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Complementary cancer medication

Victor Grech

Complementary cancer therapy such as herbal products have never been proven to be of efficacy, at least not by the evidence-based standards of today's medical care. Moreover, such therapies may, in many ways, interact negatively with conventional cancer treatment. Indeed, cancer patients should inform their health care providers if they are taking herbal products because some of these compounds may actually reduce the efficacy of conventional and standard medications, treatments of proven effectiveness in extensive and expensive clinical trials. These points were recently highlighted at an international level by Professor Maria João Cardoso, Head Breast Surgeon at the Breast Unit of the Champalimaud Cancer Center in Lisbon, at the Advanced Breast Cancer Fifth International Consensus Conference.

For example, garlic, ginger and ginkgo pills may delay wound healing. Prof Cardoso stressed that for these reasons, doctors need to be proactive and ask their patients whether they are contemporaneously taking any complimentary therapies along with their prescribed medications, especially in cancers that had spread to the skin. This is because herbal therapies and creams may actively interfere with hormone therapy or chemotherapy and may also interfere with blood clotting, such that wounds take longer to heal and may do so with more scarring. Culprits include green chiretta, feverfew, garlic, ginkgo, ginseng, hawthorn, horse chestnut and turmeric. Furthermore, grapefruit and orange, for example, are known to affect enzymes which break down cancer drugs.

On the other hand, there are complementary therapies that may help to reduce treatment symptoms such as pain and fatigue. These include relaxation, talking therapies, meditation, visualisation, acupuncture, aromatherapy, reflexology, music therapy, art therapy, massage, yoga, mindfulness, reiki and acupuncture. These may all have a positive impact on patients' quality of life.

Primum non nocere.

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Cover Picture:

'View of Barrakka Gardens at Night'

Watercolours

By Christian Camilleri

Christian Camilleri is an anaesthesia trainee who began painting in childhood. His preferred medium and subject consist of watercolour figures, portraits and battle scenes. He derives inspiration from both Baroque and early 20th Century sources.

Assessing the see-and-treat approach for the management of high-grade squamous intraepithelial cervical lesions

Sarah Xuereb, Jessica Pavia, Mark R Brincat, Charmaine Tanti, Isabelle Saliba

Abstract

Objectives: To assess local histological outcomes in patients with HSIL cytology results on cervical smears, in both the see-and-treat and three-step approach.

Study Design: A retrospective analysis of patients with HSIL on cervical cytology was performed, obtaining an 83 patient cohort. The histological result following the primary investigation (colposcopic-directed biopsy or excisional procedure) was noted for each patient together with their demographic variables and HPV status.

Results: Of 83 patients with HSIL cytology on cervical smear, 43 underwent LLETZ as a primary procedure, while 40 patients underwent a colposcopic-directed biopsy. There was no statistically significant difference in terms of demographics and HPV status between the two groups. In those patients who had LLETZ as a primary procedure, 29 had CIN2+ on histology. On the other hand, following colposcopic-directed biopsies, 17 resulted in CIN2+ on histology.

Conclusion: The conventional approach within our local setting potentially has inferior sensitivity in picking up CIN2+ lesions when compared to the see-and-treat approach. On the other hand, primary excisional procedures were associated with an overtreatment rate of at least 20.9%, subjecting patients to unnecessary risks. Local improvement of colposcopic skill will aid to reduce this overtreatment rate and missed lesions at biopsy.

Keywords

Colposcopy, Cervical intraepithelial neoplasia, Squamous Intraepithelial Lesions of the Cervix, Overtreatment, Diagnostic Errors

Introduction

Cervical carcinoma is the fourth most common malignancy in women worldwide, with an estimated 4.68 per 100,000 being affected locally per year while 9.8 per 100,000 are affected in the UK per year.¹ Cervical cancer is in the large majority of cases preceded by Human Papilloma Virus (HPV) infection and pre-malignant changes, with HPV 16 and 18 responsible for about 70% of all cases. HPV persistence results in the integration of viral genetic material into the cellular genome, inactivating tumour suppressor function leading to genetic instability and precancerous changes.² Cervical screening and HPV typing through a

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Papanicolaou smear or liquid based cytology form the basis of cervical cancer screening programmes worldwide.

High-grade squamous intraepithelial lesion (HSIL) on cervical cytology is one of the categories of the Bethesda classification system used in cervical screening programmes. HSIL cytology results identify women at substantial risk of cervical intraepithelial neoplasia (CIN).³ Women with HSIL carry a 7% five-year risk of cervical cancer regardless of HPV status.⁴

In most screening algorithms, abnormal cervical cytology is followed up by colposcopically-directed cervical biopsies. If CIN2+ is detected on colposcopic biopsies, the cervix may be treated by excising the transformation zone by using various methods, such as a large loop excision of the transformation zone (LLETZ). This is referred to as the conventional three-step approach.⁵

Bigrigg⁶ initially pioneered the see-and-treat protocol for women with abnormal smear results. This approach involves assessing the cervix macroscopically at colposcopy and directly performing a LLETZ procedure should abnormal epithelial changes be confirmed. Therefore in this approach simultaneous histologic diagnosis and treatment is carried out.² Some 60% of women with HSIL on cervical cytology are found to have CIN2+ on histology. Thus the American Society for Colposcopy and Cervical Pathology (ASCCP) recommends immediate excision of the transformation zone for non-pregnant females over the age of 25, especially if colposcopic examination is inadequate. However, primary colposcopy including full assessment of the transformation zone is also an acceptable approach.³

Both approaches have their drawbacks. Overtreatment is a potential drawback of the 'see-and-treat' approach, whereby patients might undergo excisional procedures only to have normal or low-grade results on histopathological assessment. On the other hand, high-grade CIN may be under evaluated in colposcopic-directed biopsies, partly due to the subjectivity involved in the selection of the site for biopsies.⁷

This study aims to assess local histological outcomes in patients with HSIL cytology results on

cervical smears, in both the see-and-treat and three-step approach.

Methodology

This study is a retrospective analysis of an 83 patient cohort gathered over two years (2015-2017). Patients with HSIL on cervical cytology were identified through Mater Dei Hospital's histopathological records after the appropriate data protection approval was acquired.

Demographic variables and HPV status, including serotypes present, were noted for each patient with an HSIL cytological result. The histological result following the primary investigation in their management plan (colposcopic-directed biopsy or excisional procedure) were evaluated.

Results

Of 83 patients with HSIL cytology on cervical smear, 51.8% ($n=43$) underwent LLETZ as a primary procedure, while 48.2% ($n=40$) patients underwent a colposcopic-directed biopsy. Of the latter, 14 patients required a LLETZ procedure after their first colposcopic-directed biopsy, while 4 patients underwent a repeat colposcopy, two of which ultimately required a LLETZ procedure. The remaining 22 patients were followed up with cervical cytology (Figure 1). The transformation zone was present in 98.8% of cervical biopsies taken.

There were no statistically significant differences in mean patient age and HPV positivity on statistical analysis of the two main treatment arms with a non-paired student t-test. The mean age of the LLETZ group was 34.4 years, while the mean age of the colposcopic-directed biopsy group was 35.1 ($p=0.5917$). The HPV risk profiles were also very similar between the two groups (Table 1).

In those patients who had LLETZ as a primary procedure, 67% ($n=29$) had CIN2+ on histology. On the other hand, following colposcopic-directed biopsies, 42.5% ($n=17$) resulted in CIN2+ on histology (Figure 2 and Table 2). Figure 3 shows a more detailed breakdown of histological results according to the management approach taken.

Figure 1: Management pathway for HSIL patients included in the study

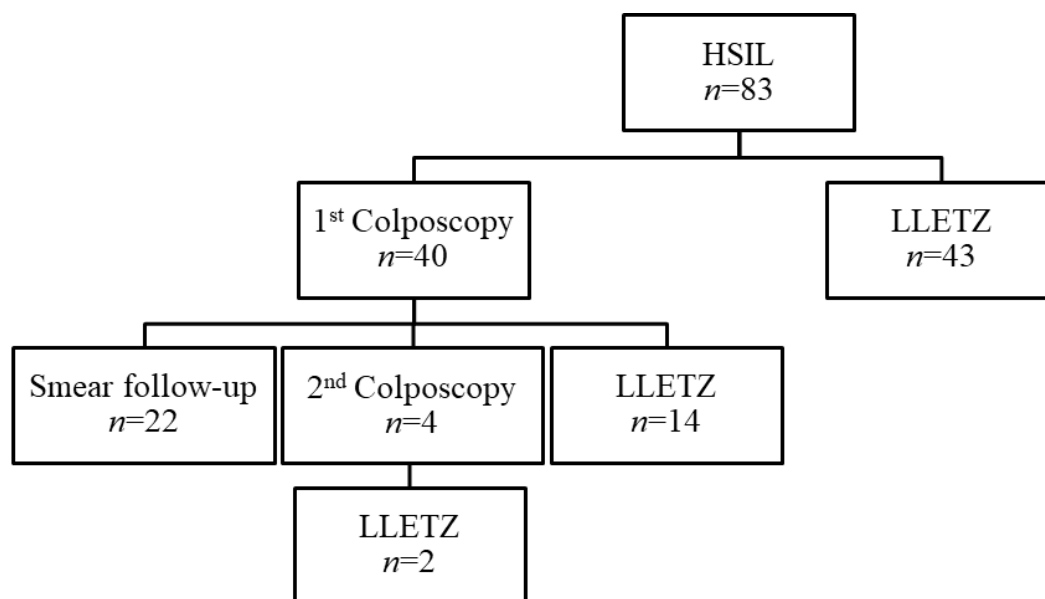


Table 1: Prevalence of HPV infection and HPV 16/18 serotype infection in the two sub-groups

	See-and-treat Approach % (95% CI)	Conventional Approach % (95% CI)
HPV Positivity	76.7 (61.4 - 88.2)	80.0 (64.4 – 90.9)
HPV 16 or 18	55.8 (39.9 – 70.9)	55.0 (38.5 – 70.7)

Figure 2: Histological outcome of the primary procedure performed in the two sub-groups

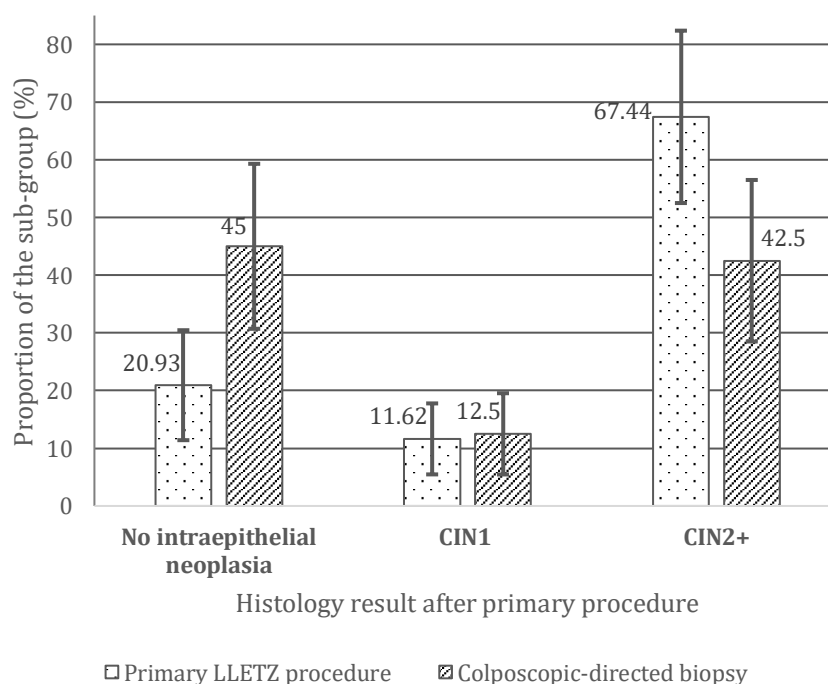
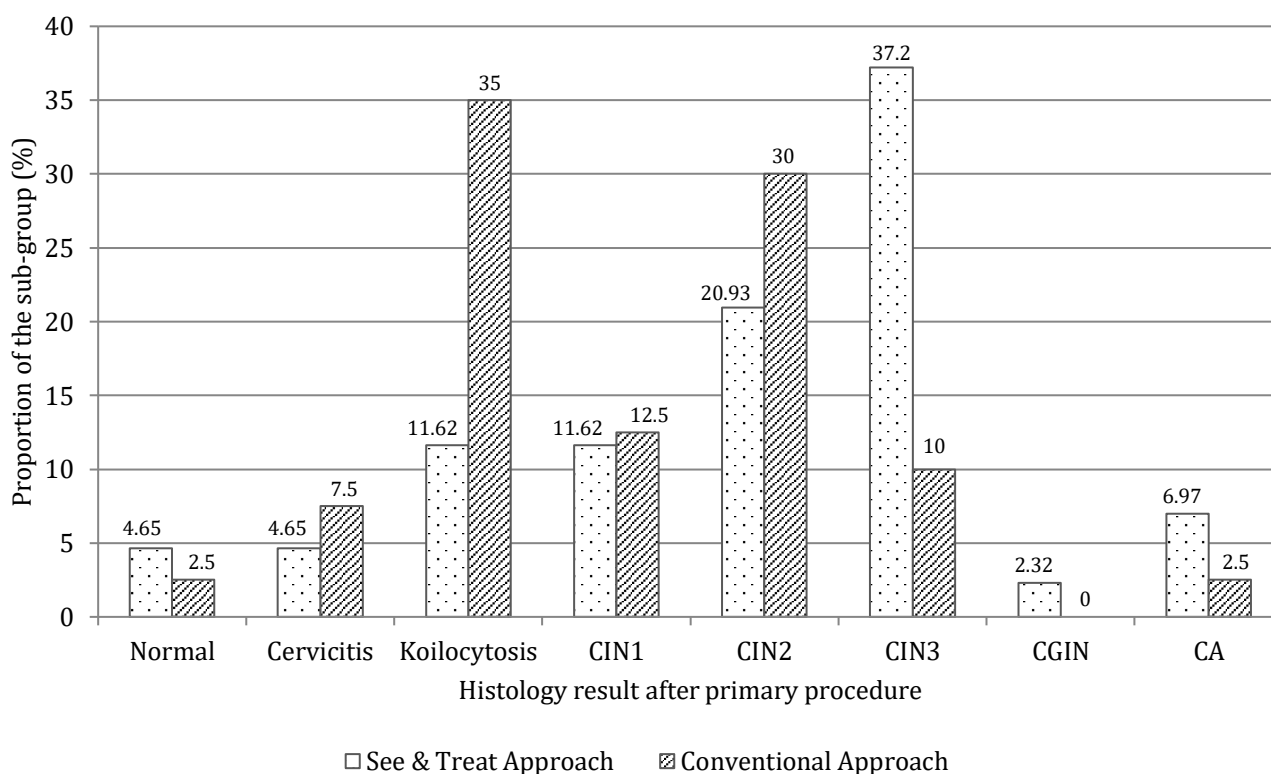


Table 2: Primary histological outcome in two study sub-groups

Histology	See & Treat Approach	Conventional Approach
	% (95%CI)	% (95%CI)
Normal/Cervicitis/Koilocytosis	20.9 (11.40-30.46)	45.0 (30.70-59.30)
CIN1	11.6 (5.47-17.77)	12.5 (5.46-19.54)
CIN2+	67.4 (52.50-82.38)	42.5 (28.50-56.50)

Figure 3: Detailed breakdown of the histological outcome in the two study sub-groups



Discussion

Papanicolaou’s discovery in the 1940s laid the foundation of cervical screening. The aim of cervical screening is to identify precancerous lesions at an early stage and thus reduce the incidence, morbidity and mortality from cervical cancer. Since the implementation of the UK NHS Cervical Screening Programme in 1988, the incidence of cervical cancer in the UK has decreased from 15 per 100,000 in 1986 to 8.9 per 100,000 in 2012 saving up to 4,500 lives per year.⁸

HSIL cytology results identify women at substantial risk of CIN2+. Each year approximately 1-2% of screened women are diagnosed with

CIN2+, which is found in some 60% of women with HSIL.³ This compares well with an overall rate of 55.42% of CIN2+ diagnosed in our HSIL patient cohort, regardless of the management strategy.

