic power of the DN4. Contrarily, the criteria proposed by the IASP system are objective and reproducible therefore limiting bias. Another strength of the current study is the adoption of the same inclusion and exclusion criteria as those used in the development study of the original DN4 questionnaire.

Conclusion

The results of this study support the transcultural internal consistency, inter-rater, test-retest reliability and validity of the Maltese DN4 questionnaire to differentiate between NP and nociceptive pain in patients with chronic spinal and spinal-radicular pain due to degenerative spinal disease. Therefore, this simple tool can be used both in daily clinical practice but also in the clinical research setting.

Summary box

What is already known about this subject:

- A significant proportion of spinal and spinal-radicular pain has a neuropathic pain component.
- The IASP grading system is considered the gold standard for diagnosing NP.
- Considering that the grading system can be a lengthy procedure, diagnostic questionnaires like the DN4 can quickly screen for

neuropathic pain in the busy clinical setting.

What are the new findings:

- The Maltese version of the DN4 has the same diagnostic powers as the English DN4 in chronic spinal and spinal-radicular pain.
- Both the English and the Maltese DN4 are quick to administer and easy to score.
- Contrarily to previous studies, which used the physicians´ diagnosis of NP as the gold standard, both the English and the Maltese DN4 exhibited a lower sensitivity but an excellent specificity in diagnosing NP when compared to the IASP NP grading system.

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Appendix 1. DN4 Questionnaire

Please complete this questionnaire by ticking one answer for each item in the 4 questions below:

INTERVIEW OF THE PATIENT

Question 1: Does the pain have one or more of the following characteristics?

	Yes	No
1 – Burning	___	___
2 – Painful cold	___	___
3 – Electric shocks	___	___

Question 2: Is the pain associated with one of more of the following symptoms in the same area?

	Yes	No
4 – Tingling	___	___
5 – Pins and needles	___	___
6 – Numbness	___	___
7 – Itching	___	___

EXAMINATION OF THE PATIENT

Question 3: Is the pain located in an area where the physical examination may reveal one or more of the following characteristics?

	Yes	No
8 – Hypoesthesia to touch	___	___
9 – Hypoesthesia to prick	___	___

Question 4: In the painful area, can the pain be caused or increased by:

	Yes	No
10 – Brushing	___	___

The total score is calculated as the sum of the 10 items and the cut-off value for the diagnosis of neuropathic pain is a total score of 4/10.

Bouhassira D, Attal N, Alchaar H, et al. "Comparison of pain syndromes associated with nervous or somatic lesions and development of a new neuropathic pain diagnostic questionnaire (DN4)." Pain 114.1-2 (2005): 29-36.

Appendix 2. Il-Kwestjonarju DN4

Jekk jogħġbok kompli dan il-kwestjonarju billi tittikkja tweġiba waħda għal kull parti f'dawn l-4 mistoqsijiet li ġejjin:

L-Intervista lill-Pazjent/a

L-ewwel mistoqsija: L-uġigħ għandu xi waħda, jew aktar, minn dawn il-karatteristiċi?

	IVA	LE
1. Ħruq	___	___
2. Kesħa li tweġġa'	___	___
3. Xokkijiet	___	___

It-tieni mistoqsija: L-uġigħ marbut ma' wieħed, jew aktar, minn dawn is-sintomi fl-istess naħa?

	IVA	LE
4. Tnemnim	___	___
5. Tingiż	___	___
6. Stat imtarrax	___	___
7. Ħakk	___	___

L-Eżami tal-Pazjent/a

It-tielet mistoqsija: L-uġigħ jinsab f'naħa fejn l-eżami fiżiku jista' jikxef waħda, jew aktar, minn dawn il-karatteristiċi?

	IVA	LE
8. Hypoesthesia malli tmissha	___	___
9. Hypoesthesia mat-tingiż	___	___

Ir-raba' mistoqsija: Fin-naħa li tuġgħek, jista' l-uġigħ ikun ġej jew jiżdied minn

	IVA	LE
10. Ibbraxxjar?	___	___

L-iskor totali huwa kkalkulat mill-għadd ta' dawn l-10 *items* il-valur li jimmarka l-limitu għad-dijanjosi tal-uġigħ newropatiku huwa skor totali ta' 4/10.

TOTAL

_____

Bouhassira D., et al, "Comparison of pain syndromes associated with nervous or somatic lesions and development of a new neuropathic pain diagnostic questionnaire (DN4)". *Pain* 114.1-2 (2005): 29-36.

Original Article

Addressing the need for an adult allergy clinic in Malta

Caroline Gouder, Patrick Sammut, Stephen Montefort

Abstract

The incidence of allergy is globally on the increase. Allergology is a relatively new speciality with rapidly growing needs. Many patients have co-existent allergic conditions including asthma, eczema, allergic rhinitis, food and drug allergy. It is recommended internationally that patients suffering from allergic conditions including anaphylaxis are investigated, treated and followed up by an allergy specialist in a safe environment with resuscitation facilitations readily available, especially when certain investigations are performed. This article highlights the importance of the need for such an allergy service for adult patients at Mater Dei Hospital, in patients with new onset or previously undiagnosed allergic conditions as well as transition of care from paediatric services, with the intention of performing specialist investigations, providing optimal expert management to allergy sufferers locally whilst improving patients' quality of life. A multidisciplinary team approach would further improve this service.

