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Editorial

Victor Grech

"To state that those who don't publish may as well not do the work in the first place is undeniably harsh, though not unreasonable".

The Faculty of Medicine and Surgery will be holding the IX Malta Medical School Conference at the Hilton Malta Hotel, St Julians between 3 - 5 December 2015. The conference habitually grows from strength to strength, thanks not only to the hard work of successive organizing committees, but also to the participants. These are young and old, doctors and other health care professions, all of whom recognize the importance of showcasing their research.

The number of abstracts submitted increases each time, and indeed this year, a record number of abstracts (over 900) have been tendered.

An open talk with regard to abstract preparation has already been given to all interested parties. For the purposes of furthering the quality of submitted research and presentations, another open talk regarding the preparation of posters and PowerPoint presentations will also be given shortly.

This is all well and good but it does not detract from the fact that "unless it is published, it is as if your research has never been done." This is a favourite adage of this editor, one that is repeated ad nauseam at every opportunity. This is also the universal viewpoint of all academics. "To state that those who don't publish may as well not do the work in the first place is undeniably harsh, though not unreasonable".[1] The workplace and academia are increasingly competitive and "publish or perish", an exhortation that has been with us in medicine for decades,[2] has arguably never been more applicable.

The reverse hardly ever occurs, and indeed, the physicist Wolfgang Pauli reportedly admonished a colleague, "I don't mind your thinking slowly. I mind your publishing faster than you can think". [1]

Each abstract that remains unpublished is regrettable, and constitutes what is in effect a "scientific crime". [1] This is because research (usually funded) is lost, and those of us who receive funding have an obligation to publish our work. In addition, writing up one's research forces the researcher to organize and think about work done as well as in progress, sometimes in ways hithertofore unimagined. Furthermore, the peer review process that comprises part of parcel of publication exposes unnoticed mistakes and sharpens one's work.

Dear colleagues, one final exhortation: do write up and publish your work – do not let your efforts go to waste.

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Victor Grech
Editor
Malta Medical Journal

Cover Picture:
'Nude'
Watercolour
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.

Original Article

Tuberculosis in Malta: Thirty-five years of epidemiological trends in the native population

Brian Farrugia, Charmaine Gauci, Julian Mamo, Wafaa Ahmed, Joseph Cacciottolo

Abstract

Background: Malta, the smallest island state in Europe, with an approximate population of 400,000, has one of the lowest reported incidence rates for tuberculosis (TB) in its native-born population.[1] Long-term trends for TB among this population were investigated.

Methods: A period of 35 years (1979-2013) for the Malta-born population was investigated using single-age population numbers for each year, retrospective, and partly prospective analysis of notified TB cases. Mean five-yearly populations were then used to calculate 5-yearly incidence rates for birth-cohorts, age-groups, major site and gender. Annual reported TB incidence rates were also calculated.

Results: In the Malta-born population, over the 35-year period, reported yearly TB incidence shows a downward, albeit decelerating trend. Consecutive follow-up of 5-year age-cohorts and 5-year age-groups confirms that incidence has fallen, with the highest rates being observed in progressively older age-groups. A falling trend in TB incidence according major site and gender was also observed.

Conclusion: TB is being successfully controlled among the Malta-born population, and confirmed to be slowly approaching the elimination phase.[2]

Keywords

Malta-born population, low incidence, epidemiology, tuberculosis.

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Introduction

While tuberculosis is a worldwide pandemic, incidence varies enormously across populations, geographical regions, countries and even within cities.[3,4] The highest reported incidence rates are still seen in sub-Saharan Africa, while most cases originate from South-East Asia (35%). Although global TB incidence has been gradually falling since 2002, absolute cases numbers had continued to rise until 2006, and are only, until recently, recognized to have been falling since that year.[5]

The European Centre for Disease Control (ECDC) publishes yearly national data on reported TB cases and incidence in country populations but not on incidence rates in foreign-born populations;[1] this may be partly due to difficulties in determining a constantly changing or unknown denominator population to calculate the incidence rate in foreign-born persons.