In this local study a relatively higher incidence of CIN2+ pathology was identified in patients who underwent a primary excisional procedure as opposed to those who had a colposcopic-directed biopsy (67% and 42.5% respectively). Since the mean age, HPV prevalence and HPV 16 and 18 prevalence have been shown to be relatively equal in both sub-groups, one would expect the histological outcomes to be equivalent. Since LLETZ is a larger biopsy it enables better

histopathological representation of the cervical epithelial abnormalities and thus can be considered a gold standard in terms of histopathological diagnosis sensitivity.⁵

The see-and-treat approach is controversial due to the possibility of overtreatment. Thus, patients might be unnecessarily exposed to risks associated with a LLETZ procedure. These include infections, bleeding and preterm labour. The overtreatment rate following LLETZ in this study was 20.9%. This is referring to those patients with a normal, cervicitis or koilocytosis primary histological result. If LLETZ for CIN1 is also regarded as overtreatment, this figure increases to 32.5%. The overtreatment rate varies widely in different studies, but has been reported to be between 13.3-83.3% for LLETZ performed following HSIL cytology. The large majority of these studies do include CIN1 histologies when defining overtreatment, since CIN1 has a relatively high spontaneous regression rate.⁷

Excisional procedures carry a higher rate of complications than biopsies, both short-term and long-term. Short-term complications, though usually minor, include bleeding, pelvic pain, and infection. There is also conflicting evidence associating LLETZ procedures with a higher risk of preterm delivery in future pregnancies. Nonetheless, the see-and-treat strategy is the primary mode of treatment in several centres due to lower costs, decreased patient anxiety, and increased compliance making it appealing for patients at risk of being lost to follow-up.^{9, 10} Nevertheless there has never been a local study assessing compliance to treatment and outpatient clinical follow-up. This would be of value, since the issue of non-compliance may not play a significant role in a small country with one state hospital.

Histological diagnosis from definitive treatment, such as excisional procedures, as already discussed, sometimes identify a more advanced stage of CIN than do colposcopic biopsies, where the severity of the cervical lesion may be underestimated.¹¹ Although cervical biopsies should represent the worst epithelial changes present on the cervix, this is not always the case in view of the subjective nature of colposcopic examination and possibly suboptimal colposcopic technique.

In a prospective study by Buxton EJ et al of 243 women, there was a higher rate of detection of severe lesions obtained following excisional

procedures versus colposcopically-directed biopsies; a difference of 25.5%.¹² Similarly in this study, a 24.9% discrepancy in CIN2+ detection was noted between the conventional approach and the see-and-treat approach, with the highest pick up rate obtained with primary excisional procedures. This potentially represents an underestimation of CIN, which can have potentially serious implications on patient outcome since it could lead to false reassurance for both clinician and patient.

Moreover, inter-observer variation in interpretation of colposcopic images exists, resulting in unfavourable colposcopic biopsies. There is also significant potential error due to the subjective nature of the examination as reflected in selection of the site for biopsy. In a prospective study by Pretorius RG et al in 2004, a comparison was made between histological results obtained from colposcopically-directed biopsies versus cervical biopsies taken at random without the guide of a colposcope. It was reported that 57.1% of colposcopy-directed biopsies were CIN2+ while only 37.4% of random biopsies showed this same histology result.¹³ This implies that colposcopic skill has a significant effect on diagnosis and patient management. CIN2+ rates in our local study fall just above the rate of random biopsies described in the latter study. One could thus hypothesise that local colposcopic expertise could be limiting the accurate diagnosis of CIN2+ in HSIL patients.

With the mean age of the two patient cohorts being relatively equal, differences in outcome variables could be more reliably linked to respective mode of management. One would expect a discrepancy in the mean ages as women below the age of 24 years are advised to undergo a colposcopy first, while for women over 24 years a colposcopy or a primary excisional procedure may be considered. This is due to the higher rates of regression in women under 24 years of age and risks of preterm labour following surgical cervical trauma.¹² This could be due to a large proportion of older patients being channelled through the more conservative interval approach despite their age.

Conclusion

Local management of patients with HSIL cytology remains controversial. Our results have shown that the conventional approach within our local setting potentially has inferior sensitivity in picking up CIN2+ lesions when compared to the

see-and-treat approach, with a discrepancy of 24.9%. This possibly represents a proportion of false negative results which could carry implications on patient outcome. On the other hand, primary excisional procedures were associated with an overtreatment rate of at least 20.9%, potentially subjecting patients to unnecessary risks.

Certainly, our local colposcopic service would benefit from improved colposcopic expertise, with the aim of improving the sensitivity of colposcopic-directed biopsies. Furthermore, the basis of the see-and-treat approach involves primarily assessing the cervix macroscopically via colposcopy, and only proceeding to a LLETZ if the colposcopic impression is suggestive of high-grade findings. Thus by improving the skill and confidence of the colposcopist, patients with HSIL who are found to have a macroscopically healthy cervix could be shifted to the three-step approach. In this way, the rate of overtreatment would be expected to decrease.

In conclusion, we recommend improving local colposcopic skill in order to reduce the rate of overtreatment and missed lesions at biopsy. This could be achieved by having these procedures performed by experienced and accredited colposcopists, as well as by setting up a structured colposcopy training programme for specialty trainees. This study could be repeated in the future once the necessary improvements to our colposcopic service have been enacted.

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The Prevalence of Trunk Asymmetries in the small Island state of Malta

Mark Sacco, Michela Catania

Abstract

Background: Malta, the smallest member state of the European Union is constituted of two inhabited islands Malta and Gozo. In the Maltese islands there has not been any large population size definitive study concerning the incidence of trunk asymmetries that may indicate Adolescent Idiopathic Scoliosis (AIS) amongst the general population. Scoliosis is one of the most deforming orthopaedic conditions confronting children. To confirm the orthopaedic condition of scoliosis one has to carry out a visual examination that usually consists of the Adam's Forward Bend test, this is followed by the measurement of trunk rotation with the use of a Bunnell Scoliometer. Should the angle of trunk rotation be more than five degrees then the positively screened student be referred for x-Rays and a 10 degree Cobb angle taken as being required to confirm the diagnosis of Scoliosis. The lack of a full scale study together with the apparent lack of awareness regarding the condition has prompted the authors to research the situation on all Gozitan children aged between 13 and 15 years of age.

It was decided to measure Trunk Asymmetry and the aim of the study was to obtain statistical data on the occurrence of trunk asymmetries amongst the Gozitan population, to further analyse the ratio of distribution of trunk asymmetries between female and male students and finally to refer the positively screened students to the relevant medical authorities for x-ray to confirm a scoliosis diagnosis.

Methods: This quantitative study design was carried out on all children aged between 13 to 15 years old over a five-month period. An Adam's forward bend test and Scoliometer reading were taken for each participant consenting to this study. To minimise bias a qualified full time Physiotherapist graduated with a Bachelor of Science Honours degree in Physiotherapy since 2012, carried out these tests in the selected schools.

Results: The results of the study concluded that 5.3% of the adolescent population in Gozo suffer from trunk asymmetries (13 out of 245). Prevalence of trunk asymmetry was calculated using the 95% confidence interval and the Chi square tests had a significant p-value. Further analysis showed that 69% of these were female and 31% were male. These results demonstrate that the prevalence of trunk asymmetries in Gozitan adolescents is comparable to that stated within the current literature.

Conclusions: Results from the study confirms that trunk asymmetry is relatively common within the Maltese population. This might be indicative that a significant portion of the Maltese adolescent population might suffer from Adolescent Idiopathic Scoliosis. The intention of this research is to increase the general public's awareness of the condition AIS, to make this condition more prominent to members of the allied professions, to reinforce the need for school screening projects and finally to ensure that the condition Trunk Asymmetry and Scoliosis is given the importance that it requires in the curriculum of study for physiotherapists.

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Keywords

Adolescent Idiopathic Scoliosis, Trunk Asymmetry, Cobb Angle, Prevalence, Scoliometer, Adam Forward Bend Test

Background

The total population of the Maltese islands is 429,344. According to the demographic review in 2015, Gozo has a population of 15,624 males and 15,822 females creating a current population of 31,446 inhabitants. Due to its geographic status and its small population size it can be considered an entire entity and the whole population of a particular age group can be researched. AIS being a common orthopaedic condition that effects a percentage of any population warrants further investigation. This has led the researchers to study the prevalence of asymmetrical trunk rotations that can be referred for further radiographic investigations within the Gozitan population in an effort to quantify the condition scoliosis. A high incidence of asymmetrical trunk rotation that might equate to an increase in the diagnosis of scoliosis may suggest it to be included within the physiotherapy curriculum. Also an early diagnosis of the asymmetrical trunk rotation and an early intervention by a physiotherapist may result in amelioration or preventing further complications that may lead to this condition scoliosis or surgery. Scoliosis has been described as one of the most deforming orthopaedic problems confronting children (Pavlu et al., 2009). According to the National Scoliosis Foundation (NSF), scoliosis affects 2 - 3% of the population, or an estimated 6 million people in the United States (National Scoliosis Foundation, 2019).

Scoliosis is, ‘‘a three dimensional torsional deformity of the spine and trunk’’ (Grivas et al., 2008) According to Konieczny, Senyurt and Krauspe (2013) adolescent scoliosis develops at the age of 11-18 years and accounts for approximately 90% of cases of idiopathic scoliosis in children (Konieczny et al., 2013).

Patients suffering from scoliosis are typically classified according to cause. Congenital scoliosis is an abnormality in the vertebral column, which may lead to progressive spinal deformity. On the other hand neuromuscular scoliosis, is a deformity caused by an abnormality of the central nervous system (such as spastic quadriplegia) or the peripheral nervous system (such as muscular

dystrophy) or a combination of both the sensory and motor nerves (such as syringomyelia). Degenerative disc disease has also been attributed as a cause to the development of scoliosis in adults. Certain connective tissue diseases and patients suffering from neurofibromatosis are also prone to having this condition. However the commonest cause of scoliosis is idiopathic. Idiopathic scoliosis is further sub classified as infantile when a child up to 3 years of age is affected; juvenile when a child up to 10 years of age is affected and adolescent scoliosis affecting children over 10 years of age (Hresko et al., 2013).

Not all trunk asymmetries are classified as scoliosis, curvature of the spine may be related to various factors. In fact, cobb angle of $\geq 10^\circ$ is regarded as the minimum angulation to define a curvature in the spine as scoliosis. (Konieczny et al., 2013).

The aim of this research study was:

1. To obtain statistical data on the occurrence of trunk asymmetries amongst the Gozitan population in both male and female students between the ages of 13-15 years.
2. To determine the ratio of distribution of trunk asymmetries between female and male students.

Method

Population

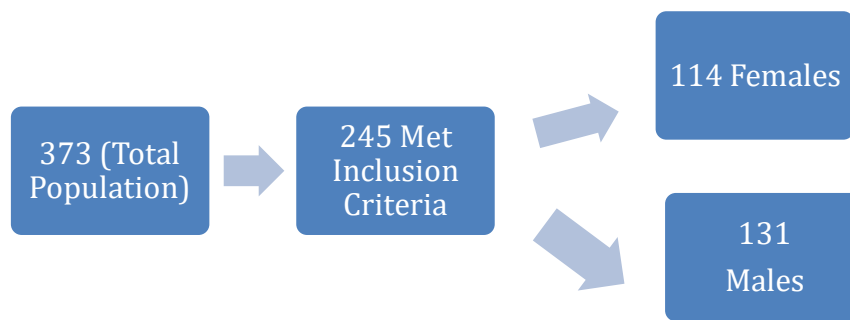
Following approval from the Department of Education, each Head of School was approached and approval obtained to carry out the study. An information letter together with a consent form was distributed to all students by members of staff from the schools. The premises that the examinations took part were identified all having privacy, good lighting, adequate space and considered to be safe. Each student was asked to enter the room individually. All students were advised to wear appropriate clothing, changed and examined in the presence of a teacher. The floor was marked with a horizontal line indicating where the students had to stand.

All school children aged between 13-15 years (373 students) were invited to participate in the study. The whole of the age group population chosen was used for the findings of this study. A random selection did not to be used owing to the small Gozitan population.

The reasons behind this age bracket being chosen were that; according to WHO, the period between the ages of “10-19 years” are adolescence years. Thus, this study commenced at 13 assuming that should there be a spinal deformity present; this would be picked up during the screening process (Scoliosis Research Society, 2019). This reasoning also led to the cut off point of 15 years as literature supports the fact that most scoliosis patients will have an element of deformity present by this age, being the age at which changes at the spine commonly occur (UCLA Spine Centre, 2016). The cohort in the study were Caucasian.

The inclusion criteria included all 373, 13-15 year old students in state and church schools, who were Maltese citizens living in either Malta or Gozo for the last ten consecutive years. Another inclusion criteria is that they needed to be capable of standing and bending forward unaided. Out of these 373 students 178 were female and 195 were male. 245 students met the inclusion criteria, thus the percentage population for this study was 65.7%, out of which 131 were males and 114 females (see figure 1 breakdown of population sample). Children without parental consent were excluded.

Figure 1: Breakdown of population sample



Procedure

All participants performed the Adam Forward Bending Test with the hands clasped and trunk asymmetries were measured by a Bunnell Scoliometer

The students were first observed in the standing position and asked to stay in their natural standing position with their arms by their sides. Any abnormalities or asymmetries were noted. The participants were then asked to place their feet on the markings present (10 centimetres apart). They were instructed to grasp their hands with their elbows straight and to bend forwards as far as they could go, keeping their knees straight. At this stage they were observed at eye-level in this position from the back and side. If a rib hump was observed then a Scoliometer was placed along the spine with

the ‘0’ mark at the top of the spinous process and the greatest reading noted. For the purpose of this study an angle of more than 7 degrees was taken to be positive for scoliosis. As Grivas et al states in his study in 2002, “a Scoliometer reading of 7 degrees should be an indication for radiographic evaluation of the whole spine. The Scoliometer threshold reading of 7 degrees or more is used by the majority of practitioners”. This procedure on average took four minutes, with female students taking slightly longer. All students in which a trunk asymmetry of a 7 degree Scoliometer reading was noted, were given a pre-prepared letter informing their parents/guardians about the results and advised to seek medical assistance (Grivas et al., 2002).