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Key Words

Allergy service, adults, Malta

Introduction

Allergy is a form of exaggerated sensitivity (hypersensitivity) to a substance which is either inhaled, swallowed, injected, or comes into contact with the skin, eye or mucosa. The term 'allergy' is used for situations where hypersensitivity results from heightened (or 'altered') reactivity of the immune system in response to external or 'foreign' substances. Foreign substances that provoke allergies are called allergens.[1]

The incidence and prevalence of allergic diseases has been steadily increasing globally.[2] In Western countries the prevalence of respiratory allergies (asthma and allergic rhinitis) has stabilized[3] while the prevalence of food allergy has shown a consistent increase.[4] Developing countries on the other hand have shown a sustained increase in all types of allergies, in children and young adults.[3,5]

While the prevalence of allergic disease has increased, many countries have struggled to develop dedicated allergy services in line with demand, while in others still, the specialty is not established. And it is not just the overall prevalence of allergy that has increased, but there is evidence suggesting that severe reactions are on the increase as evidenced by increasing incidence of presentations at emergency departments.[6] On top of this the same pathophysiological mechanism may manifest as multisystem disease in the same patient, resulting in a complex disorder requiring the input that only a specialist in the field can provide. This 'multi-system allergic disease' may manifest as asthma, eczema, food and drug allergy in the same patient, with inputs from specialists in different fields, leading to a piecemeal, sub-optimal, inefficient and non-holistic healthcare delivery. Specific testing to uncover the offending allergen with resultant management options such allergen elimination and allergen specific immunotherapy, requires a level of expertise that can only be acquired through specific

training. A further setback to allergy sufferers is that policy makers fail to grasp the gravity of mis/un-managed allergic disease and its negative impacts on quality of life, economic burden on health services and family, and even adverse long-term health effects, lower educational achievement and life earnings. In addition, allergy is not generally perceived as a serious condition with major implications for health and quality of life.[7]

Studies have shown that effective allergy services can not only improve quality of life, but can also be cost-saving.[8,9] Allergy needs a 'whole system' approach in which allergy is treated as a condition in its own right, and not as a series of diseases depending on the organ system involved.[1]

Allergic conditions

Anaphylaxis

In line with the rising prevalence of allergic disorders there is reported to be a corresponding increase in patients presenting to an emergency department with anaphylaxis .[8] Anaphylaxis is the most severe form of allergic reaction and requires urgent medical treatment. Patients presenting to the emergency department with symptoms of anaphylaxis should be treated according to local guidelines, admitted according to the severity and prescribed an adrenaline auto-injector and given an anaphylaxis action plan. According to a recent yet unpublished audit carried out locally, 68.6% participants who included medical doctors across various working grades and pharmacists, did not feel confident explaining to patients when to use an adrenaline auto-injector while 72.5% of participants did not feel confident explaining how to use it. It is unacceptable to provide an adrenaline device to someone without teaching how and when to use it.

Following an international retrospective analysis, it has been recommended that appropriate follow up to a specialist allergy service is strongly recommended for patients with anaphylaxis.[10,11] Allergist referral rates ranged from 0% to 84%, with a mean of 33%. However, to date, Maltese patients suffering from anaphylaxis are managed by emergency physicians with no out-patient referral and are admitted under the care of general physicians, when hospitalization is deemed necessary. Very often, the trigger for anaphylaxis is identified. However, in certain cases, the cause is not found and in such cases it is advisable to refer to an allergist for organization of further investigation, confirmation of the diagnosis, education about use of the adrenaline auto-injector, to provide sensible expert advice as well as to provide an anaphylaxis action plan.

Food allergy

Food allergies are IgE, non-IgE or mixed immune-mediated hypersensitivity reactions, broadly grouped into acute reactions or chronic allergic reactions. The role of an allergist includes making the diagnosis of food allergy or indeed excluding it! Requesting and interpreting the correct investigations, excluding food allergy or diagnosing food intolerance,[12] identifying quantities/level of cooked food tolerated, finding suitable and well-tolerated alternatives and investigating for possible co-existing allergies, are the remits of a specialist. Getting it wrong can have fatal consequences to the patient, and disastrous consequences to professionals dabbling in this area without the necessary knowledge and experience. The lack of regulation and control in this area has led to patients falling victims to speculation at best and harmful advice at best. Patients are being made to pay good money for unreliable tests (such IgG testing for food allergy, the notorious 'food intolerance' test) and then given dangerous advice based on these tests with elimination of staple foods from their diet with potentially devastating effects on their health. Follow up and exact, low-risk timing of introduction of foods can only be offered by experts in the field. Less common conditions such as oral allergy syndrome, lipid transfer protein syndrome and food-exercise induced anaphylaxis require an allergy specialist to make the diagnosis and provide appropriate advice. In addition, the role of a paediatric allergist is to identify certain conditions such as food protein induced-enterocolitis syndrome, eosinophilic oesophagitis which are sometimes associated with failure to thrive.

The oral food challenge (OFC) test remains the gold standard for the diagnosis or exclusion of immediate or delayed immediate or delayed. Decisions to undertake such tests are only taken once a risk assessment is performed in each case based on history and allergy testing including skin testing and blood measurements of food specific IgEs,[12] and should only be undertaken in a unit with the capacity to deal with severe allergic reactions.[13] A negative oral food challenge result allows introduction of the food into the diet, whereas a

positive oral food challenge result provides a sound basis for continued avoidance of the food.[13]

An appropriately trained dietitian's role in managing food allergy is invaluable.[12] Patients and relatives need to be taught how to interpret the list of ingredients on the labels of manufactured foods, identify hidden ingredients, be educated on cross-reactivities and find alternatives to avoided foods. An important parallel role is to ensure that those with established food allergy, especially growing children, have a nutritionally adequate diet. The provision of recipes, advice when eating out, and general encouragement are additional measures that are helpful. An allergy department should have the services of both adult and paediatric dietitians.[1]

Policies governing safety in the food and beverage industry rely on expert advice from allergy experts. Food labelling and proper food handling to avoid cross-contamination are essential to ensure safety of consumers. There are still big lacunae in this area although there is a move in the right direction. One dangerous example pertaining to the local setting is the potential confusion of ingredients in the traditional Easter pastries, the 'figolla', which traditionally includes an almond paste as one of its ingredients, but which has frequently been replaced by a peanut paste, without the necessary labelling. Imagine the disastrous consequence to a severely peanut allergic patient!