In 2009, Europe representing 5.6% of the global TB burden, and is divided into three main geo-political regions. These include the European Union (EU) including European Economic Area (EEA) countries, the Balkans, and the East (former Soviet Union countries and Russia). Malta forms part of the former region which has the lowest incidence rates of the three; EU rates are approximately 15.8 per 100,000 person-years.[1] Reported TB incidence in Malta remains among the lowest in Europe, at about 13/100,000 person-years

during 2009[5], despite the increase in absolute number of cases diagnosed in Malta after 2001. A relatively large influx of irregular migrants, led to a proportional increase in the number of cases diagnosed among the sub-Saharan population.[1,6]

In 1930, the Norwegian Kristian Ardvord was the first physician to perform longitudinal cohort analysis using country-wide retrospective mortality data to investigate epidemiology, using data pertaining to TB. He presented a classical study using 5-year aggregate data, his discoveries revealed a pattern, enabling him to make accurate predictions on future TB mortality rates among the populations studied.[7]

This study was our investigation of trends in reported incidence rates in a small island population similarly using 5-year aggregate data, over the period 1979 - 2013. Fortunately, TB mortality rates have fallen drastically over the years and could not be used, as in the study by Ardvord, leading us to investigate a number of 5-year mean incidence rates in isolation.

Methods

Thirty five years of data, from 1979 to 2013 pertaining to all TB notification for those native-born were available and investigated. All data was collected from cases seen at the Chest (TB) Clinic at the main hospital, including notifications made centrally by physicians to Public Health, and cover the whole population of Malta. This data was considered highly reliable because TB remains a mandatory notifiable infection by law, nearly all (98%) patients were followed up medically by one Chest Clinic, the number of prescribing consultant physicians were strictly limited and controlled, anti-TB drugs were cost free for all patients and could not be bought on the free market, in addition TB drugs are only dispensed by two designated government pharmacies. These pharmacies in turn inform both Public Health and the Chest Clinic every month of anti-TB medications dispensed. The data set included all cases considered previously as definite and other-than-definite, and nowadays referred to as confirmed, probable and possible. A TB case specifically refers to new reported cases, diagnosed in Malta, among those Malta-born, and commenced on standard anti-TB treatment. The denominator populations used to calculate all 5-year mean reported incidence rates were estimated using the mid-year population values obtained from the yearly produced single-year tables. These tables provided population numbers for each specific age for each year. The source of this population data was the official state publication; The Yearly Demographic Review of the National Statistics Office of Malta.[8]

The original population values for years 1978 to 1984 were revised in 2000 (following the 1995 census), these were considered more accurate than earlier estimated values, and were thus used.[9] Four cases notified in 2003, they were excluded from the official data following a request for declassification from the diagnosing physician. In retrospect, there was a near certainty that their positive cultures were cross-contaminated, as they were asymptomatic on starting treatment and had normal chest x-rays.

The thirty five years under review were apportioned into seven consecutive 5-year periods, because both denominator populations and yearly case numbers were small. The 5-year periods were 1979-1983, 1984-1988, 1989-1993, 1994-1998, 1999-2003, 2004-2008, and 2009-2013. Each of these 5-year periods were further sub-divided according to 5-year age-groups, specifically birth to 4 years of age, 5 to 9 years, 10 to 14, 15-19, 20-24, 25-29, 30-34, 35-39, 40-44, 45-49, 50-54, 55-59, 60-64, 65-69, 70-74, 75-79, 80-84, 85-89, 90-94, and 95 to 99 years. The mean reported TB incidence for each of the separate age-groups in each of the seven 5-year periods was calculated using mid-year population numbers and 5-year aggregate data. Seven 5-year cross-sectional studies were produced and merged (figure 2). The calculated mean TB incidence for 5-year age cohorts, for each of the 5-year periods, was successively followed over the 35 years. Similarly, mean incidence trends for 5-year age-groups for each of the seven 5-year periods were followed. Finally, mean 5-year TB incidence was estimated according to major site and gender over the study period.

Results

During the study period there were a total of 566 new cases; 368 males and 198 females which included 378 and 188 cases of pulmonary and non-pulmonary TB respectively.

The yearly trend in TB incidence (Figure 1) among those born in Malta show yearly fluctuations but has fallen throughout the thirty five years, resulting in an overall pattern resembling that of exponential decay.

The combined seven 5-year cross-sectional plots, according to 5-year age-groups, of reported TB incidence show that incidence has fallen in nearly all age-groups and that the higher incidence rates tended to occur among progressively older age-groups (Figure 2). The resulting composite figure of seven 5-year cross-sectional plots reveals a general shift downwards and to the right.