The Scoliometer is known to have a high inter-rater reliability and validity. According to Murrell

et al., study in 1993 intra-rater reliability for the use of the Scoliometer has been described as outstanding and thus reliable to use, being a reproducible tool that can compare easily (Murrell et al., 1993). This was further confirmed by Bonagamba et al., in 2010 (Bonagamba et al., 2010). Therefore it is a useful tool when used in screening programmes. Traditionally, screening procedures relied heavily on the forward bend test but this only offers subjective examination. One scoliometer measurement alone does not stand instead of radiographic Cobb angle measurements and therefore, clinicians should not use the Scoliometer exclusively as a diagnostic tool. Having said that a recent study in 2017 has shown that “ The maximal trunk rotations at the thoracic and lumbar regions were recorded with a scoliometer. Right asymmetry hump was deemed positive (+), and left asymmetry hump was deemed negative (-). The Cobb angles were measured with a Picture Archiving and Communication System. Statistical analysis included Pearson’s correlation coefficient, multivariate regression and Bland–Atman analysis...Based on the results of these two-parameter formulas for thoracic and lumbar curves, the Cobb angles can be predicted more accurately by the readings of the scoliometer. Physicians and other healthcare practitioners can thus evaluate patients with scoliosis more precisely than before with a scoliometer” which can be a worthy indication of use for future studies (Ma et al., 2017)

Data analysis

The chi-squared test was used to evaluate whether there was a significant association between gender and a significant trunk asymmetry. Therefore it was used to find whether scoliosis is more likely to be common in males or females. This test was used to determine prevalence and compare findings using the Statistical Package of Social Sciences (SPSS) through the inputting of raw data. Descriptive analysis was used to interpret results.

The Prevalence of trunk asymmetry was calculated using the 95% Confidence Interval formula, confidence interval (CI) = ± z σp of which:

1. P is the sample proportion which is

$$\frac{\text{Number of positive findings}}{\text{Total sample size}} = \frac{13}{245} = 0.0531$$
2. z is a constant = 1.96 assuming a 95% confidence interval
3. σp is the standard error = $\sqrt{p(1-p) / n}$ x (N (total population 373)-n (sample size 245)) / (N-1)

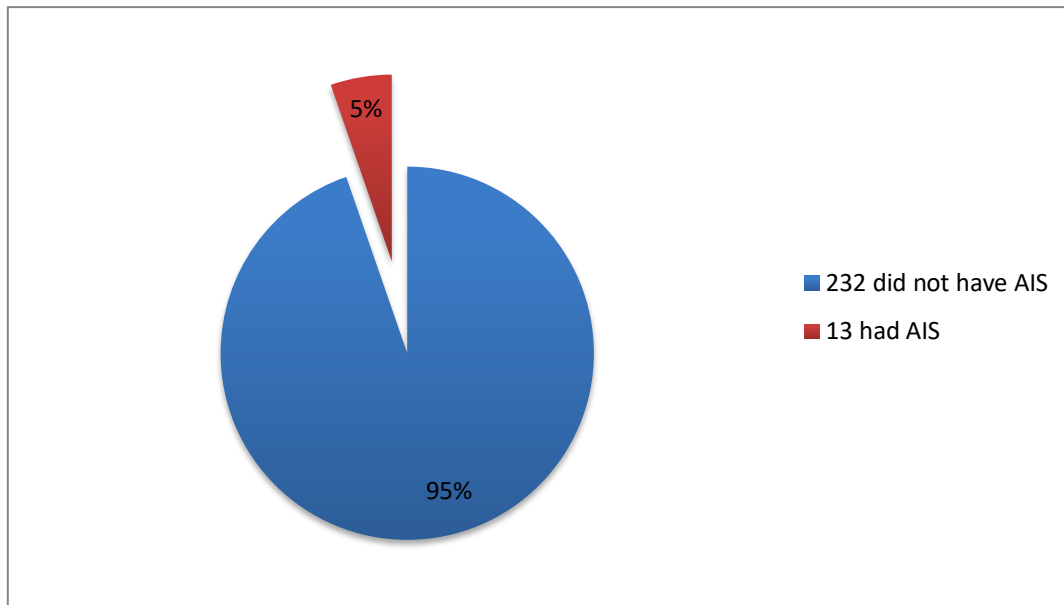
Results

The findings from the research concluded that 13 adolescents had a positive result (see Figure 2), which was determined by a reading of trunk asymmetry of 7 degrees or more on the Scoliometer, together with a positive Adam Forward Bending Test. Thus, the Prevalence of students with trunk asymmetries in Gozitan children was found to be 5.3% within this age group. “Further analysis of the data revealed that the prevalence of trunk asymmetries was higher in the females (N=9) than in the males, as found to be 79% is to 31% respectively (N=4)”. Thus the female to male ratio was 9:4 which is equivalent to 2.25:1 (see Table 1).

Table 1: Prevalence of trunk asymmetries in male and female children

	Males	Females	Total
Number of Trunk Asymmetries	4 (31%)	9 (69%)	13 (100%)
P Value			0.092

The research result of 5.3% demonstrated a 95% confident that the prevalence of trunk asymmetry is between the lower (3.66%) and upper (6.96%) limits of the 95% confidence interval of the prevalence. These readings, if confirmed by further radiographical examination or two parameter scoliometer vales may further confirm and quantify the presence of scoliosis amongst Gozitan adolescents aged 13-15 years.

Figure 2: Total Sample Population

The CI was calculated using the formula $CI = \pm z \sigma_p$. The Chi Square P value was calculated to be 0.092, whilst the σ_p was calculated to be 0.0084 ($\sqrt{(0.0531)(1-0.0531) / 245 \times (373-245) / (373-1)}$). Therefore the confidence Interval = $pbar \pm z \sigma_p$
 $= 0.0531 + 1.96 (0.0084) = 0.0366$
 And
 $= 0.0531 - 1.96 (0.0084) = 0.0696$
 Therefore $0.0366 < p < 0.0696$

Since the p-value lies in between the lower and upper limits of the 95% confidence value we can conclude that readings are 95% confident of findings.

Discussion

Presently there is little evidence or literature supporting the prevalence of trunk asymmetries and scoliosis in children in Malta or Gozo. The two studies that have been carried out so far (Sultana 2001 and Spiteri et al., 2005), appear to have substantial weaknesses in the research methodology including varying definitions of scoliosis, the rigour of the study protocol, a small sample size, different age-groups, and different research tools.

A small study on Maltese students aged 10 to 14 using the Adam Forward Bend Test and Scoliometer concluded that 24.1% tested positive to the forward bend test (Sultana, 2001). Sultana in 2001 carried out a study on 676 students taking 7 degrees as the angle of trunk asymmetry with 32

(4.7%) being diagnosed as having this. He goes on to state that the female to male ratio was 5.4:1 (Sultana, 2001). This study was carried out on two schools and hence the sample as compared to the total population in Malta may have been too small although the total sample was larger than that carried out in this study. The researcher was the individual actually carrying out the readings hence an element of bias might have been included. However the results from this study are relatively similar to another carried out in Malta by Spiteri et al in 2005. In this other study, the Department of Orthopaedic Surgery in St. Luke's Hospital Malta, concluded that out of a population of 611 patients already diagnosed with scoliosis aged between 10 and 16 years, 344 of them were diagnosed as having adolescent idiopathic scoliosis with the scoliometric angle being taken as greater than 5 degrees. The Incidence from this study was of 0.69% for females and 0.15% in males hence the female to male ratio was 5:1 similar to that of Sultana in 2001 (Spiteri et al., 2005).

The authors in this study acknowledge the fact that a Scoliometer was the tool used to measure the angle of the deformed spine and that scoliosis can only be diagnosed by means of radiographic measurements. Hence the results from this study measure trunk asymmetry and are an over estimation of scoliosis prevalence. Only a percentage of the participants who presented with a curve measured by the Scoliometer are likely to be

diagnosed as suffering from scoliosis. In a bid to prevent children being exposed to unnecessary x ray exposure the use of a Scoliometer as the research tool was solely used to measure trunk asymmetry. This article is the first step towards further studies for radiographical evidence

In comparison to the previous results this study concluded that the prevalence of trunk asymmetry amongst 13 – 15 year old Gozitan children is of 5.3%, with a female to male ratio of 2.25:1. This percentage result may appear relatively high when compared to other countries that have carried out prevalence studies but unfortunately very hard to compare as the study has only measured trunk asymmetry. This is due to the fact that very few countries especially those bordering the Mediterranean Sea have published any studies concerning trunk asymmetry and the fact that there is still such a discrepancy at which angle AIS is diagnosed. Seven degrees of trunk asymmetry was taken as the deciding angle to refer for further radiographic investigations. Hence, the relatively high incidence of trunk asymmetries generated from this study could have resulted in a lower incidence of scoliosis when comparing to the same ranges of other countries and studies.

Prevalence of trunk asymmetry also depends on the age and gender of the population being studied and modern literature supports the fact that the incidence of trunk asymmetry is higher in females and is genetically determined (Wynne-Davies, R., 1968). Gozo being a very small island with a relatively high population could lend itself to a certain amount of inbreeding which might have influenced the prevalence of trunk asymmetries and possibly scoliosis. These three reasons could also be the possible cause why these results showed a higher likely incidence of AIS in Gozo when compared to other larger countries or studies.

The uniqueness of this research is that even though at face value the research population looks small, this study was not carried out on a sample of a population, but on all the 13 to 15 year olds of the island's population. Results from this study did not concur with Adobor (2011) who stated that there is a higher prevalence of AIS in the northern European geographic latitudes and lower in southern countries (Adobor et al., 2011), possibly due to what Grivas, et al. stated in 2006, that there might be a link between hours of sunshine, commencement of menarche and prevalence of AIS

(Grivas et al., 2006). Adobor's study on a total population of 4000 concluded that 1.5% or 60 presented with a positive Scoliometer test of more than 7 degrees. However only 0.55% or 22 were found to have true scoliosis that were confirmed by x ray examination with a Cobb angle of more than 10 degrees. Another study in a northern country confirmed a low incidence, which was carried out by Willner and Uden (1982) regarding the prevalence of AIS in southern Sweden. In this study, 17,181 concluded that 108 (0.6%) were found positive with a Cobb angle of 10 degrees taken as the lower limit to diagnose scoliosis (Wilner et al., 1992). On the other hand another study in Finland has contradictory results as they recorded high levels of incidence (Nissinen et al., 1993). Nissinen et al., in 1993 carried out a study on 855 school children and 29.2% were found to have trunk asymmetry that were further examined by means of radiography to confirm that the prevalence of scoliosis taking a Cobb angle of more than 10 degrees was of 9.2%.

Another study conducted in Greece which can be considered as a southern country by Soucacos et al., in 1997 had 82,901 children participating (41,939 boys and 40,962 girls) of ages between 9 to 14 years. Results revealed that 4,185 (5%) having a positive forward bend test led to further investigation by means of x rays confirming that scoliosis was present in 1.7 % of the population with a Cobb angle of 10 degrees or more (Soucacos, et al., 1997). Replicating this study in Gozo also resulted in a higher prevalence similar to the above study by Soucacos et al., when compared to the statement by Adobor et al., that the incidence of AIS in northern countries is more prevalent than that of southern countries. In fact, this research resulted in 13 out of 245 (5.3%) having trunk asymmetry. This is similar to that conducted by Soucacos et al., (5%) in Greece. However these results in the Maltese Islands were not further investigated by means of x rays to confirm the incidence of scoliosis. Still, these results do not reflect the study in Sivas, Turkey, by Cilli et al., carried out in 2009 with a population of 3,175. Results from a forward bend test and palpation of the spine resulting in an incidence of scoliosis at 0.47% and a female to male ratio of 2:1. Yet not confirmed by radiographic studies (Cilli et al., 2009). Ugras et al. (2010) on the other hand determined the prevalence of scoliosis and the cost

effectiveness of a school screening programme also in Turkey taking a Cobb angle of more than 10 degrees on a research population of 4,259 children aged 10-14 years showed a prevalence for AIS of

2.5%, with a ratio of girls to boys of 2.5:1 (Ugras et al., 2010) (see Table 2 for a summary of findings).

Table 2: Summary of findings

Malta, 2001. Forward bend test and Scoliometer (Sultana 2001)	Reviewed 676, 24.1% positive
Malta 2005. Scoliometer (Spiteri et al., 2005)	Reviewed 611 with scoliosis, 344 positive
Norway, 2011. Adam Forward Bending Test and measurement of gibbus using a scoliometer. (Adobor et al., 2011)	Reviewed 4000, The prevalence of idiopathic scoliosis defined as a positive Adam Forward Bending Test, gibbus > 7° and primary major curve on radiographs > 10°, was 0.55%
Greece, 2006. The scoliometer readings in both standing and sitting position (Grivas et al., 2006)	Reviewed 2071, The mean difference of frequency of asymmetry (ATR > 0 degrees) at standing minus sitting forward bending position for boys and girls was 10.22% and 9.37%, respectively. The mean frequency of asymmetry of 7 or more degrees was 3.23% for boys and 3.92% for girls at the standing forward bending position and 1.62% and 2.21% at the sitting, respectively.
Sweden, 1982. Children with clinical signs of scoliosis including a positive forward bending test were admitted to the Department of Orthopedic Surgery for reinvestigation and AP roentgenograms. (Wilner et al., 1992)	Reviewed, 17181. There were 474 children with a scoliosis measuring 5 degrees of more (prevalence 2.8 per cent).
Finland, 1993. Trunk asymmetry was measured by the forward bending test and moiré topography. A posteroanterior standing radiograph of the spine was taken of those 250 (29.2%) children who had a trunk hump > or = 8 mm. (Nissinen et al., 1993)	Reviewed, 855. Only 8.3% of the children were found to be symmetric (hump 0-2 mm) in the forward bending test: 65.5% had a hump of 3-7 mm and 26.2% had a hump > or = 8 mm at 13.8 years.
1997, Greece. Forward bend test and radiographs (Soucacos et al., 1997)	Reviewed, 82,901. Five thousand eight hundred and three children had clinical signs of scoliosis and, of these, 4185 were referred for posteroanterior radiographs (to be made with the patient standing) because they had a positive result on the forward-bending test
Turkey, 2009. Forward bend and palpation (Cili et al., 2009)	Reviewed 3175. 6 to 8 were selected from 16,103 students using a stratified sampling method, 15 positive
Turkey, 2009. Forward bend and radiographs (Ugras et al., 2010)	Reviewed 4259. Prevalence of 25/1000. Thirty-nine children (0.91%) from sample population displayed abnormalities on the bending test, and 29 children (0.68%) came to our hospital for further evaluation (Table 1). Eleven of these (0.25%) showed radiographic evidence of abnormal curvature.
Korea, 2011. Scoliometer reading $\geq 5^\circ$ were referred for radiograms. (Suh et al., 2011)	Reviewed 1,134,8. 37,339 of them had positive results with Cobb angles $\geq 10^\circ$

<p>Singapore, 2005. Those with scoliometer readings of more than 5 degrees underwent radiographic evaluation (Wong et al., 2005)</p>	<p>Reviewed 72,699. Prevalence rates were 0.05% for girls and 0.02% for boys at 6 to 7 years of age, 0.24% for girls and 0.15% for boys at 9 to 10 years of age, 1.37% for girls and 0.21% for boys at 11 to 12 years of age, and 2.22% and 0.66%, respectively, for girls and boys at 13 to 14 years of age</p>
<p>1997, Crete. Scoliometers are used for the selection of children who should be referred for radiological evaluation (.7 degrees) (Koukourakis et al., 1997)</p>	<p>Reviewed 21,220 children, 9.6% were referred for radiological examination; 1.7% of the screened children were found to have sine deformities with angular values >10 degrees. The prevalence of severe abnormalities (.20 degrees) requiring conservative treatment was 0.06%. Thirty percent of the scoliotic deformities involved the thoracolumbar region, whereas 48 and 22% of curves were confined to the thoracic or lumbar area respectively.</p>

There are numerous other studies in the literature from outside Europe that demonstrate a varying percentage incidence of AIS, the following two are just two examples that are being quoted to serve as examples. The large study by Suh et al., conducted in Korea in 2011 with a research population of 1,134,890 children participating (584,554 boys and 550,336 girls) showed an overall prevalence of 3.26% and a female to male ratio of 2.2:1, however the decisive angle defining AIS was taken as more than 5 degrees (Suh et al., 2011). In Singapore, taking a Cobb angle measurement of 10 degrees on a total population of 37,141 Wong et al 2005 report a prevalence of 0.93% range (Wong et al., 2005).