Respiratory Allergy - Asthma and Allergic Rhinitis (Hay fever)

Asthma is among the most common chronic diseases of the western world. In adults and children, the asthmatic response can be triggered by a wide variety of agents including allergens. Allergy is a common cause of childhood asthma, and the substantial increase in incidence of asthma over the last three decades is largely allergy-driven. It is important to establish the relative contribution of ongoing poor asthma control versus triggers, by means of careful history-taking and appropriate investigations to establish which allergens mat be contributory. The significance of a specific allergen in a particular individual may be suspected from the clinical history. However, allergy testing may be required. Awareness of the cause allows allergen avoidance which may result in better control of the condition, leading to a reduction in the need for drug therapy.[1]

Allergic rhinitis, whether seasonal or perennial, represents a major cause of morbidity with impairment of quality of life for many sufferers. The results of skin prick tests or allergen-specific IgE, together with the history provide helpful supportive evidence. The mainstay of treatment of rhinitis remains the identification and, if possible, the avoidance of provoking allergens, together with conventional treatment options, which are routinely managed by ENT or respiratory specialists. Allergen specific immunotherapy is an effective treatment for allergic rhinitis patients but requires an accurate within selected patients and would require expert allergist input, in order to manage the patient appropriately. The fact that in the ISAAC study, Maltese teenagers had the third highest rate of allergic rhinitic symptoms in the world,[4] strengthens the claim for the need of an adult allergic clinic in Malta

Atopic Eczema

The allergist has a role to play, mainly to determine allergic and other triggers. The role of allergic triggers can be very variable and is important to determine precisely. It can be difficult to determine in atopic dermatitis. Other forms of eczema are dealt with by dermatologists.[1] Affected individuals often have other atopic disorders such as allergic rhinitis, asthma or food allergy, and commonly several disorders are present in the same patient,[1] suggesting that an allergist should be involved in such cases.

Urticaria/Angioedema

Urticaria and angioedema can be IgE- or non-IgE-mediated, and the allergist has a role to play in both.[1] Isolated urticaria is often dealt with primarily by dermatologists, but allergists will have a role in some patients, such as, if there is associated angioedema or if an allergic cause is a possibility. Angioedema may occur alone, with urticaria, or with a variety of other symptoms as part of a multi-system disorder. Angioedema may be a manifestation of anaphylaxis. An allergist is best placed to manage such patients, whether the disease is IgE-mediated, as in food allergy, or due to other mechanisms, as with drugs such as angiotensin converting enzyme inhibitors. It is important to determine whether there are specific triggers or whether urticaria and angioedema are idiopathic.[1]

Drug allergy

Drug allergy is an adverse drug reaction mediated by a specific immune response directed at the drug, or a drug breakdown product, either alone or in combination with a body protein acting as an allergen. Allergic drug reactions are immediate or delayed, local or generalised. Both anaphylaxis and severe delayed drug allergic reactions can be fatal. Few allergy centres in the UK are able to investigate drug allergy fully, and diagnostic tests are not straightforward.[1] The current local situation includes the availability of a limited number of specific IgE testing, as is in the UK.[14] Drug provocation tests which include a direct challenge with specific drugs should be undertaken at specialist allergy centres only when investigations have been exhausted and the diagnosis remains in doubt. The challenge should be designed either to implicate or exclude a drug, or to identify a suitable alternative agent. The risk/benefit must be assessed in every case. These tests, which are very time-consuming, should only be carried out in a specialist centre by staff trained in the treatment of anaphylaxis.[1,14] No such service is available to date in Malta.

Venom Allergy

The incidence of venom allergy in Malta is not known. Local venom reactions have only a low risk of anaphylaxis. However, systemic reaction do occur. The risk of a further reaction will depend on a number of factors. Immunotherapy (desensitisation) treatment is available for bee and wasp venom. Patients may be prescribed an adrenaline auto-injector, if they are considered at risk of a severe reaction. At risk patients would require assessment to assess the degree of risk, provide professional advice and possibly prescribe immunotherapy when clinically indicated. Venom immunotherapy is highly effective, protecting about 95% of patients with vespid venom allergy and 80–90% of those allergic to bee venom. Quality of life is also improved. This is best done in a specialist allergy centre where many patients are being treated, with good systems for monitoring and early treatment of systemic reactions.[1]

Quality of life

Several studies have shown that patients suffering from allergic conditions, particularly food allergy, together with their caregivers, have been identified to suffer from anxiety[13,14] and depression,[23] resulting in a worsened quality of life,[16,18-20] due to the burden associated with this condition, namely the persistence of allergen avoidance as well as the constant fear of developing an allergic reaction,[21] possibly complicated by life-threatening anaphylaxis.[22] In fact, in the Euro Prevall project, the quality of life in such patients has been given great importance.[18] Completing one of the several quality of life questionnaires available for patients with food allergy[23] might have been useful to achieve a baseline for this patient and monitor response after the intervention of the play specialist. Questionnaires have been developed to assess the impact both on the child as well as the caregiver.[20] Milk and egg allergy demonstrated a worsened quality of life compared with other food allergies.[18]