Five-year birth cohorts (Figure 3a and 3b) were followed over the study period and show a clear fall in reported incidence over time, with the exception of the 1989-1993 period. Five-year reported incidence in all age-groups (Figure 4) also show a fall over the same period. Five-year reported incidence rates over the 35 years for both gender and major site reveal a clear downward trend (Figure 5).

***Figure 1**: Yearly TB incidence for the Malta-born population (1979-2013)*

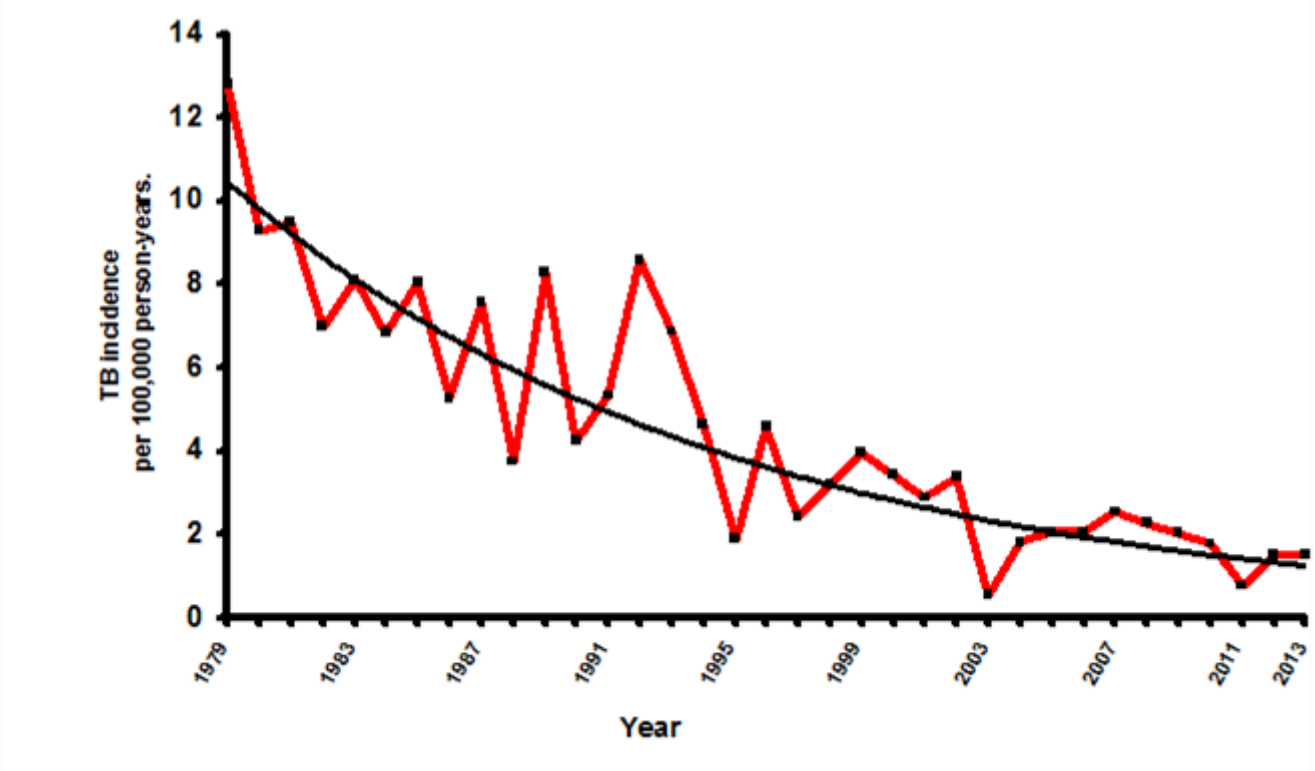


***Figure 2**: Combined plot of TB incidence for 5-year age-groups for each of the seven 5-year periods (Malta-born 1979-2013)*