The study that is closest to this research must be that by Koukourakis et Al. in 1997 in Crete, as both countries are islands situated in the Mediterranean Sea, approximately on the same longitude. Trunk asymmetry was found to be present in 9.6% with a Scoliometer reading of 7 degrees, whilst 1.7% found to have scoliosis of more than 10 degrees (Koukourakis et al., 1997). The literature has shown that the prevalence of trunk asymmetry in Northern countries was between 1.5% and 29.2%. While in southern countries it was that of 5% to 9.6%. Hence this study with an incidence of 5.3% is similar to the literature findings.

Conclusion

This study has concluded that the overall prevalence for trunk asymmetry taking a defining angle of 7 degrees within a total population of the island of Gozo was 5.3%. However these results are

not definitive confirmation of diagnosis of the condition scoliosis but indicative. All children who presented with these results were asked to have further investigations to confirm the diagnosis. Results from the study reconfirm that there is a high incidence of trunk asymmetry, within the Maltese population. Thus the knowledge and treatment about this condition that could lead to AIS should be included within the local physiotherapy curriculum, taught at the University and the results made public to the local physiotherapy association that can influence the early intervention by the physiotherapist in preventing further complications that may lead to surgery.

Future Recommendations:

1. Further studies comparing rates in different counties would be interesting.
2. This study could also be taken further into analysing results using the two parameter Scoliometer screening.

List Of Abbreviations

AIS: Adolescent Idiopathic Scoliosis

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A study of the pulmonary complications of preterm infants after prenatal corticosteroids prophylaxis in a major Bulgarian hospital

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Abstract: An increasingly common problem in obstetrics and neonatology is premature birth. This problem is the cause of many health complications in premature neonates and is leading to neonatal mortality. These complications affect the whole body of premature babies, the respiratory system has the largest percentage due to lack of the period for intrauterine maturation of the lung. The purpose of this study is to analyze data on complications, and especially pulmonary complications that develop preterm infants, and to analyze the impact of premature corticosteroid prophylaxis.

A retrospective case-control study was carried out at the Clinic of Obstetrics and Gynecology, University Hospital "St. Georgi" Plovdiv, Bulgaria for the period 2015-2016 year. 167 preterm infants have been studied. They were divided into two main groups: a working group of 89 preterm infants with prenatal corticosteroid prophylaxis and a control group of 78 preterm infants without prenatal prophylaxis. Data on clinical outcomes, health status, background complications of prenatal corticosteroid prophylaxis have been analyzed. The summary, however, of the results that is: the 3.6% difference has been found between newborn children with RDS and those with all other disabilities; this shows that in preterm infants the priority is to damage the respiratory system. Over 60% of the prematurity develop Respiratory distress syndrome. The presence of respiratory complications is due to the earlier gestational week of birth and the older age of the mother and is somewhat limited by the prenatal administration of corticosteroids.

Key words: prenatal corticosteroid prophylaxis, preterm birth, pulmonary complications

Introduction

Premature birth is a leading medical, social and economic problem. It is the most common cause of neonatal mortality in developed countries.¹⁻⁴ Its consequences are multiple complications leading to a high neonatal mortality in the national and global world. Birth before the term does not provide the baby with enough time to develop. The earlier before the term a child is born, the more serious health problems can be caused by early or late complications.⁵ Among the most common complications in the prematurity are severe

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ventilation deficiency syndrome, apnea, respiratory distress, broncho-pulmonary dysplasia, pulmonary edema, cerebral haemorrhage, renal damage, heart damage, necrotizing enterocolitis, infections and many others.

The Bulgarian statistics produced data that 10-12% (2015) of all pregnancies terminated with a preterm birth. In spite of the series of surveys in this field and the efforts of specialists in Gynecology and Obstetrics preterm births, follow a continuous trend to increasing.⁶ According to data from the National Statistical Institute for 2015, 65 446 children were born in Bulgaria⁷. 6 413 children were born in Plovdiv and 2100 of them were born in the Clinic of Obstetrics and Gynecology at UMHAT "St. George "Plovdiv, Bulgaria where the present study was conducted. The rate of preterm infants for this clinic is 11% or approximately 231 newborns were born prematurely.

Complications of the respiratory system are numerous in premature babies due to lack of the period for intrauterine maturation of the lung.

One of the pathological syndromes of premature neonates is precisely related to the development of the lungs and is referred to as a Hyaline membrane disease (HMD) or neonatal Respiratory Distress Syndrome. It is caused by a deficiency in the synthesis of surfactant combined with structural immaturity of the lungs. It may also be a consequence of a neonatal infection.⁸⁻⁹ Hyaline membrane disease affects 1% of premature neonates in the world and is the leading cause of death in this group of patients.¹⁰ Complications of the respiratory system are numerous in premature babies due to lack of the period for intrauterine maturation of the lung.

Respiratory distress syndrome is the most common cause leading to death among premature neonates.¹¹ Even those who survive are at high risk of developing cerebral palsy, subsequent problems in the educational process and respiratory disorders.¹² Statistics show that in high-income countries the percentage of pre-natal births varies from 7% to 12%, while in low- and middle-income countries, such as those in Africa, it can reach 20%.

The premature babies are at risk of apnea (sudden breathing stoppage). It leads to a varying rate of change in heart rate, decrease in oxygen in the blood or hypotension. For this reason, it is necessary to monitor the occurrence of complications in preterm newborns.¹³

Pulmonary haemorrhage - this complication leads to death in a large percentage of the cases in which it occurs. Since etiology and pathogenesis have not yet been fully elucidated, there is insufficient adequate prophylaxis and treatment. The factors associated with it and the accompanying clinical picture continue to be clarified.¹⁴

In the long term, complications may reflect the overall development of surviving preterm infants. Premature babies more often suffer from chronic health problems, some of which may require hospital treatment.

Aim

The purpose of this study is to analyze data on complications, and especially pulmonary complications that develop preterm infants, and to analyze the impact of premature corticosteroid prophylaxis.

Materials and methods

The University Hospital St. Georgi, which has a 140-year history and is the largest hospital in southern Bulgaria, serving 1300 hospital beds. The Clinic for Obstetrics and Gynecology serves 131 hospital beds and has a Maternity ward, Neonatology ward, Ward of Pathological Pregnancy and Surgical Gynecology ward. A retrospective and prospective case-control study was conducted at the Clinic of Obstetrics and Gynecology, UMHAT "St. Georgi "Plovdiv, Bulgaria for the period of one and a half years. Documentary method is used, with primary data for pre-term infants recruited from "Case History", "Mother's Epicrisis" and "Newborn's Epicrisis." All mothers of newborns covered by the study signed an "Informed consent" document, consenting to the use of their data. An individual protocol was created and completed for each of cases. The data were processed with a statistical program SPSS Vol. 19.

The study involved 167 preterm infants and all of them were born in the Maternity ward at the Clinic of Obstetrics and Gynecology of St. George University Hospital in period March 2015 – September 2016. All of 167 participants in the survey were divided into two main groups: a working group of 89 preterm infants to whose mothers it was administered prenatal corticosteroid prophylaxis - "cases" and a control group of 78 preterm infants without prenatal prophylaxis "controls".

For the purposes of the study, additional intragroup regrouping is performed based on the next indicators: according to the gestational week when the birth occurred, the newborns are divided into: early premature born - up to 32 and gestational week lately prematurely born from 32 gestational week to 36 gestational week+ 6 days; whether or not a prophylactic corticosteroid course has been completed or missing; the weight of newborns; etc.

The workgroup of 89 preterm infants was divided into 43 infants with a full course of corticosteroid prophylaxis of two or three applications of dexamethasone administered prenatal of their mothers. 22 of their mothers were administered with 2 applications (12 mg) and 21 with 3 applications (18 mg) of dexamethasone. And 45 children with incomplete course of corticosteroid prophylaxis with administered one application of 1 amp. x 6 mg/ml of dexamethasone administered prenatal of their mothers. According to the practice in the clinic is accepted to be considered completed course of corticosteroid prophylaxis of both 2 and 3 applications of dexamethasone (2 ampoules x 6 mg/ml a total 12 mg and 3 amp. x 6 mg/ml, total 18 mg). Only one dexamethasone application is considered an incomplete course.

According to the postnatal complications, two groups were formed – 25 preterm infants with complication of neonatal RDS (HDM) and a group of 101 infants with complication of other forms of RDS. It was formed a group with a life-saving surfactant regimen of 37 children with single or multiple insufflated exogenous surfactant.

An individual research protocol is completed for each patient – a questionnaire has been specifically designed for the purpose of the study.

Criteria for including in the study: each live birth before 37 gestational week, according to the new standards of Obstetrics and Gynecology and Neonatology in Bulgaria from 2009, are in accordance with the European criteria for a live birth child. For the purpose of the study, all children with signs of life at birth, including those weighing less than 1000g, who died before the 168th hour, they hadn't been registered as live births till 2008, as well as those weighing less than 600g, who died before the third day after birth, they are recorded as aborted.

Criteria for exclusion from the study are newborns with severe malformations; newborns

with severe hereditary diseases; born after termination of pregnancy by medical check-up late; died in the first hours of their birth without intensive care.

Collection of primary data: After carefully checking the adequacy and completeness of the questionnaire completion, a corresponding code is placed and the primary data is entered into a statistical processing program. The data is entered and processed with the IBM SPSS Statistics Ver.19.0 statistical package. For a significance level where the zero hypothesis is accepted, $p < 0.05$ is taken.

Results and discussion

According the study 167 preterm infants, the mean gestational week of birth was 32.42 ± 3.38 gestational week. According to the study 89 (53.3%) were girls, and 78 (46.7%) were boys. The structural distribution, including the number and percentages of newborn children in each gestational week, is presented in Table. 1. Most children were born in 36 gestational week - 40 (24%), followed by children born in 35 gestational week - 26 (15.6%). The least born children were born in 25 gestational week. - 2 (1.2%), and in 29 gestational week - 4 (2.4%).

Table 1: Gestational Week of Birth

<i>Gestational Week</i>	<i>Number</i>	<i>Percentages</i>
25	2	1,2
26	13	7,8
27	6	3,6
28	8	4,8
29	4	2,4
30	16	9,6
31	16	9,6
32	10	6,0
33	6	3,6
34	20	12,0
35	26	15,6
36	40	24,0
Total	167	100,0

Table 2: Anthropometric characteristics of the newborn children studied

Anthropometric data	Number of children	Minimum	Maximum	Average	Deviation value
Child weight (gram)	167	700	2490	1687,19	521,240
Height (cm)	167	31	47	41,43	4,466

Table 3: Grade of prematurity according to the weight of the newborn child

Grade of prematurity	Number	Percentage
I –grade – from 2500g. to 2001g.	56	33,5
II –grade - from 2000g. to 1501g.	52	31,1
III - grade - from 1500g. to 1001g.	36	21,6
IV - grade - from 1000g. to 501g.	23	13,8
Total	167	100,0

Table 4: Number of applications with dexamethasone

Type of application	Number	Percentage
1 - multiple applications with dexamethasone 6 mg/ml	45	51,1
2 - multiple applications with dexamethasone 12 mg/ml	22	25,0
3 - multiple applications with dexamethasone 18 mg/ml	21	23,9
Total	88	100,0

Table 5: Premature newborns with HMD

Presence of HMD	Number	Percentage
No	142	85,0
Yes	25	15,0
Total	167	100,0

Table 6: Premature newborn children with others forms of RDS

Presence of RDS	Number	Percentage
No	66	39,5
Yes	101	60,5
Total	167	100,0

Table 2 shows the average weight and growth of preterm infants, respectively, showing the minimum and maximum values of the variables.

The average age of the surveyed mothers is $26,24 \pm 6,17$ years, the youngest is 15 years old and the oldest is 40. These who live in cities are 127 (76%) and these who live in villages are 40 (24%).

Table 3 presents the four stages of prematurity according to the weight of preterm infants, with 23 (13.8%) of newborn children are the fourth grade. Those with a third grade of prematurity are 36 (21.6%), and the most are newborn children with first grade of prematurity - 56 (33.5%).

89 (53.3%) from the 167 preterm newborn children that have been studied a prenatal prophylaxis with dexamethasone has been realised. The number and percent distribution, depends on the number of applications with dexamethasone, and is presented in table. 4. The highest is the percentage of cases with uncompleted corticosteroid prophylaxis, i.e. one application was applied - 45 (51.1%), and the cases with completed dexamethasone prophylaxis were the remaining sum of 2 and 3 applications - 43 (48.9%).

25 (15%) of premature newborns has developed neonatal Respiratory Distress Syndrome (nRDS) - Hyaline membrane disease (HMD) and at 101 (60.5%) have developed various other forms of Respiratory Distress Syndrome (RDS) (Table 5 and Table. 6). From the total registered premature infants with some (other) health complications, nearly 2/3 of the newborns are 107 (64.1%) of the cases (Table 7). There is a difference of 3.6% between newborns with Respiratory distress syndrome and those with other disabilities, all these shows that premature newborns priority damaging the respiratory system.

Table 8 shows the percentage distribution of preterm infants who have nRDS (HMD) and other forms of RDS. Approximately 1/4 - 25 (24.8%) of newborn children with RDS developed HMD.

Other established health complications in preterm infants are presented in Table 1. 9. The most common complications in newborn children are: transient tachypnea + hypoventilation + dyspnoea - 13 (12.4%). The following frequency indices (here they are as single complications) are pulmonary edema - 10 (9.5%) of cases and pulmonary hypoventilation, also in 10 (9.5%).