Paediatric allergy services

For the allergic child, optimal growth, educational attainment, and social and psychological development, as well as health and wellbeing, are all at risk. Children with allergic disease therefore have a set of needs which are distinct from those of adult allergic patients and which place particular importance on early recognition and effective management of allergy.[24] The appropriate treatment of allergy is particularly important in children whose quality of life, education and growth may be greatly affected by their condition.[1] Food allergy is common and can be life-threatening. Asthma has been identified as potentially preventable if it is treated in early life. Many children have allergic diseases affecting several organ systems, and are inadequately treated because the allergic trigger goes unrecognised.[1]

In our local hospital, paediatric patients are investigated and managed by a paediatric allergist with limited facilities in a clinic, which is part of an adult ward. Investigations are limited to a small number of different allergens available for skin prick testing. Food components are brought in by parents/carers for prick-to-prick testing, resulting in parents spending a considerable amount of money to buy certain food products of which only a tiny amount is utilised. The service is run in the absence of a nurse or a dietician.

Adult allergy services

Adult allergy services in our local hospital so

far, have traditionally been provided by different non-allergy specialists according to the organ system affected; for example severe allergic asthma by respiratory physicians, food allergy and eosinophilic gastrointestinal conditions by gastroenterologists, allergic rhinitis by ENT specialists, allergic conjunctivitis by ophthalmologists and atopic dermatitis, urticaria by dermatologists. Alternatively, many allergy cases are dealt with by general practitioners. However, most organ-based specialists and general practitioners have no formal clinical training in allergy and have no ready source of expert advice to date. Whilst these specialists have an important role in the management of allergic disorders, a partnership needs to be developed with specialist allergists.

In international hospitals providing allergy services, allergy specialists deal with a wide range of disorders, such as rhinitis, asthma, urticaria, angioedema (including hereditary angioedema), eczema, anaphylaxis, and allergy to food, drugs, latex rubber and venom. The above disorders may result from generation of IgE antibody (allergic antibody), but the same disorders and symptoms, such as anaphylaxis, drug or food allergy, can occur through mechanisms that are independent of IgE. Whilst symptoms may be restricted to one organ, many allergic disorders may demonstrate multisystem disease.[1] This implies that it would be ideal to review and manage the patient in a multidisciplinary approach.

Current deficits

Current deficits in local allergy services include the complete absence of a structured adult allergy service in a recommended set-up, a paediatric service in limited environment without the appropriate facilities, a lack of allergens available for skin prick testing as well as lack of availability of food products available for performance of prick-to-prick testing and for food challenges. In addition, there is no specialist nurse or dietician for direct, easy access referral.

Benefits of a specialist allergy service

- The provision of specialist allergy care led by allergy specialists formally trained in both adult and paediatric allergic disease so that appropriate standards of care can be achieved and maintained.
- The availability of a referral centre for patients suffering from anaphylaxis, to be reviewed and managed urgently.
- The provision of accurate diagnosis and management of allergic diseases using readily available tools and equipment, while excluding allergy in others, allowing the patient to proceed with other appropriate investigations.
- Well-equipped facilities for diagnostic challenge tests, day-case services, and allergen immunotherapy.
- The availability of allied healthcare professionals such as a specialist nurse and dietician.
- Implementation of evidence-based guidelines of various allergic conditions.

Conclusion

We recommend that a co-ordinated and structured allergy service is developed to diagnose and treat a whole range of allergic diseases, providing expert advice, diagnostic tests and practical help for patients affected by allergies. It should be run by skilled allergists having the expertise to manage both adult and paediatric patients, supported by a skilled dietician as well as a trained allergy nurse, with access to a wide array of necessary investigations, in a safe well-equipped environment. A multidisciplinary approach would be ideal to diagnose and manage allergic conditions particularly when co-existent, whilst expertly managing less common allergic cases in an appropriate setting. The aim would be to improve patient care, prevent severe and fatal allergic reactions, avoid inappropriate under- and over-management as well as avoid the costs implicated with mismanagement.

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Original Article

A survey of energy drinks consumption amongst medical students and foundation year doctors in Malta

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Abstract

Objectives: To explore the consumption patterns of energy drinks and associated factors, amongst medical students and foundation year doctors in Malta.

Methods: Data was collected from medical students and foundation year doctors from the Faculty of Medicine and Surgery, University of Malta, by means of an electronically administered cross-sectional, self-reported survey. The response rate was 42% (*n*=305, M=124, F=181). IBM SPSS 23 was used for statistical analysis.

Results: Energy drinks consumption amongst the sample was 68.2% (n= 208). Most participants (60.1%) started consuming energy drinks between 16-20 years, followed by those between 11-15 years (34.6%). Males are more likely to consume energy drinks than females. Participants who consume energy drinks are more likely to also drink coffee (85.1%), alcohol (88.0%) and smoke tobacco (18.3%). Common reasons for drinking energy drinks were for mixing with alcohol (37.5%) and during studying/major projects (30.8%). The majority of the participants (52.1%) experience psychological side effects due to energy drinks, the most common being stimulating/hyperactivity (42.6%), followed by anxiety (14.8%). Over half of the participants (54.8%) claimed to suffer from physical side effects

Conclusions: Energy drink consumption is common amongst this population and certain aspects of consumption are a cause for concern. Greater public education of the risks of these drinks is recommended especially to young age groups. Legislation may be required to control the marketing and sales and accessibility of these drinks.