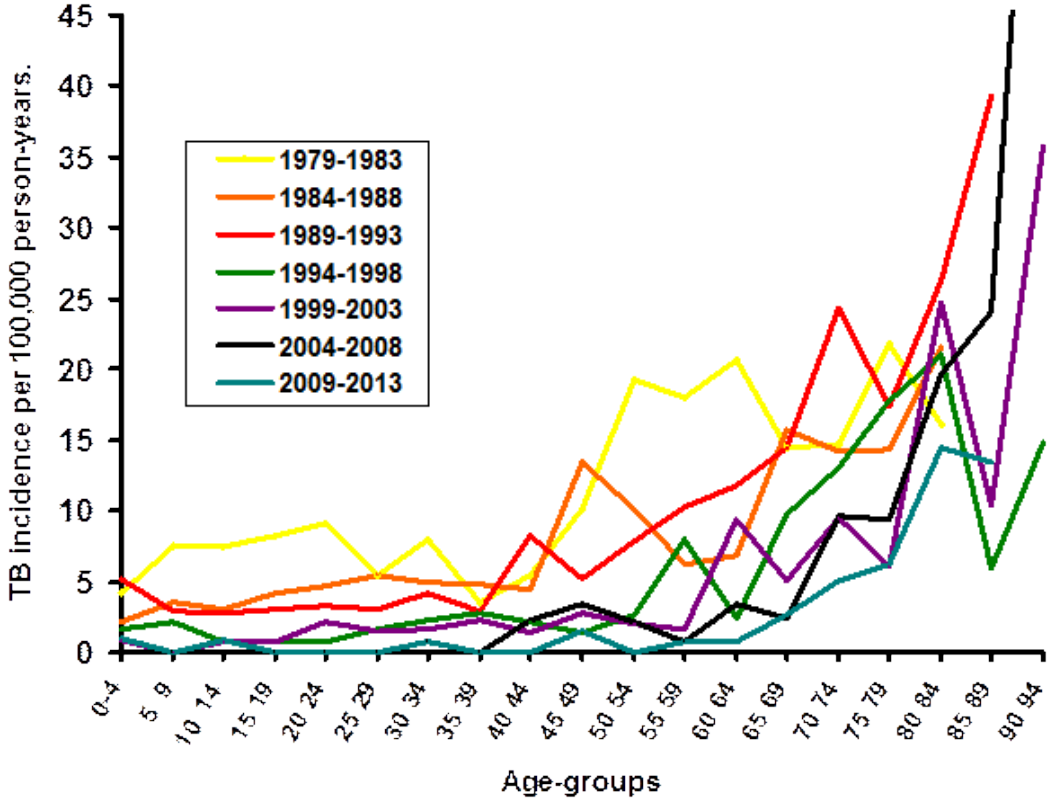


***Figure 3a**: Mean 5-year TB incidence for 5-year birth cohorts for 1979-1983 followed at 5-year intervals (Malta-born from 0 to 44 years)*