Table 7: Other health complications in preterm infants

Existence of other health complications	Number	Percentage
No	60	35,9
Yes	107	64,1
Total	167	100,0

Table 8: Structural distribution of preterm infants with HMD and other forms of RDS

Presence of RDS	Presence of HMD		Total
	No	Yes	
No	66	0	66
	100,0%	0,0%	100,0%
Yes	76	25	101
	75,2%	24,8%	100,0%
Total	142	25	167
	85,0%	15,0%	100,0%

Table 9: Other health complications in preterm infants

Healthy complications	№p Number.	%
exhaust-gas collections + intraventricular hemorrhage	2	1,9
pulmonary edema	10	9,5
pulmonary edema and intraventricular hemorrhage	2	1,9
acute bullous insufficiency	4	3,8
overlaid infection	8	7,6
bronchopulmonary dysplasia	4	3,8
pneumothorax	2	1,9
cardiovascular diseases	2	1,9
intraventricular haemorrhage + infection + bronchopulmonary dysplasia + pneumothorax + retinopathy + necrotizing enterocolitis	2	1,9
transient tachypnea	4	3,8
pulmonary hypoventilation	10	9,5
atelectasis	4	3,8
respiratory failure	2	1,9
transient tachypnea + hypoventilation + dyspnoea	13	12,4
transient tachypnea + atelectasis	2	1,9
hypoventilation + respiratory failure	2	1,9
dyspnoea + hypoventilation	6	5,7
atelectasis + respiratory insufficiency (DN)	2	1,9
transient tachypnea + cardiovascular complications	2	1,9
transient tachypnea + dyspnea + hypoventilation	4	3,8
transient tachypnea + dyspnea + atelectasis + hypoventilation	2	1,9
dyspnoea + transient tachypnea + respiratory failure	2	1,9
transient tachypnea + dyspnoea + pulmonary haemorrhage	2	1,9
respiratory failure + pulmonary edema	2	1,9
respiratory failure + hypoventilation + transient tachypnea	2	1,9
dyspnoea + transient tachypnea	2	1,9
transient tachypnea + hypoventilation	2	1,9
pulmonary edema + dyspnoea + hypoventilation	2	1,9
transient tachypnea + pulmonary edema	2	1,9
Total	105	100,0

The overlaid infection presents in 8 (7.6%) of newborn infants. In 6 newborn children, poly-systemic combined disorders were observed - apart from respiratory lesions there was also intraventricular hemorrhage, and in one case PDS was associated with cardiovascular damage. It should be noted that most of the newborn children have registered polypathology, which includes several respiratory tract damages. In summary, 94.3% of the pathology in preterm infants includes mainly single or combined respiratory disorders.

Those who have only extra-pulmonary pathology have a total of 6 cases: 4 (3.8%) acute kidney failure and 2 (1.9%) with cardiovascular disease. This relative share represents only 5.7% of all registered complications in preterm infants.

A surfactant has been administered to 37 (22.2%) children enrolled in the study. According to the premature born children survey -24 (14.4%) died.

Conclusions

The 3.6% difference between newborn children with RDS and those with all other disabilities shows that preterm infants have respiratory system damaged primary. Over 60% of premature infants developed respiratory distress syndrome.

The presence of respiratory complications is exacerbated by the higher rate of prematurity as well as by increasing maternal age and somewhat limited by prenatal corticosteroids.

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Regional differences in Childhood BMI data - The Malta Childhood National Body Mass Index Study

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Abstract

Introduction: Obesity is a problem of major public health concern all over the world and Malta has high obesity prevalence rates. With over a third of Maltese children being overweight or obese, the Malta Childhood National Body Mass Index study was devised to quantify the extent of the problem precisely. This paper looks at regional differences in the BMI data obtained.

Methods: Training in measurement was provided to physical education teachers and identical stadiometers were used. Data was processed using World Health Organisation cut-offs for underweight, overweight and obesity.

Results: A total of 41,343 students from 145 schools were measured. Age range from 4.7 to 17 years. Approximately 40% of school-aged children in Malta were overweight or obese, with higher percentages of obesity than overweight being observed. Results show significant differences in BMI between children living in Northern and Southern regions of Malta.

Conclusion: Results from this study further confirm the high levels of overweight and obesity in Maltese children. The North-South differences should help better target public health resources and should be further evaluated in more focussed research.

Keywords

child, health, nutrition, obesity, region, Malta

Introduction

The world has seen the prevalence of obesity increasing year on year reaching epidemic levels in many countries.¹ For this reason, Public Health entities have put obesity on the forefront of their agenda. Particular focus is being given to childhood obesity. It is well known that overweight children become overweight adults and therefore tackling the problem from an early stage may be helpful in reducing the prevalence of obesity and its detrimental effects on health.²

In 2015, a national study was carried to measure the body mass index (BMI) of all children attending school in Malta thereby covering ages 5 to 15. This study was unique since all children were included for measurement rather than just a sample.⁶

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Schools in Malta are run by three main groups: 1) State schools are free and government-led; 2) Church schools are partly subsidized and run by the Roman Catholic Church; and 3) Independent schools are a mixture of schools privately run by different organizations against a set fee. Primary schools usually cater for children from 5 till 10 and secondary schools cater for students from 11 to 16 approximately.

Part of the data collected from the Malta Childhood National BMI study (2015-16) included the locality of residence of the child⁶. The purpose of this study was to describe the geographical distribution of prevalence of childhood overweight and obesity in Malta.

Method

Ethics

Ethical approval for the Malta National Childhood BMI study was obtained from the Ethics Committee of the Malta Education Division and the Malta University Research Ethics Committee. The Malta National Commissioner for Data Protection also endorsed this project. Permissions were also obtained separately from the Central Church schools authorities and from the Independent schools.

Data Collection

Data was collected using identical scale-stadiometers (GIMA 27288 PEGASO DIGITAL SCALE) in all schools. Measurements were carried out by the Physical Education teachers in each respective school or college. Teachers were shown how to measure height accurately and a reminder handout was attached to each weighing scale. Teachers were also responsible for data inputting into standardized and bespoke spreadsheet⁷. Physiotherapists coordinated by the Malta Association of Physiotherapists and other administrative staff also helped with data collection.

Current World Health Organisation (WHO) BMI cut-offs were used. Key values were overweight (between WHO 85-95 percentiles), obese (greater than WHO 95th percentile), and underweight (less than the 5th percentile).⁸

Students' BMI data was grouped according to geographical locality and region of birth. The

Maltese islands are divided into six regions by Malta's National Statistics Office: North, Northern Harbour, Southern Harbour, South East, West, and Gozo & Comino.

Results

This study included 145 schools – 39 Church, 94 State and 12 Independent schools, some of which have primary and/or secondary components, and some of which are coeducational and while others are not. Data was available for 41,343 students – 21,147 males and 20,196 females – ranging in age from 4.7-17years.

Summary statistics and number of children overweight, obese and underweight, by gender for primary and secondary schools by region, are shown in table 1. Table 2 displays percentages for the same data for overweight, obese and underweight. Figures 1 and 2 display ranked body mass index mean (and 95% confidence intervals) by region for primary and secondary schools respectively.

After ranking, chi test for trend for overweight and obesity by region showed highly significant trends for male primary (chi for trend=38.7, $p<0.0001$), male secondary (chi for trend=11.0, $p=0.001$), females primary (chi for trend=30.6, $p<0.0001$) and females secondary schools (chi for trend=30.6, $p<0.0001$).

Discussion

This analysis shows significant differences in BMI between children living in the North and those living in the South parts of the island, despite the small size of the country at just 316km². This disparity has been shown in previous studies but a study in 2011 seemed to suggest that this trend was fading.⁹ However, the trend is clearly still significantly present. Data from the Maltese National Statistics Office provide a picture of a wealthier North when compared to a less prosperous South.¹⁰⁻¹¹ For example, on average, persons living in the North were also found to live in larger residences, have better literacy levels, have a higher chance of owning their home (rather than renting) and have lower levels of unemployment when compared to the South.¹⁰⁻¹¹

Review Article

Table 1: Summary statistics and number of children overweight, obese and underweight, by gender for primary and secondary schools by region

	North	North Harbour	South Harbour	South Eastern	Western	Gozo and Comino
Males Primary						
N	1964	3405	2081	1972	1670	739
Mean	17.8	17.8	18.4	18.2	18.0	18.2
Standard error	0.1	0.1	0.1	0.1	0.1	0.1
Standard deviation	3.5	3.5	3.8	3.8	3.6	3.6
Overweight & obese (≥ P85%)	763	1347	971	858	669	328
Obese (≥ P95%)	493	833	677	577	445	222
Overweight (P85-95%)	270	514	294	281	224	106
Underweight (%)	49	73	51	40	34	4
Females Primary						
N	1891	3046	1948	1840	1551	855
Mean	17.6	17.7	18.3	18.1	17.8	18.1
Standard error	0.1	0.1	0.1	0.1	0.1	0.1
Standard deviation	3.3	3.5	3.9	3.8	3.6	3.6
Total Measured	1891	3046	1948	1840	1551	855
Overweight & obese (≥ P85%)	660	1050	798	725	544	337
Obese (≥ P95%)	377	633	515	448	319	215
Overweight (P85-95%)	283	417	283	277	225	122
Underweight (%)	32	71	38	22	29	3
Males Secondary						
N	1533	2428	1695	1552	1391	717
Mean	21.9	21.8	22.2	22.4	22.0	22.4
Standard error	0.1	0.1	0.1	0.1	0.1	0.2
Standard deviation	4.9	4.9	5.1	5.2	5.1	5.8
Overweight & obese (≥ P85%)	672	1068	782	739	586	322
Obese (≥ P95%)	444	709	544	508	400	230
Overweight (P85-95%)	228	359	238	231	186	92
Underweight (%)	45	85	50	36	40	30
Females Secondary						
N	1564	2368	1555	1494	1361	723
Mean	22.1	21.9	22.7	22.8	22.3	22.3
Standard error	0.1	0.1	0.1	0.1	0.1	0.2
Standard deviation	4.6	4.6	5.3	5.1	5.0	4.9
Overweight & obese (≥ P85%)	610	892	694	671	563	280
Obese (≥ P95%)	344	494	433	407	327	165
Overweight (P85-95%)	266	398	261	264	236	115
Underweight (%)	27	68	30	33	27	19

Table 2: Percentage of children overweight, obese and underweight, by gender for primary and secondary schools by region (as per table 1).

	Northern	Northern Harbour	Southern Harbour	South Eastern	Western	Gozo and Comino
Males Primary						
Normal weight	58.7	58.3	50.9	54.5	57.9	55.1
Obese	25.1	24.5	32.5	29.3	26.6	30.0
Overweight	13.7	15.1	14.1	14.2	13.4	14.3
Underweight	2.5	2.1	2.5	2.0	2.0	0.5
Males Secondary						
Normal weight	53.2	52.5	50.9	50.1	55.0	50.9
Obese	29.0	29.2	32.1	32.7	28.8	32.1
Overweight	14.9	14.8	14.0	14.9	13.4	12.8
Underweight	2.9	3.5	2.9	2.3	2.9	4.2
Females Primary						
Normal weight	63.4	63.2	57.1	59.4	63.1	60.2
Obese	19.9	20.8	26.4	24.3	20.6	25.1
Overweight	15.0	13.7	14.5	15.1	14.5	14.3
Underweight	1.7	2.3	2.0	1.2	1.9	0.4
Females Secondary						
Normal weight	59.3	59.5	53.4	52.9	56.6	58.6
Obese	22.0	20.9	27.8	27.2	24.0	22.8
Overweight	17.0	16.8	16.8	17.7	17.3	15.9
Underweight	1.7	2.9	1.9	2.2	2.0	2.6

Figure 1: Ranked body mass index mean (and 95% confidence intervals) by region for primary school males and females

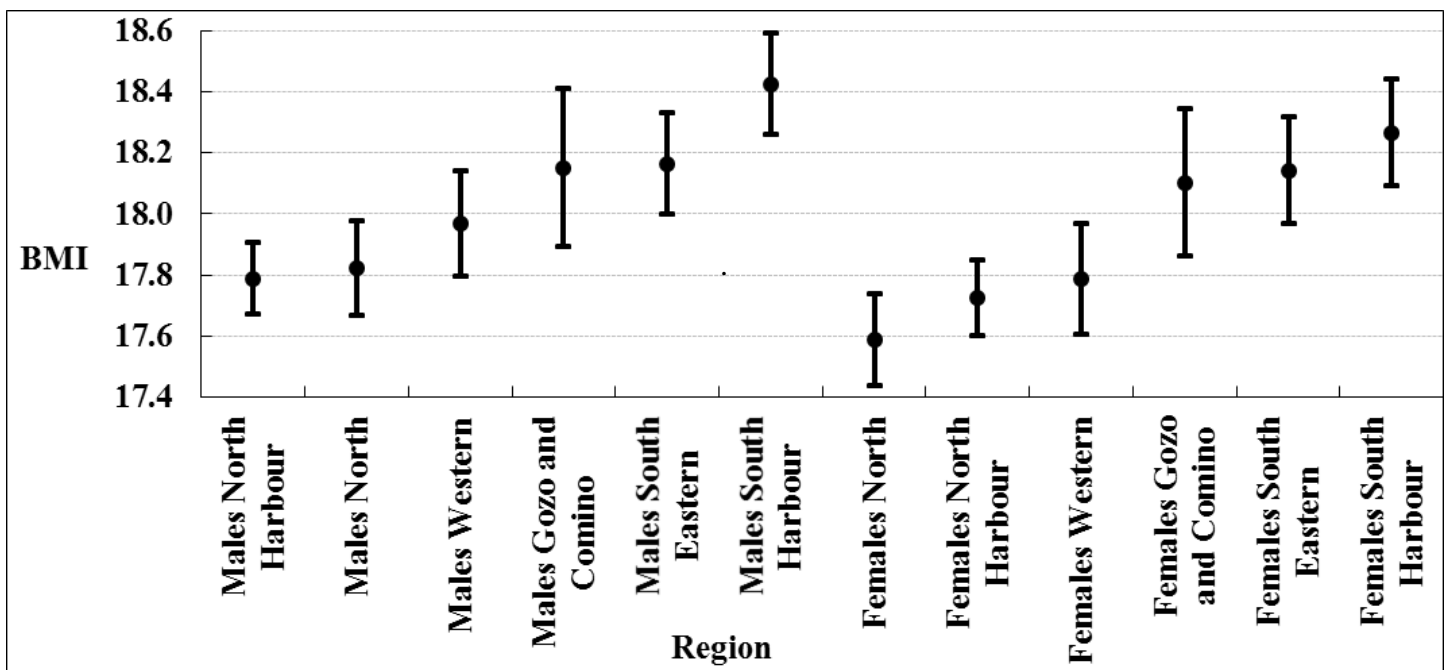
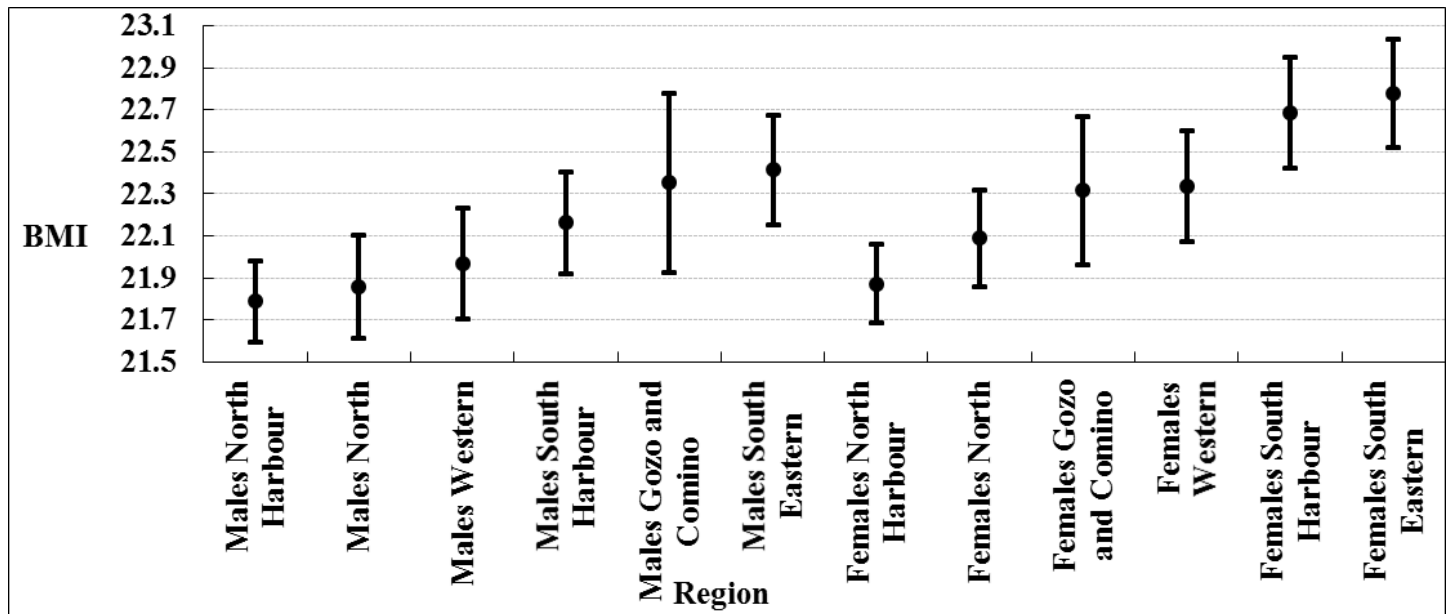