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Energy drinks, medical students, foundation year doctors, caffeine, anxiety

Introduction

'Energy drinks' is a collective term applied to a vast array of caffeinated soft drinks that invariably claim to boost performance, stamina and endurance.[1-2] Drinks that have purported to increase energy have been available for many decades but it is commonly held that it was the introduction of Red Bull© in the 1980's which pre-empted the widespread availability of such drinks and the consequent increase in their popularity.[2-3]

Energy drinks are usually composed of caffeine, carbohydrates, taurine and water-soluble

vitamins. Other ingredients that may be found in these drinks, such as guranà and kola, may potentiate the caffeine content[4], and the effects of sustained intake of the additives, either alone or in combination with the caffeine, are not established. Energy drinks have been the focus of an abundance of research and review articles within the extant literature and they have both proponents and opponents based on the potential benefits and hazards of these drinks. There is significant debate as to whether energy drinks are safe for consumption.[5] Published research has indicated that energy drinks have been shown to effect significant improvements in mental performance (i.e. reaction time, concentration and memory, a decrease in tiredness), with their effects taking hold within an hour of consumption and being sustained for around 90 minutes.[3,6-7] By far the greatest concern regarding the consumption of energy drinks is the caffeine content. This is by no means standard with some drinks containing as much caffeine as a cup of coffee[8] (around 100mg), right up to as much as 505mg per can[9]. Although previous research has found that low to moderate caffeine doses[7] (up to 200mg), can enhance cognitive performance and mood and positively impact speed, accuracy and alertness[3,7], other studies report that excessive consumption of energy drinks may lead to negative physical effects such as gastrointestinal disturbances, cardiovascular changes[8], and insulin resistance[10], in addition to agitation, anxiety, irritability and insomnia[6]. The effects of energy drinks on mental health is one that has produced somewhat dichotomous findings within the literature[2,11]. Whilst some studies have shown that caffeine has an enhancing effect on mental health other research has found that anxiety, depression and behavioural problems are higher amongst consumers as opposed to non-consumers.[2,11] The difference in effects is invariably related to the levels of caffeine consumed.

Another area of concern is the association between energy drink consumption and increased risk-taking behaviour, most often referring to the common practice of mixing alcohol with energy drinks, the latter masking the effects of the alcohol. Studies suggest that this increases the risk of inappropriate sexual activity, drink driving and other potentially risky behaviour.[8,12]

It is perhaps understandable that young people facing long hours of study and pressure related to exams are attracted by manufacturers' claims that energy drinks are the ultimate study aid, boosting energy, promoting wakefulness, increasing attention span and heightening intellect[1]. Furthermore, since energy drinks are unregulated and are sold alongside ordinary soft drinks, their accessibility may be another attractive feature. Irrespective of the reason, their popularity is undeniable given that they are the fastest growing beverage category and are now available in over 140 countries[9]. Energy drinks account for 1% of the total soft drinks market and this figure is still rising. In Western Europe alone, the energy drink market increased by 12.9% between 2007 and 2011[4]. In 2015 global sales reached €38.2 billion and it is projected that this will increase to €53.4 billion by 2020[13]. Although the literature states that the target demographic for the sale of these drinks is adolescents and young people, particularly males[6], other authors have noted that older consumers are responding to manufacturers' attempts to attract their business by for example, introducing new flavours, diet and sugar free variations[13].

One demographic group that has been the focus of a number of studies examining consumption, reasons for use, and awareness of side effects of energy drinks, is medical students. This attention is seemingly based on the assumption that this particular group would have a greater knowledge and understanding of nutrition and health[1]. However, the collective findings of these numerous studies conclude that the consumption of energy drinks amongst this particular group is widely prevalent,[4,6,8-9,14-16] with a higher rate of use by males.[1,4,10,14-18] The main reasons for consumption are reported to be predominantly related to the energy boosting properties of the beverages, utilised by medical students when studying or sitting for exams. They are also used to allay the need for sleep, and during the course of socialising, commonly being mixed with alcohol.[15-16] Furthermore, several researchers noted an association between energy drinks and the consumption of coffee and smoking.[4,9,17]

The aims of the present study were firstly to determine the consumption patterns of energy drinks amongst medical students and foundation year doctors in Malta and to establish the common reasons for consumption. To date this is not a subject that has been explored within Mediterranean countries. Additionally, this study sought to

establish if there is an association between energy drinks and coffee consumption and tobacco smoking amongst this group. Finally, the study investigated whether a correlation exists between anxiety levels and the consumption of energy drinks.

Methods

Participants

A cross sectional survey was conducted amongst medical students and foundation year doctors from the Faculty of Medicine and Surgery, University of Malta. The sample included students who graduated between 2009 – 2015 (5 cohorts of medical students spanning 5 years, and two years post-graduate 'Foundation' doctors). Data was collected between September 2015 and September 2016.

Procedures

The study was approved by the University of Malta. The questionnaire was disseminated in an online interactive format by the Dean's Office via the Medical School's portal: MMSA (Malta Medical Students Association). Participation was voluntary and responses were completely anonymous.

Instruments

A 34-item questionnaire was developed based on the existing literature. The questionnaire consisted of categorical (nominal or dichotomous) questions. Some of the questions allowed multiple responses. The GAD-7 was incorporated into the main questionnaire. It is a reliable and validated self-reported questionnaire used for detecting probable cases of generalised anxiety. The GAD-7 score is calculated by assigning scores of 0, 1, 2, and 3, to the response categories of 'not at all', 'several days', 'more than half the days', and 'nearly every day', respectively, and adding together the scores for the seven questions. The Generalized Anxiety Disorder Scale (GAD-7) screening tool was developed in 2006.[19]

The questionnaire was piloted on a focus group of 12 medical students and 2 newly graduated doctors. No changes in the questionnaire were identified following piloting. The questionnaire included five sections: the first section asked for demographic information; the second section concerned anxiety (GAD-7); the third section asked about consumption of energy drinks, the fourth section enquired about coffee consumption and the final section asked about other legal substance use and psychological effects of energy drinks.