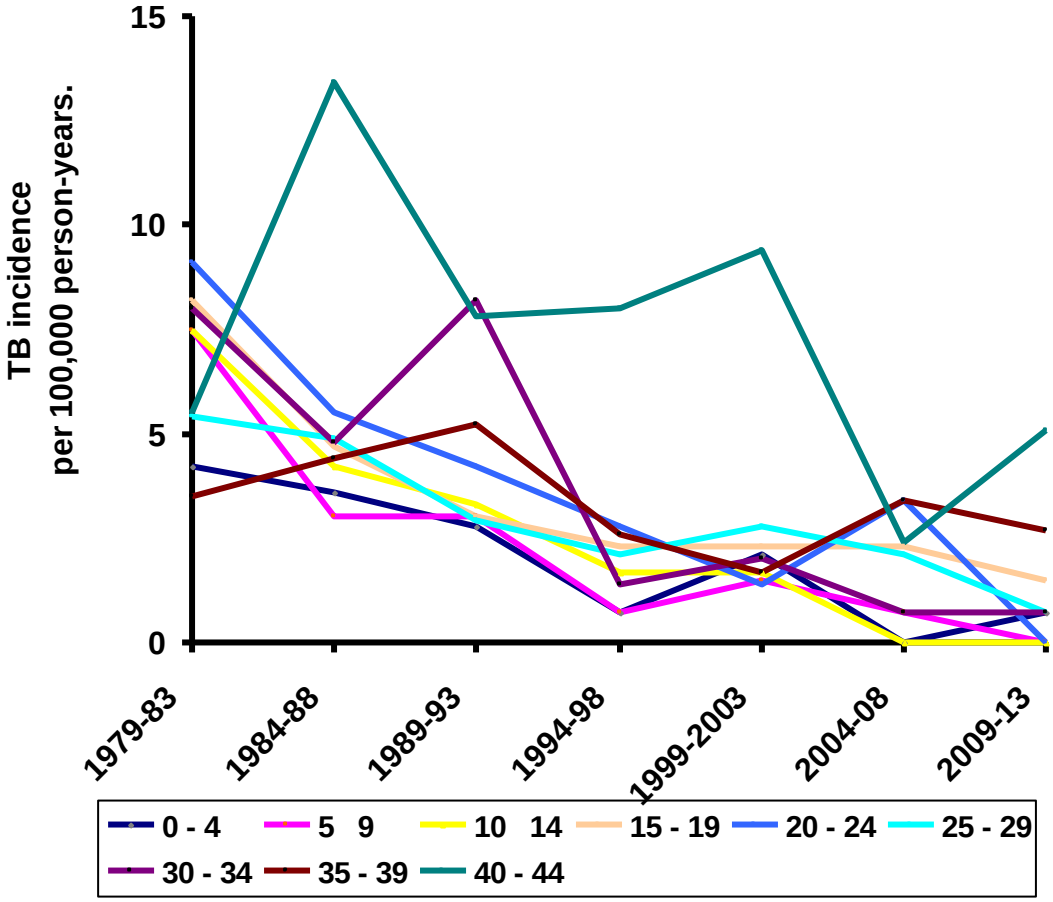


***Figure 3b**: Mean 5-year TB incidence for 5-year birth cohorts for 1979-1983 followed at 5 year intervals. (Malta-born 45 to 94 years)*

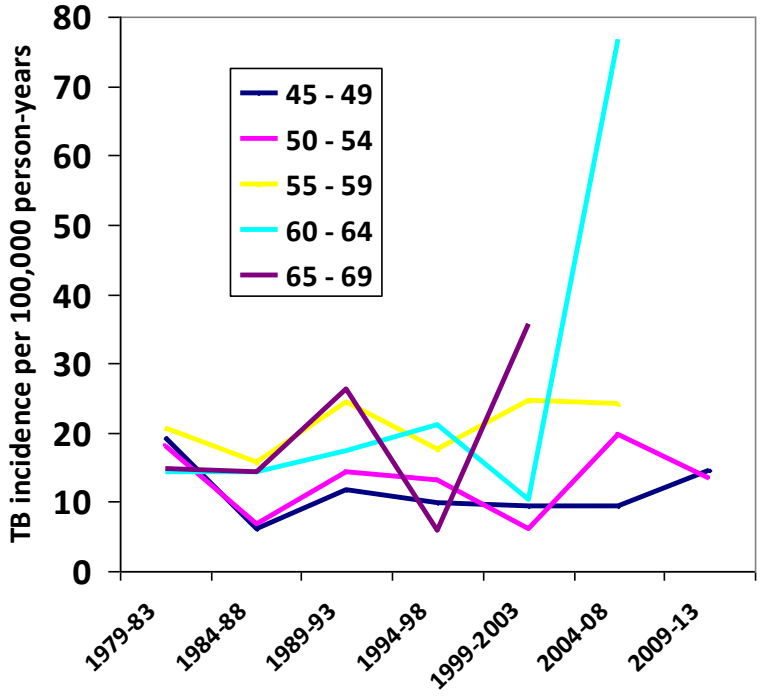


Figure 4: *Mean 5-year TB incidence for 5-year age-groups for each 5-year period (Malta-born 1979-2013)*