Figure 2: Ranked body mass index mean (and 95% confidence intervals) by region for secondary school males and females



These trends demonstrate a relationship between socioeconomic status and obesity, reinforcing studies done in other countries. For example, American datasets over the years have shown that higher levels of childhood overweight and obesity were present in families with parents having a lower level of education, those living below the poverty level and those living in low-income neighbourhoods¹². However, this is overlaid by increasing trends in obesity rates in children of parents of all income levels and educational levels.¹³

The main strengths of this study are derived from the inclusion of the entire childhood school-age cohort. This provided the researchers with a detailed picture of the real situation regarding the obesity epidemic in Malta and will assist the local authorities when channelling limited resources into the right areas. These results show that the South East and Southern Harbour areas need the highest focus of attention. Other strengths are that results reported were measured directly, not self-reported as in several other studies. Using the same instruments helped reduce inter-observer bias. A regular mechanism of checking and recalibration of scales was done before and after the end of each study period. Training teachers also helped reduce bias using measurement techniques that were part of standard operating procedures developed for the purpose of the pilot European Health Examination Survey.¹⁴ Due to the large number of students

involved, data collection was limited to a number of key factors.

Obesity is an important health determinant. Despite the North-South differences, all regions show a high prevalence of overweight and obesity. Following these results, further research into socioeconomic determinants of local overweight and obesity should be embarked upon as these may yield insights into how best to target the problem from both the prevention and intervention aspects. A regular repetition of this study would also be beneficial to determine trends of childhood overweight and obesity in Malta. For more detailed information, our research group suggests obtaining more details from each child's address (e.g. postcode) in future which would help us map in quite some detail the problem of obesity on our island and help us search for any hotspots that require particular attention. Detailed mapping would enable further correlations to causes, other than socioeconomic factors, of obesity like fast food chain outlets and lack of outdoor spaces in the area. The research group will also strive in future repetitions of this study to connect our data to the National Obstetric Information System to link childhood obesity to maternal prenatal nutritional issues. This study is showing our Government how big the problem of obesity is on our island and also attempts at showing which regions need special consideration. Government should strengthen all preventive measures possible to try and stop

children from becoming overweight. While the overall percentage of overweight and obese children has remained relatively stable over recent years, our results show that the rate of obesity has now surpassed the rate of overweight in Maltese children. These children should be given the best possible support by our national health service to tackle their weight issues and thus the creation of an obesity clinic run by a dedicated multidisciplinary team is needed, now more than ever.

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Psychological interventions in post-partum depression: A critical analysis

Rachel Buhagiar

Abstract

Non-pharmacological interventions are often the preferred treatment modalities in perinatal mothers suffering from mental health problems. Cognitive-behavioural therapy (CBT) and interpersonal therapy (IPT) are the two main evidence-based psychological treatment interventions in the management of post-partum depression. Various studies have been conducted-to-date to assess the efficacy and effectiveness of both CBT and IPT in this specialised group, yet there is no data contrasting the two. This report aims to provide a comparative critical evaluation of the evidence base for the two interventions, including their respective strengths and limitations. Research possibly indicates a stronger evidence base for IPT in the treatment of depression post-delivery, perhaps as a result of larger scale studies having been performed for this treatment modality. Nonetheless, valuable positive outcomes for CBT-treated individuals have been observed. Consequently, a number of recommendations for future research will be put forward with the main objective of advancing the literature in this area of expertise.

Keywords

Post-partum depression; cognitive-behavioural therapy (CBT); interpersonal therapy (IPT); psychological interventions.

Introduction

During the perinatal period, mothers tend to show preference for non-pharmacological interventions, viewing them as “first-choice treatment”.¹⁻³ This report focuses on the role of two evidence-based psychological interventions, cognitive behavioural therapy (CBT) and interpersonal therapy (IPT) in the management of postnatal depression (PND). Whilst research evidence pertaining to the efficacy and effectiveness of these treatment modalities in perinatal mothers is extensive, caveats can still be identified. A comparative critical evaluation of the literature data related to these two interventions will be provided.

Body

CBT, originally known as cognitive therapy, is based on the principle that “cognition, the way in which people think about their life circumstances” influences their emotional state and behavioural mechanisms. In contrast, IPT is based on psychodynamic theory and “guided by attachment and interpersonal theories”, whereby interpersonal relationships are believed to play a crucial role in the formation and maintenance of emotional distress.⁴ Indeed, it focuses mainly on current interpersonal distress in three main areas of life, namely role transitions, role disputes and unresolved grief.¹ Scholars reasoned that face validity for use of IPT in the treatment of perinatal distress would be particularly strong because transition to parenthood might result in transition of other important roles causing conflict and challenges within significant interpersonal relationships.^{1,4} Stuart⁵ states that the most pronounced disruptions are those with the woman’s spouse or significant other. Some of the main goals

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of IPT include increasing the woman's self-awareness about these problems, teaching her to minimise her "excessive expectations and overcome maladaptive communication styles".⁶

In contrast to this, through its educative nature, CBT coaches clients to develop "tangible tools and strategies" to address their emotional distress and life challenges in the here-and-now.¹ The client's active participation in completing homework assignments outside the therapy room is thus essential. Indeed, this may be one limiting factor as mothers suffering from perinatal distress might feel de-motivated and yearn for a passive role in simply following their therapist's role. On the other hand, the adoption of an active approach enables clients to become their own personal therapists, especially when faced with future adversities, and to maximise the use of their strengths. As highlighted by Wenzel and Kleiman¹, CBT therapists "must be creative in devising ways to generalise the work done in session to the lives of new mothers". Both CBT and IPT are time-sensitive form of therapies and can be conducted within a few weeks.⁷⁻⁸ This is advantageous given that perinatal mothers need to juggle several other responsibilities and commitments.¹

Wenzel and Kleiman² describe evidence-based practice as a "three-legged stool" consisting of research evidence, clinical expertise and the clients' preferences and values. Indeed, research evidence is a key component in a professional's decision-making process. Multiple studies have been conducted to-date to assess the efficacy of psychological treatments in treating perinatal depression. CBT and IPT have been shown to have a greater effect size compared to control conditions in the management of PND.³ Overall, there seems to be more evidence pointing towards IPT being a "highly efficacious form of psychotherapy for postpartum depression"^{1,4} compared to CBT, for which "mixed evidence" exists.¹ Indeed, a meta-analysis by Sockol, Epperson and Barber⁹ identified a greater effect size for psychotherapeutic interventions which utilise interpersonal methods as opposed to cognitive strategies. Also, efficacy of IPT has been established relative to a credible control condition by at least two independent research groups.² Furthermore, as shown in a meta-analysis by Cuijpers, Brannmark and van Straten in 2008,² there is less conclusive evidence for CBT in perinatal depression compared to the general adult

population. However, according to Wenzel and Kleiman², there is nothing to suggest that CBT cannot be adapted and generalised to perinatal mothers. In addition, there appears to be a paucity of therapists in the community who have been adequately "trained and achieved competency" to deliver IPT.²

In a systematic review by Miniati et al.¹⁰ which included eleven clinical trials conducted between 1995 and 2003, the efficacy of IPT in treating PND was assessed. Results demonstrated significant improvement in post-partum depressive symptomatology and complete recovery in most treated clients. Similar outcomes were observed in a meta-analysis by Sockol et al.⁴ whereby IPT was shown to be superior to other comparison conditions. In addition, anxiety was also reduced in non-psychotic unipolar depressed mothers. Previously conducted meta-analysis failed to capture possible accompanying anxiety symptoms due to lack of appropriate symptom measures.⁴ Indeed, assessing for primary or comorbid anxiety is important to better characterise the true extent of the mother's symptoms. Another key finding included "improvements in relationship quality, social adjustment, and social support" among depressed perinatal women treated with IPT. Nonetheless, although the latter results look promising, few randomised controlled trials (RCTs) have been conducted-to-date to assess interpersonal outcomes.

In another study, O'Hara, Stuart, Gorman and Wenzel¹¹ examined the efficacy of IPT in a community sample of women with postpartum depression, comparing it to a wait list control conditions. This RCT stands out particularly for its methodological rigour.³ Results demonstrated a significant greater reduction in depressive symptoms with improved social functioning and partner relationship in the IPT treated group. However, Cuijpers et al.³ state that comparison of an active treatment with wait-list control conditions as opposed to treatment as usual control, will result in greater effect size. One identified strength included the extensive training and supervision provided to therapists, and their adherence to standardised manuals.¹¹ In fact, use of manualised therapy was found to have a greater effect as opposed to non-specific therapy.³ Despite the existence of treatment manuals specific to perinatal women⁴, use and/or compliance to them varies

across studies, potentially impacting on treatment outcomes. Thus, the term “interpersonal psychotherapy” may characterise a wide array of interventional methods across different studies.⁴

As yet, “no comprehensive large-scale study, like that of O’Hara et al.,¹¹ has been conducted to evaluate the efficacy of CBT for postpartum depression using highly trained clinicians.¹ However, in a systematic review by Sockol¹² which included twenty-six randomised and quasi-randomised controlled trials, a significant reduction in depressive symptomatology was observed for the CBT-treatment group compared to control conditions. However, the wide variety in the methodology quality of the included studies possibly limits the quality of the findings, emphasizing the dire need for future more methodologically rigorous studies to better assess potential mediators of treatment effects.^{3,12} In another highly cited study by Chabrol et al.,¹³ between “72.2% and 88.8% of the treatment group were deemed responsive to treatment” consisting of one-hour 5-8 sessions in-home CBT intervention delivered by master’s level students. Although these results are outstanding, the provided treatment was not consistent with the “traditional CBT model” and included a psychodynamic component.¹ These latter components are “unequivocally inconsistent with the way in which cognitive behavioural therapists conceptualise their course of treatment and deliver therapy”.² On the other hand, in another study by Burns et al.,¹⁴ a Beckian, conceptualisation-based CBT approach was adopted to address specific cognitions and behaviours related to core issues faced by perinatal women. Despite its small sample size, CBT was shown to be effective in reducing depression during the antenatal and postpartum period, possibly showing that such an approach might be a good match in this client group.

Group formats have been studied for both IPT and CBT. Individual treatment has the advantage of being tailored to individuals’ specific needs. On the other hand, group sessions, can be a source of social support.³ Moreover, since many women are managed simultaneously, group interventions are cost-effective² and improve access to care.¹² Studies examining the efficacy of group IPT show promising results, including evidence for its enduring effect.^{1,10} In comparison, results from studies comparing group CBT to control conditions

tend to be mixed.² Indeed, as demonstrated by Sockol et al.,¹² individually-administered CBT may be more effective than group sessions.

Conclusion

In conclusion, notwithstanding the caveats and limitations in the research data, compelling evidence for the beneficial use of both IPT and CBT in postnatal depression exists. However, further research comparing the two, as well as identification of individual characteristics which would improve treatment response would be valuable. In addition, a closer examination of the specific treatment components which could be “enhanced to maximise success”² and a better understanding of “moderators and mediators of treatment effects”, and the “use of particular therapy techniques”³ would advance the literature considerably.

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Glioblastoma with leptomeningeal dissemination

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Abstract

Here we report a case of glioblastoma (GB) with leptomeningeal dissemination (LMD) in a 21 year old female presenting with generalized tonic-clonic seizures. After a brain MRI confirmed a non-enhancing left frontal lobe mass, histopathological examination and molecular analysis showed a glioblastoma with features of gliosarcoma that was an IDH wild type, MGMT unmethylated, TERT amplified tumor. She received standard care with combined chemoradiation with temozolomide and targeted radiation. MRI showing disease progression prompted the addition of bevacizumab after which the patient quickly deteriorated and died eight months after initial presentation. Incidence of LMD is an uncommon occurrence and associated with a significant decrease in overall survival when diagnosed at initial presentation. More research is needed to determine what role histopathologic variants and molecular profile plays in prognosis and treatment.

Keywords

Glioblastoma, leptomeningeal dissemination, gliosarcoma, IDH wild type

Case Report

A 21-year-old lady presented in September 2016 with a generalized tonic-clonic seizure. For a few weeks prior to presentation, the patient had also noticed increasingly worsening headaches. She reported a medical history of attention deficit hyperactivity disorder (ADHD) and anxiety. Her family history included hypertension, diabetes, and asthma. A neurological exam at presentation was normal. Routine bloodwork was unremarkable. MRI brain done at the time of presentation showed a non-enhancing left frontal lobe mass as shown in Figure 1A.

The patient was offered a resection of the mass but failed to attend her follow-up appointment. Four months after initial presentation, a repeat MRI showed change in the radiographic characteristics with significant increase in size, development of necrosis, heterogeneous enhancement and evidence of leptomeningeal spread (Figure 1B, black arrows). Leptomeningeal spread along the spine was not demonstrated with a spinal MRI. The patient had a subtotal resection (Figure 2A) with histology showing this to be glioblastoma (GB) with gliosarcoma features and evidence of subarachnoid involvement (Figure 3). Molecular studies showed an Isocitrate dehydrogenase (IDH) wild type, O⁶-methylguanine DNA methyltransferase (MGMT) unmethylated, Telomerase reverse transcriptase (TERT) amplified tumor. These genetic alterations are associated with poorer prognosis and a more aggressive disease course.