Data Analysis

IBM SPSS 23 (Statistical Package for the Social Sciences) was used for statistical analysis. Descriptive statistics were first used to describe the basic features of the data and the sample decomposition. The chi-square test was used to determine whether there was or was not an association between two categorical variables. Cramer's V was used to provide an estimate of the strength of the association between the two nominal variables. *Cohen's kappa (κ) coefficient*[20] was used to determine the agreement of consumption of energy drinks between during and outside study/examination period. Cohen's kappa (κ) can range from -1 to +1. The non-parametric tests, *Mann-Whitney U test* and *Kruskal-Wallis test* were used to compare mean GAD-7 scores between two or more independent groups (e.g. gender, age group, energy drinks consumption, coffee consumption, alcohol consumption and tobacco smoking). A General Linear Model (GLM) was implemented in order to compare how several variables affect the variations in the GAD-7 scores.

Results

Composition of the Sample

726 questionnaires were sent. Response rate was 42 %, of which 40.7% of were males and 59.3% were females. The majority of males were aged between 22 and 25 years (41.9%) followed by those aged between 17 and 21 years (41.9%). More than half of the female participants were aged between 17 and 21 years (55.2%), followed by 39.8% who were aged between 22 and 25 years. The majority of the participants (80.0%, N 246) were medical students. The remaining participants were foundation year doctors (20.0%, N 59).

Consumption of energy drinks

More than half of the participants in the sample (68.2%) consume or have consumed energy drinks in the past. The majority of these started consuming energy drinks between the ages of 16 and 20 years (60.1%). However, approximately one third of those who consume or have consumed energy drinks started consuming them between the ages of

11 and 15 years. Males are more likely to drink energy drinks than are females (82.3% of males as opposed to 58.6% of females) (102 males consumed energy drinks out of 124 in the sample; 106 females consumed energy drinks out of a total of 181 females). There was a statistically significant, moderate association between gender and energy drinks consumption, X^2 (1) =19.049, p<0.0005, Cramer's V = 0.25. In contrast, there was no association between age group and energy drinks consumption, X^2 (3)=3.034, p=0.386. The most preferred brand of energy drink consumed was Red Bull©, containing 80mg of caffeine per 250ml (87.0%). More than half of the participants (62.5%) stated that their first consumption was in the context of a social setting, 23.6% consumed them based on recommendations from friends or family and the remainder were attracted to them through advertising (18.3%), or by seeing them on display in a store (15.9%). Multiple responses were allowed when participants were asked how they were first introduced to energy drinks. In a typical session, most of the participants drink only one energy drink (45.2%), whilst 15.4% prefer to drink two, and 2.9% prefer to drink more than three. The most common reasons for consuming energy drinks were to mix them with alcohol (37.5%) and due to insufficient sleep or to ward off sleepiness and stay awake (17.3%). Furthermore, 30.8% of the participants consumed energy drinks during the time of studying / exams / major academic projects. In fact, Cohen's κ was applied to determine if there was an agreement of consumption of energy drinks between 'during' and 'outside' the study/examination period. Table 1 is showing that, in general, participants increase the consumption of energy drinks during the study/examination period by taking more than 5 energy drinks per month, of whom normally they do not consume any energy drinks outside the study/examination period. Only one third of the respondents stated that the consumption of energy drinks during and outside the study/examination period remain the same.

***Table 1**: Measure of agreement: Energy drinks consumed during and outside the study/examination period per month*

Consumption of Energy Drinks ...			**DURING** the study/examination period per month						
			1 to 5	6 to 10	11 to 20	21 to 40	> 40	None	Total
OUTSIDE the study/examination period per month	1 to 5	Count	34	15	8	5	0	52	114
		%	**56.7%**	**51.7%**	**57.1%**	**41.7%**	**0.0%**	**59.8%**	**54.8%**
	6 to 10	Count	4	0	1	3	3	3	14
		%	**6.7%**	**0.0%**	**7.1%**	**25.0%**	**50.0%**	**3.4%**	**6.7%**
	11 to 20	Count	0	2	1	0	1	0	4
		%	**0.0%**	**6.9%**	**7.1%**	**0.0%**	**16.7%**	**0.0%**	**1.9%**
	21 to 40	Count	0	0	0	2	0	0	2
		%	**0.0%**	**0.0%**	**0.0%**	**16.7%**	**0.0%**	**0.0%**	**1.0%**
	> 41	Count	0	0	0	0	0	0	0
		%	**0.0%**	**0.0%**	**0.0%**	**0.0%**	**0.0%**	**0.0%**	**0.0%**
	None	Count	22	12	4	2	2	32	74
		%	**36.7%**	**41.4%**	**28.6%**	**16.7%**	**33.3%**	**36.8%**	**35.6%**
Total		Count	60	29	14	12	6	87	208
		%	100.0%	100.0%	100.0%	100.0%	100.0%	100.0%	100.0%