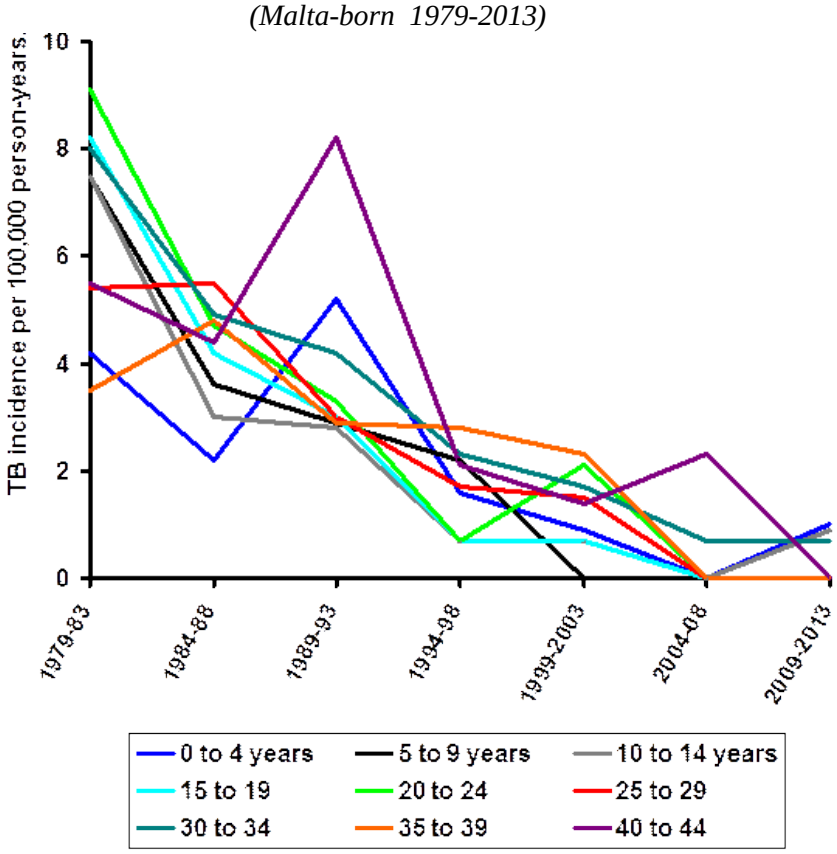
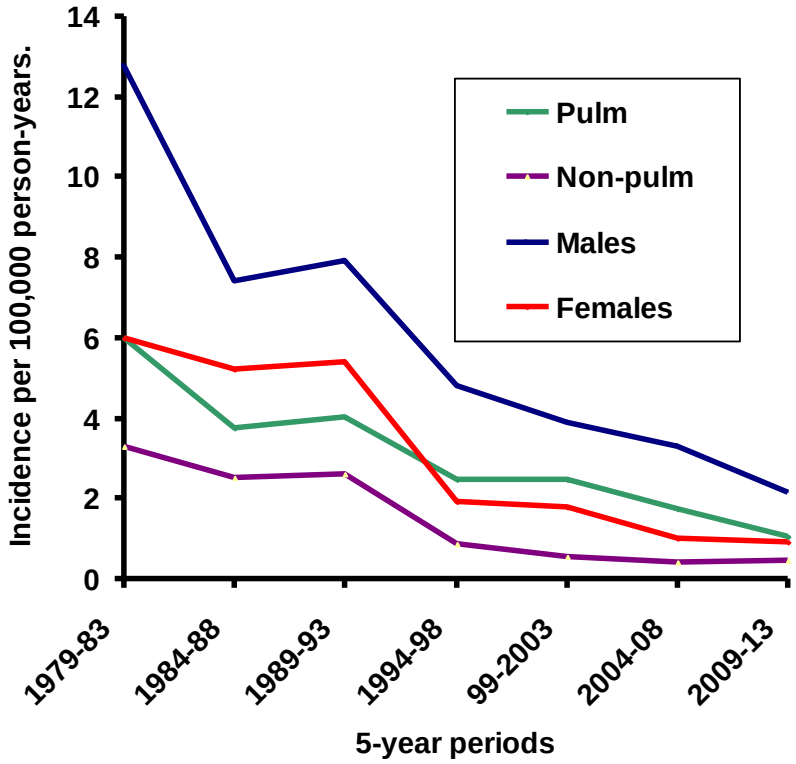


Figure 5*: Mean 5-year TB incidence according to major site and gender. (Malta-born: 1979-2013)*



Discussion

Longitudinal studies examine how data pertaining to specific birth cohorts behave over time, and while prospective studies are preferred, they are often prohibitive due to financial and temporal restraints. In contrast, retrospective studies, less hampered by these obstacles, are useful when data collection is considered reliable, even more so if considered nearly complete, as in our case. Analysis of incidence data for specific age-groups and birth cohorts, which are followed up over time, may give a comprehensive picture of changing epidemiological trends. The patterns may reveal the progression of a disease in a population, and when specific interventions might be indicated, they have also been shown to possess predictive value.[7] In contrast, cross-sectional studies examine variables in a population, or representative sample, over a specific time period.