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Figure 1: A. Axial T2 sequence showing increased T2 signal abnormality in the left frontal lobe (black arrow) B. Axial T1 post contrast sequence showing a large necrotic, heterogeneously enhancing mass in the left frontal lobe. Black arrows point to areas concerning for leptomeningeal spread of tumor with enhancement seen within the sulci. C. Axial FLAIR sequence shows large T2 hyper-intense mass, significantly increased in size compared to original presentation 4 months earlier (Figure 1 A)

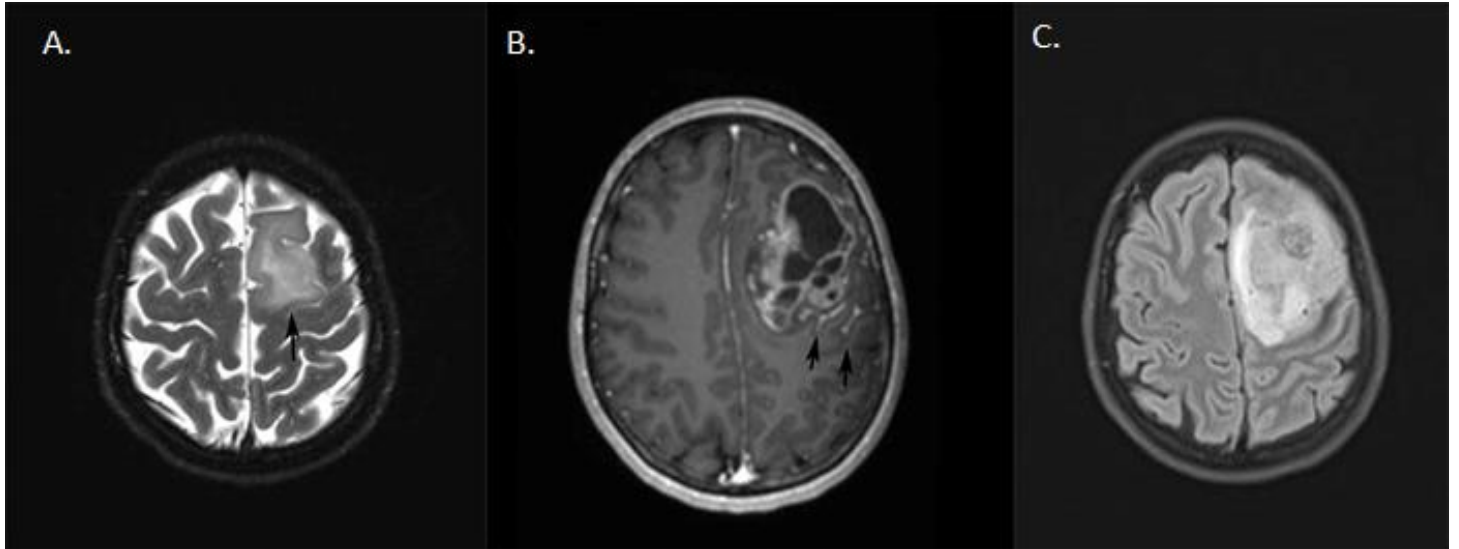
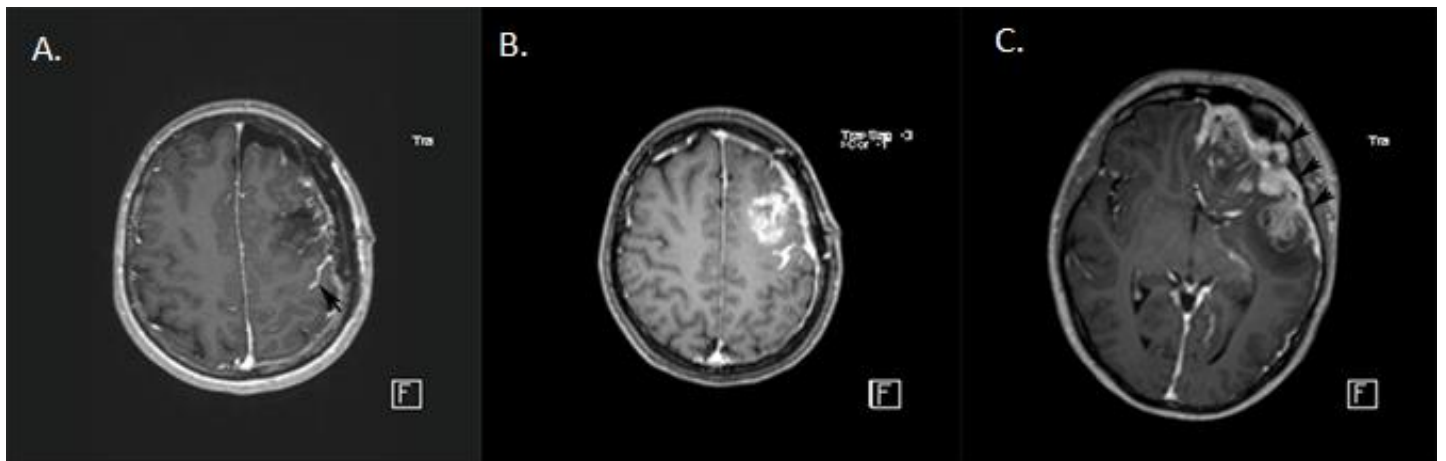
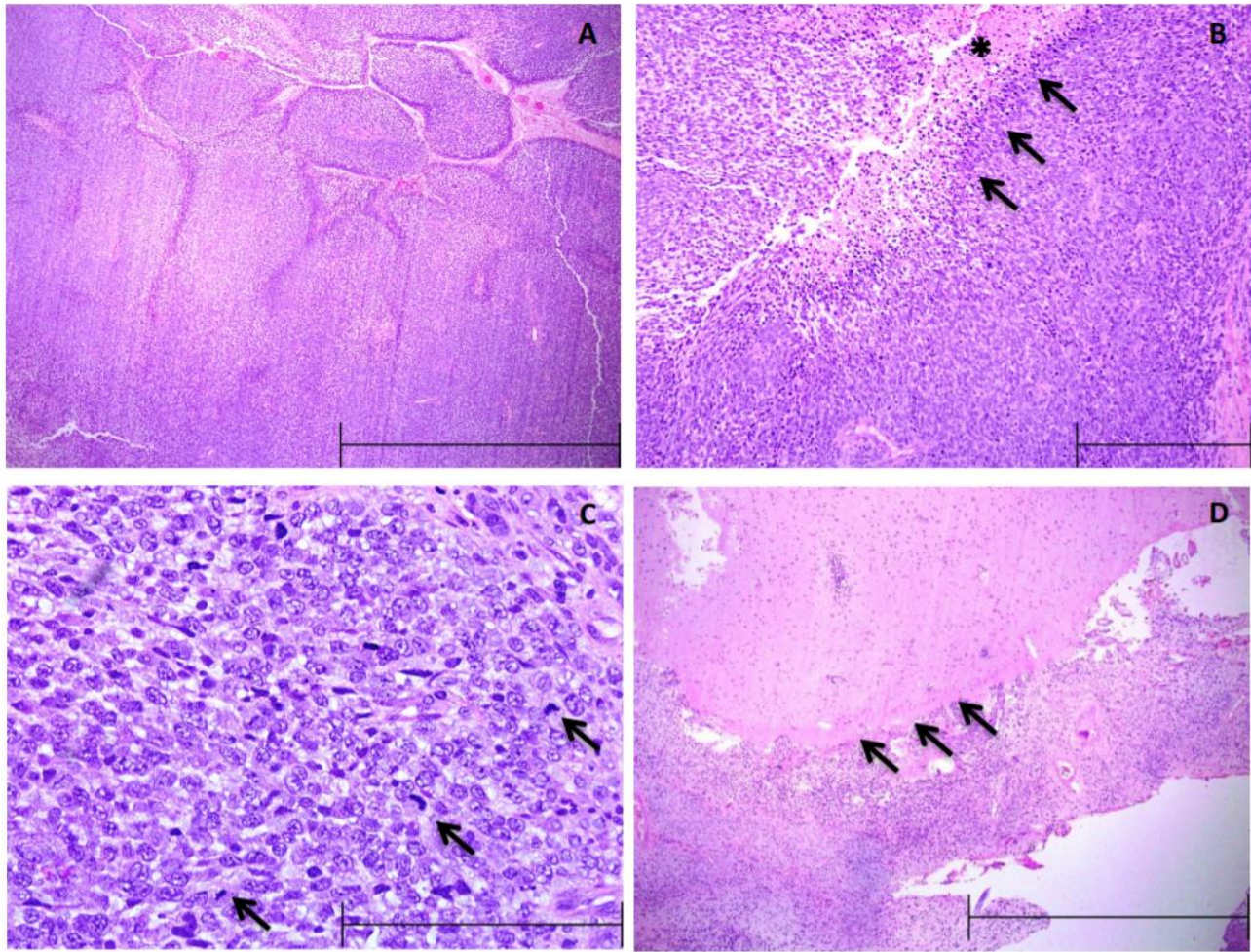


Figure 2: A. Axial T1 post contrast sequence showing post operative scan. Note persistent evidence of leptomeningeal disease (black arrow). B. Axial T1 post contrast sequence prior to initiation of concurrent radiation and chemotherapy shows significant recurrence of disease over a 4 week period from prior scan. C. Axial T1 post contrast sequence post completion of concurrent radiation and chemotherapy shows further progression of disease. Note significant dural involvement of disease (black arrowheads)



Case Report

Figure 3: Histological characteristics of glioblastoma. This low power view demonstrates one of the most recognizable characteristics of GBM showing small foci of necrosis surrounded by centrifugally oriented glial cells creating a pseudopalisading appearance (40x objective) B) A higher magnification shows necrosis (*) and pseudopalisades (arrows, 100x). The rapid proliferation of neoplastic glial cells makes the brain parenchyma appear much more cellular. Additionally, the tumor eventually outgrows its blood supply and cells begin to die, creating foci of necrosis. C) The cell morphology of glioblastoma shows small, pleomorphic cells with clumpy, irregular chromatin and occasional prominent nucleoli. Many mitoses (*) can be seen and correlates with the increased aggressiveness of glioblastoma (400x). D) Subarachnoid spread of the tumor is demonstrated. Normal brain parenchyma appears less cellular in the upper half of the frame. Tumor is adherent of the molecular layer of cerebral cortex (arrows, 40x).



Repeat MRI brain done 3 weeks later prior to initiation of radiation (RT) and chemotherapy showed significant recurrence of disease. (Figure 2B) The patient was treated by standard of care treatment for GB consisting of 6 weeks of intensity modulated radiation therapy (IMRT) with a total dose of 60Gy in 30 fractions and temozolomide, an alkylating chemotherapeutic agent. Post completion of RT and temozolomide, repeat MRI showed further progression. (Figure 2C) She received 1 dose of bevacizumab, a VEGF inhibitor approved for the treatment of recurrent GB but passed away one day after infusion and eight months after initial

presentation. CT scan of the brain done a day prior to her passing away showed increased mass effect and rightward midline shift. (Figure 4) There was also marked effacement of the left lateral ventricle and third ventricle. After the initial seizure at presentation, she was started on prophylactic anti-epileptics (leviteracetam 750mg bid) and steroids. Throughout the disease course she experienced neurological symptoms including headaches, right sided weakness (hemiparesis), and anger outburst that were likely related to frontal lobe involvement of the tumor. Despite treatment, her disease continued to progress.

Case Report

Figure 4: CT head without contrast shows progression of disease with increased size of left inferior frontal and temporal lobe heterogeneous masses. Increased mass effect with effacement of adjacent sulci and increased effacement of the left lateral ventricle. There is rightward midline shift.



GB is the most common primary brain tumor in adults. Despite advances in surgical techniques, radiation treatments and chemotherapy, it continues to have a dismal prognosis with a median overall survival of around 14-16 months.^{1-2,4} Surprisingly, given the location of glioblastoma in the central nervous system and relatively high exposure of the ventricular system during tumor resection, the incidence of leptomeningeal dissemination (LMD) is thought to be uncommon though data on the subject is scarce. In a recent retrospective study of 595 patients with a diagnosis of glioblastoma enrolled in clinical trials, only 4% of these patients developed LMD.³ Patients who were diagnosed with LMD at time of diagnosis of glioblastoma, as was the case in the patient described above, had a worse prognosis compared to those who were diagnosed afterwards (estimated overall survival of 4.7 months compared to 16.0 months). This emphasizes the need to develop better therapies that specifically target tumor cells within the cerebrospinal fluid.

With regard to the histopathology and genetics, one study looking at 20 cases demonstrated that the 85% of cases with LMD were IDH wild type, in keeping with our case.⁵ Of these cases, 50% were of the small cell variant of GB and one was a gliosarcoma variant, all of which were IDH1 wild

type.⁵ This genetic profile carries a well described poorer prognosis than IDH mutants in addition to MGMT unmethylated status and TERT mutations.⁶ There is a paucity of research describing in detail the molecular character of GB with LMD and what role these attributes play in the clinical course. In our case, overall survival was approximately 8 months from the time of diagnosis of GB with LMD. This is a better outcome than the 4.7 months overall survival reported by Mandel et al.³ More research in this area is needed to see if the histopathological variant or molecular profile affect prognosis and therefore have treatment implications.

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Plasmablastic lymphoma in the paranasal sinus in a HIV positive patient: A rare entity

Deepthi Shetty, Prashanth Shetty, Chethana Dinkar

Abstract

Non-Hodgkin's lymphoma (NHL) ranks second after Kaposi sarcoma in individuals who are infected with Human Immunodeficiency virus (HIV). Plasmablastic lymphoma (PBL) is a diffuse large B cell lymphoma (DLBCL), becoming increasingly more common in oral cavity of HIV patients. PBL has been an investigative and therapeutic challenge because of its atypical morphology, immunohistochemical profile and a clinical course which results in high rate of recurrence and demise. We have described an atypical case of PBL affecting the maxillary sinus extending to involve the ethmoid sinuses and nasal cavity in a HIV infected patient and a brief review of literature regarding PBL.

Keywords

Plasmablastic lymphoma, paranasal sinus, HIV infection

Introduction

Non-Hodgkin's lymphoma (NHL) constitutes a collection of malignant neoplasm of lymphoreticular cells and repeatedly spreads into extra-nodal sites (33%).¹⁻² "REAL (Revised European-American Lymphoma) classifies NHL as a heterogeneous group of diseases with peculiar morphological, phenotypic and molecular features".³ It ranks the second most common HIV associated malignancy, providing clue for undiagnosed HIV infection, because these individuals are 60 times more at risk than the general population.⁴⁻⁵ The most common area of presentation of extra-nodal NHL is the gastrointestinal tract and the rarest area is the head and neck region which accounts to 4% of all head and neck tumours. The most common site in the head and neck region is the Waldeyer's ring.¹

Oral non hodgkins lymphomas are extremely rare and accounts for 0.1 to 5% of the cases with palate being the predominant site.¹⁻⁵ The sites which are rarely affected by primary NHL are the nasal cavities and the paranasal sinuses.³ "Stein and coworkers in 1997 reported a series of aggressive non-Hodgkin's lymphomas (NHL) arising in the oral cavity of human immunodeficiency virus (HIV)-positive patients which consisted of large cells with plasma cell differentiation, and were called plasmablastic lymphoma (PBL)".⁶ Middle-aged and the elderly people are more commonly affected with a slight male predilection.⁵ PBL has been an investigative and therapeutic challenge because of its atypical morphology, immunohistochemical profile and a clinical course which results in high rate of recurrence and demise.⁷ We have described an atypical case of plasmablastic lymphoma in the maxillary sinus extending to the ethmoid sinus and nasal cavity in a HIV positive patient.