κ = 0.020 (95% CI, -0.066 to 0.106), p=0.634

Effects of energy drinks

When asked if they felt that the consumption of energy drinks had influenced their examination results, 47.6% of participants felt that they had made no impact on the results, whilst 33.7% were unsure, and 16.8% claimed that energy drinks had indeed positively influenced their examination results. Conversely, 1.9% stated that they felt that the consumption of these drinks had a negative impact on their examinations. In relation to side effects, 89.5% of respondents stated that they were aware of the possible side effects associated with

energy drinks and 53.1% claimed to be aware of the contents of the energy drinks they consume. A significant association was found between those who were aware of the different contents of energy drinks and consumption of energy drinks ($\chi^2(1)=6.720$, $p=0.010$, Cramer's V=0.148). Respondents who were aware of the contents of the energy drinks were more likely to consume energy drinks (58.2%) than those who did not (42.3%). More than half of the participants (54.8%) claimed to experience an increase in frequency of urination and urinary output after consuming the drinks. A high proportion of participants (42.2%) also reported experiencing palpitations; jolt and crash (39.8%), insomnia (31.9%) and headaches (21.1%). When considering psychological effects of energy drinks, 52.1% claimed to have experienced some type of psychological effect, the most common being stimulation / hyperactivity (42.6%), followed by anxiety (14.8%) Respondents who suffered from stimulation / hyperactivity were more likely to drink energy drinks (47.1%) than those who did not (33.0%) ($\chi^2(1)=5.397$, $p=0.025$, Cramer's V=0.133).

Coffee, cigarettes and alcohol

The vast majority of participants affirmed that they drank coffee (81.3%) and alcohol (82.3%). However, the majority had never smoked tobacco (85.2%). More than half of the respondents (65.7%) claimed that alcohol consumption during the study/examination period. Also, 39.1% claimed that coffee consumption has made no impact on their examination results, whereas 33.9% claimed that consuming coffee had made a positive impact on their examination results. There was no statistically significant association between gender and coffee consumption ($X^2(1)=0.003$, p=0.959) and gender and alcohol consumption ($X^2(1)=2.351$, $p=0.503$). Moreover, there was no association between age group and coffee consumption ($X^2(3)=5.081$, p=0.166), and between age group and alcohol consumption ($X^2(3)=3.388$, $p=0.336$). However, there was a statistically significant association between coffee consumption and energy drinks ($X^2(1)=6.165$, $p=0.013$, Cramer's V=0.14), and a moderately strong association between alcohol consumption and energy drinks, ($X^2(1)=14.511$, $p<0.0005$,. Cramer's V=0.22. This means that participants who consume energy drinks are more likely to drink coffee and alcohol rather than respondents who do not consume energy drinks. Of the 14.8% of participants who did smoke, the majority were male and of all smokers, 66.7% claim that their cigarette intake increased during periods of study / exams. There was a statistically significant, small association between gender and tobacco smoking, $X^2(1)=10.176$, $p=0.001$, Cramer's V=0.18, where male respondents were more likely to smoke rather than female respondents. There was no association between age group and tobacco smoking, X^2 (3)=2.351, p=0.503. In addition, a statistically significant, small association was found between tobacco smoking and energy drinks consumption, $X^2(1)=6.425$, $p=0.007$, Cramer's V=0.15.

Mental health

The majority of the respondents (88.5%) never suffered from pre-existing psychological/psychiatric conditions. Almost all of the participants stated that they were not taking any psychiatric medication (95.0%). Amongst those on medication, the most common type was antidepressants. With respect to the GAD-7 test, participants' scores were categorised as follows: 0-5 as 'No/Little anxiety', 6-10 as 'Mild anxiety', 11-15 as 'Moderate anxiety' and 16-21 as 'Severe anxiety'.

The analysis revealed that the majority of the responses (56.7%) are indicative of little or no anxiety, 23.9% of the participants are indicative of mild anxiety,12.8% of the participants are indicative of moderate anxiety and 6.6% of the participants are indicative of severe anxiety (Table 2).

A General Linear Model (GLM) was modelled in order to analyse collectively the contribution of each predictor in explaining the variations in the GAD-7 scores. The response variable in this study was the GAD-7 score and this was related to seven predictors, namely: gender, age group, marital status, coffee consumption, tobacco smoking, alcohol consumption and energy drinks consumption. The GLM identified only one predictor – gender, as contributing significantly in explaining variation in the GAD-7 scores (p-value 0.025). Gender emerged as the strongest predictor for higher GAD-7 scores since it had the smallest p-value (0.025). The remaining predictors age group, marital status, energy drinks consumption, coffee consumption, tobacco smoking and alcohol consumption were found to be weak predictors

since their p-values exceeded the 0.05 level of significance (Table 3). These predictors were removed from the model fit since their contribution in explaining variation in the response outcomes was negligible.

***Table 2**: GAD-7 Classification: Level of Anxiety in Participants*

Score	Counts	Percent	Classification
0-5	173	56.7%	No/Little anxiety
6-10	73	23.9%	Mild anxiety
11-15	39	12.8%	Moderate anxiety
16-21	20	6.6%	Severe anxiety
Total	305	100.0%	

***Table 3**: Tests of Model Effects*

	Wald Chi-Square	Degrees of Freedom	P-value
(Intercept)	21.072	1	0.000
Gender	4.999	1	0.025
Age Group	1.745	3	0.627
Marital Status	0.927	2	0.629
Energy Drinks consumption	0.002	1	0.968
Coffee consumption	0.040	1	0.842
Tobacco smoking	1.289	1	0.256
Alcohol consumption	0.771	1	0.380

Thus, the GLM was re-fitted using Gender as the only predictor.