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Case Report

Case report

A 43 year old Indian lady presented to us with the chief complaint of painless swelling in the left cheek region since 2 months. She also complaints of nasal obstruction in relation to the left nostril and watering of the left eye with no visual disturbances. Her medical history revealed that she was diagnosed with HIV (Human immunodeficiency virus) infection 6 months back and is on ART (Anti retroviral therapy). Her family history revealed that she had lost her husband who also suffered from AIDS. Extraoral examination revealed a diffuse swelling over the left middle third of the face extending superiorly from the infraorbital rim and inferiorly till a line joining the alae of the nose and tragus of the ear, anteriorly from the alae of the nose and posteriorly till the tragus of the ear. On palpation swelling was firm, non tender with the lesion seen through the left nostril [Figure 1]. She also had skin lesions on her hand which was clinically diagnosed to be molluscum contagiosum commonly found in immunodeficient individuals.

PNS radiograph was taken which revealed radiopacity in the left maxillary sinus. Contrast enhanced computed tomography (CECT) scan of the maxillary region with coronal [Figure 2] and axial sections were taken which revealed a irregular heterogeneously enhancing soft tissue density lesion in the left maxillary sinus with erosion of anterior and medial walls and central area of hypodensity suggestive of necrosis. There is

extension of the soft tissue into anterior aspect of maxilla, medially extending into ethmoid sinus and nasal meatuses. Differential diagnosis of lymphomas, squamous cell carcinoma and fungal lesions were arrived at. An incisional biopsy was carried out after doing routine blood investigations. The biopsy sections showed skeletal muscle fibres, fatty tissue and fibrocollagenous tissue infiltrated by lymphoplasmic cells and individual tumor cells with destruction of muscle fibres and fat necrosis leading to giant cell formation and granulomatous response. The tumor cells had scanty to moderate amphophilic cytoplasm with indistinct cell margin and large uniform round nuclei with prominent nucleoli suggestive of non hodgkins lymphoma, probably a plasmablastic lymphoma (PBL), a atypical variant of diffuse large B cell lymphoma (DLBCL) [Figure 3]. A confirmed diagnosis of PBL was arrived after an immunohistochemical study was done which showed malignant cells which were strongly positive for CD 138 with lambda chain restriction and negativity for CD 20, CK and CD 30 [Figure 4]. Patient was planned for chemotherapy and started on a standard CHOP regime. Day 1: cyclophosphamide 750 mg/m², doxorubicin/adriamycin 50 mg/m² and vincristine 1.4 mg/m². Day 1 to Day 5: prednisolone (oral) 100 mg. Patient was lost for further follow up.

Figure 1: Lesion seen in the left nostril



Case Report

Figure 2: Coronal CT

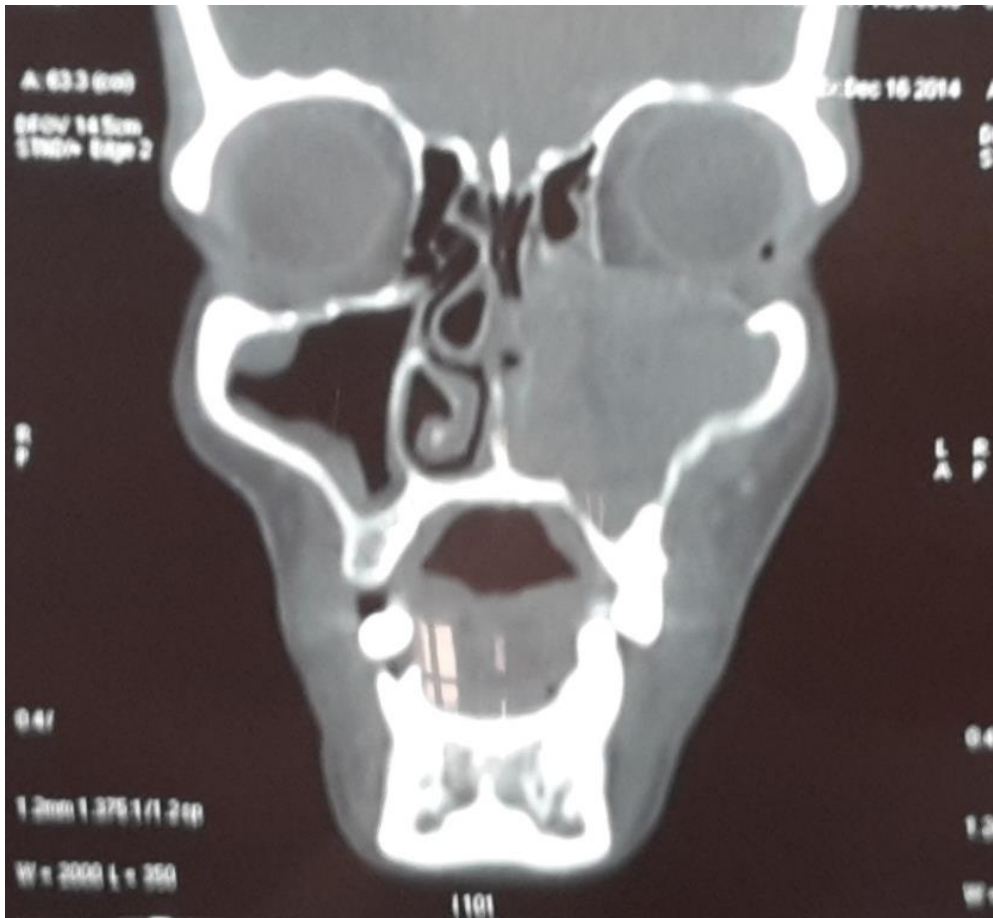


Figure 3: Large tumor cells with vesicular nucleus and prominent central nucleoli (40×)

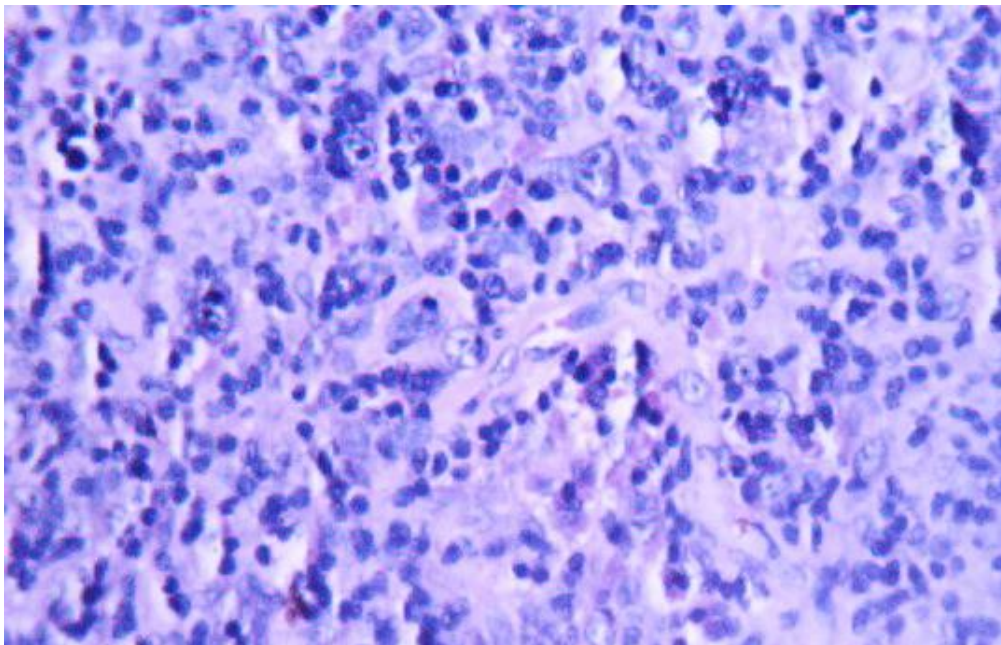
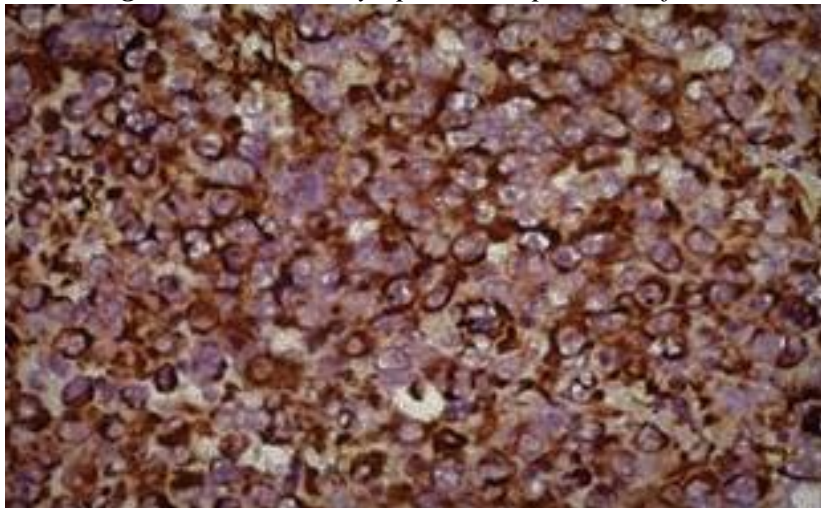


Figure 4: Positive Cytoplasmic expression of CD 138



Discussion

“Non Hodgkin’s lymphomas (NHL) are a heterogenous cluster of neoplasms affecting the lympho reticular system”.⁸ NHL of the sinonasal tract are the rarest constituting about 3% to 5% of all malignancies, with NHL comprising about 60% of all lymphomas. B cell lymphoma are predominantly seen in the paranasal sinuses and malignant cells with positive T-cell markers are predominantly seen in the nasal cavities.³ In the western countries lymphomas of the maxillary sinus are frequently seen when compared to Asian population where nasal cavity lymphomas are more common.³ However in our case the lesion was involving the maxillary sinus which extended to the nasal cavity. Plasmablastic lymphoma (PBL) is a atypical aggressive form of Non hodgkins lymphoma, accounting for approximately 2.6% of all AIDS-related lymphomas (ARLs).¹⁻⁶⁻⁷ “In the largest literature review of 228 patients with PBL, 157 patients (69%) were HIV-positive and 71 (31%) were HIV-negative”.⁷

The aetiology of NHL is unclear but it is proposed that viral infections such as human herpes virus-8, Epstein-Barr virus and hepatitis C virus,¹⁻⁶ , and immunosuppressive diseases such as HIV, Hashimoto’s thyroiditis, Helicobacter pylori gastritis, Richter’s syndrome and Sjogren’s syndrome may be the causative factors for the neoplasm.¹ “Chromosomal translocations play a key role in the pathogenesis determining oncogenic activation or the inactivation of tumor suppressor genes, with the subsequent malfunction of the mechanism of genomic rearrangement in lymphoid cells”.⁵

NHL are commonly seen in the second and fifth decades of life. It approximately affects patients around the age of 40 years and has slight male predominance (3:2).¹ The peak occurrence for the oral types occurs at 41 years (range 7–86 years) and for extraoral types occurs at 46 years (range 11– 86 years). Both are more common in males (the MF ratio is 5.7:1 for the oral type and 4:1 for the extra-oral type).⁶ Maxilla is more frequently involved than the mandible¹ with palate and gingiva accounting for almost 70% of lesions in Maxilla.⁸ The most frequently affected sites of NHL are the gastrointestinal tract, lymph nodes, and skin. Other uncommon sites include the CNS, paranasal sinus, mediastinum, lungs, liver, and testes.⁶⁻⁷ Bone marrow involvement has been reported in 30% in both HIV positive and negative patients.⁷

Squamous cell carcinomas are usually ulcerative thus differing from lymphomas which are seen submucosally.³⁻⁹ Clinical signs and symptoms of lymphomas of the paranasal sinuses includes a mass in the nasal cavity, facial pain, headache, paresthesia, recurrent sinusitis, epistaxis , nasal obstruction and discharge, eyelid swelling, diplopia and proptosis if orbital invasion has occurred.³⁻⁹ Early diagnosis of primary NHL of the paranasal sinuses was difficult in our patient, because this lesion developed in the sinus and expanded towards the nasal cavity not causing symptoms in the early stages. Symptoms appeared only after reaching a considerable size and involvement, and they mimicked other nasal or head and neck diseases. Radiological imaging is an important diagnostic tool which determines the extension of the tumor, bony destruction, mucosal thickening, and preference of biopsy site and route. CT is the best

imaging modality for demonstrating fine bony details. Among the paranasal sinuses the maxillary sinuses are the most commonly affected, followed by the ethmoidal, frontal sinuses and the sphenoid sinuses being the rarest.⁹ In our case the medial and anterior walls of the maxillary sinuses were destroyed extending to the ethmoid sinuses and nasal meatuses which was easily detected in CT.

Plasmablastic lymphoma is characterised by a monomorphic proliferation of large, round or oval cells, with copious cytoplasm and eccentrically placed nuclei, a single prominent central nucleolus or multiple peripherally located nucleoli, growing in a diffuse pattern. Apoptotic bodies and mitotic figures are common and large number of macrophages with tingible bodies are easily demonstrable, leading to a 'starry-sky' appearance.⁶⁻⁷

The malignant cells in PBL are consistently immunoreactive for CD138, a member of the transmembrane heparin sulphate proteoglycan family, that plays a role in plasma cell adherence to bone marrow stromal matrix.⁶

Therapy for PBL patients includes a amalgamation of chemotherapy/ or radiotherapy with alkylants. The prognosis is usually poor, apart from the primary site of occurrence (oral and extraoral) and the clinical scenario (HIV infection or immunocompetence).⁶ Monoclonal antibodies directed against antigens and interferon injection has also been used.⁵⁻⁸ A large literature review of treated cases of PBL shows an overall response rate (ORR) to chemotherapy of 77%, with 46% of patients achieving a complete response (CR) and 31% a partial response (PR). Patients with PBL who were not treated with chemotherapy invariably died with a median survival of 3 months. Cyclophosphamide, doxorubicin, vincristine, and prednisone (CHOP) and CHOP-like regimens have been used in half of the patients reported to date.⁷

Lymphomas in the paranasal sinuses have a poor prognosis, when compared with lymphomas in other sites in the body.^{2-6,9} In a recent review of the literature, patients with PBL and HIV infection were found to have an overall survival of 14 months when compared to 9 months in HIV negative patients. A possible justification for this finding is that the use of Highly active anti retroviral therapy (HAART) restores immune surveillance to battle the tumor more efficiently. Other factors such as extent of disease and performance status also increased the overall survival of the patients.⁶⁻⁷⁻¹⁰

Conclusion

Plasmablastic lymphoma is a unique, aggressive type of NHL which commonly affects the oral cavity of HIV positive patients. The clinical and histopathological features are frequently vague, thus making accurate diagnosis quite cumbersome in the absence of a comprehensive assimilation of clinical, morphological, phenotypic and molecular features.⁶⁻¹⁰ An early diagnosis of NHL of nasal cavity and paranasal sinuses might be even more demanding because of its extra-oral localization, which is necessary for its adequate and successful management, thereby improving the prognosis, and quality of life in such patients.

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