The parsimonious regression model with Gamma identity link function with GAD-7 score as the dependent variable is as follows:

Predicted GAD-7 score = 7.116 - 1.400*Male

The parameter estimate of males is -1.400, which implies that the expected GAD-7 score of males is 1.4 points lower than the expected GAD-7 score of females. Also, the Mann-Whitney U test revealed that the mean GAD-7 scores amongst the sample differed significantly on gender only (U=9305, Z=-2.542, p=0.011). Females had significantly higher mean GAD-7 scores (Mean=6.45 ± 0.78) than their male counterparts (Mean = 5.02 ± 0.86).Of particular interest in this study was the finding that the groups with the lowest mean GAD-7 scores were participants aged between 26-30 years (Mean=5.25±1.96), participants who consume energy drinks (Mean=5.65±0.70) and alcohol (Mean=5.74 ± 0.63) and those who do not drink coffee (Mean=5.33±1.29) or smoke tobacco (Mean=5.78± 0.63).

On the other hand, the groups with the highest mean GAD-7 scores were participants aged over 40 years (Mean=11.50 ± 31.77), participants who do not consume energy drinks (Mean=6.34 ± 1.06) and alcohol (Mean=6.48 ± 1.49), those who drink coffee (Mean=5.99± 0.66) and smoke tobacco (Mean=6.38± 1.50).

No association was found between energy drinks consumption and anxiety levels, $X^2(3)=1.823$, p=0.610.

Discussion

The findings of this study have many commonalities with similar research conducted in countries such as Poland,[12,15] Turkey,[17] Saudi Arabia,[9-10,14,18] Italy,[4] Nigeria,[6] Serbia,[16] and the USA[3]. Energy drinks consumption is found to be common amongst medical students and junior

doctors in Malta;[1,3,6,8,9,12,15-16] consumption is higher amongst males[1,9-10,12,14,16-18] and commencement of consumption started at a young age.[9] Strikingly, one third of participants in this study started drinking these beverages between the very young ages of 11 and 15 years. In Malta, the teenage years are the time when youngsters start to socialise without parental supervision during weekend evenings in the Island's entertainment areas. Since the majority of participants reported first consuming energy drinks in a social setting (62.5%) it is likely that it is at this point of their lives that they are exposed to the drinks and to the possibility of mixing them with alcohol. Added to the fact that targeted advertising of the drinks is extremely attractive to younger age groups, the uncontrolled availability and sales of energy drinks is an area which needs urgent reform.

Typically, the majority of participants only drink one energy drink per session which, depending on the brand, may not amount to more caffeine than can be found in one cup of coffee, with only a small proportion of the sample consuming more than three energy drinks in each session. Other studies have shown that mixing energy drinks with alcohol is a known factor,[3-4,12,15,17] however in this study, it was the highest rated reason for consumption of the drinks and this raises serious concerns related to an increase in risky behaviour. In addition, consistent with other studies,[4,17] cigarette smoking, and coffee and alcohol consumption are clearly correlated to consumption of energy drinks. These findings are consistent with those of other studies that identify an association between the consumption of energy drinks and other potentially harmful or risky legal substances.

Locally as elsewhere, energy drinks are also utilised as a study aid (mental agility)[12,15] and less commonly, as a means to stay awake.[12] Interestingly, most of the participants (75.0%) who stated that they consumed the drinks as a means of improving mental agility and concentration in order to study, could not definitively say whether the drinks had a positive impact on their exams, so their consumption was not based on or reinforced by personal experience.

Increased knowledge about the potentially harmful effects of legal substances is apparently not a deterrent amongst this group, despite the participants having a potentially greater knowledge of physiological and medical aspects than their non-medical peers. This finding supports those found in other studies.[12,16] It is suggested that in the case of energy drinks, this is due to the desired effects of the drinks outweighing the negative side effects experienced.

Analysis of the GAD-7 scores showed that unlike other studies[4], no association was found between the consumption of energy drinks and anxiety levels and furthermore it was found that participants who consume energy drinks rank lower on the GAD-7 score.

Limitations of the study

The survey design employed in this study i.e. self-report questionnaires, may be considered as a limitation, as this method can be affected by recall bias and reporting errors. A further limitation is a lack of collected data related to the participants' clinical history, metabolic assessment, pressure profile and cardiac frequency, since the inclusion of such data would have added depth to the participants profile and enriched the results. Had the study considered participants' use of other substances which may have a synergistic effect on caffeine products, this would have added another point of interest to the study. Furthermore, since this study was conducted amongst medical students and foundation year doctors, who may be assumed to have greater knowledge of nutrition and health, the results may not be generalizable to students from other areas.

Conclusions

This study demonstrated a widespread use of energy drinks amongst medical students and foundation year doctors in Malta. Knowledge, awareness and personal experience of side effects did not act as a deterrent to consumption. Mixing energy drinks with alcohol is common and cigarette smoking and caffeine consumption are also both correlated to the consumption of energy drinks. Participants reported an increase in consumption of energy drinks around the times of exams and increased studying. Educational bodies should investigate ways in which to help students cope with the pressures of course work in a safer manner. No association was found between energy drinks and anxiety. The young age at which the participants started consuming energy drinks is startling and indicates a strong educational need to

provide awareness and education to young people of school age, regarding the active ingredients of the drinks and their potential risks and negative effects. Although the literature is divided in terms of the potential risks associated with energy drink consumption, several studies have found there to be real cause for concern related to both known and unknown effects of the drinks. For these reasons a pressing need for more informed studies to assess the need for legislative intervention and control regarding the sale of energy drinks is recommended. Moreover, this subject is under researched in the local context and as described earlier the research sample in this study was a narrowly defined group, therefore further research which examines wider population samples is highly indicated.

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