The elimination of tuberculosis is the ultimate goal of all National TB Programmes (NTPs). The global aim (Millennium Development Goal 6) being the reduction of TB prevalence and mortality to half that of 1990 by 2015, and TB elimination by 2050.[7] The first objective has been achieved for the Malta-born population. Success, in this long-term endeavor in a particular population may well be feasible through the consistent work of a well-functioning NTP, in conjunction with public health and socio-economic measures aimed at improving environmental living conditions and elimination of poverty.[10] WHO had taken the initiative through the STOP TB Partnership in launching a new global STOP TB strategy for 2011-2015, focusing on high quality DOTS expansion and enhancement, control of HIV/TB and multi-drug resistance. It also addresses the needs of poor and vulnerable populations, strengthening of primary health care systems, engaging all care providers, and empowering patients and communities. The publication also gives an indication of the funding required to achieve these goals. It high-lights the development and timely adoption of new technologies and the need for enabling and promoting local research.[11] In Malta`s case, the strategy used in the past consisted of adopting strategies developed by WHO and other larger Western countries, although more recently, an official national strategy for Malta has been produced.[12]

For epidemiological purposes, a population can be considered to be made up of both foreign and native-born persons; both groups exhibit a host of differing dynamics and require appropriate approaches and action. Considering that by definition, the national reported TB incidence is a combined value of disease arising in both native and new entrant populations, elimination of TB, even in developed countries is challenging, if not impossible to achieve. This is simply because no country has complete control over newly-entrant foreign-born persons, legal or otherwise, arriving from high-incidence countries harbouring either latent or active TB, from crossing national borders. In addition, there are no interventions which can completely prevent reactivation in persons with latent TB. It is recognized that in high-risk new entrant populations, higher TB reactivation rates will occur, similar, if not higher, to rates found in their countries of origin. This is highest in the first 2-3 years from entry, and will continue for many years thereafter, albeit at a much lower level.[1-2,13] One of the main factors pivotal to the success of TB control include the political decision to declare the elimination of both TB as a national health and social priority. In contrast, the greatest danger to TB control is complacency which can occur at any and all levels, from patients to health-care workers to politicians. In addition, falling TB incidence can easily tempt administrators to cut on funding and prematurely scale down resources with dire consequences for TB control. The history of TB control in the United States is a case in point.[14]

Figure 1 shows wide fluctuations in reported yearly TB incidence, this is probably due to both low case and population numbers. This finding is consistent with that found in other countries with small populations, including Andorra, Iceland, Liechtenstein, Luxemburg, and San Marino in contrast to larger populations which do not show such large yearly fluctuations.[1] Moreover, as prevalence falls, one would expect a relative increase in non-tuberculous mycobacterial infections,[15-16] and an increase in the proportion of misdiagnosed TB cases relative to actual TB cases. This fact may in part explain the reduced rate of decline seen in Figure 1.

When comparing incidence, for each of the age-groups in the seven 5-year periods (Figure 2, and 4), this falls consistently over time for the younger age-groups. TB among the paediatric age-group is a very good indicator (indicator population) of on-going TB infection in the community, as they have immature immune systems and thus more easily infected and more liable to develop disease.[17] Analysis in the less-than-19 year age-group indicates that TB incidence had fallen consistently and is similarly low – both being indicators of successful national TB control and the actual low levels of TB in the community at large. The higher reported TB incidences rates shift to the right, indicating that over time TB is being mostly diagnosed in older age-groups (Figure 2, and 3b). It is recognised that, in the older population immune-senescence causes reactivation and is the usual cause of TB in the vast majority of cases.[18] For epidemiological purposes, a population can be considered to be made up of both foreign and native-born persons; both groups exhibit a host of differing dynamics and require appropriate approaches and action.

Analysis of trends (Figure 1, 3a,3b, 4, and 5)

showed an unexpected peak during the 1989-1993 period. Examination of yearly incidence (Figure 1) indicates that this was a result of unusually high incidence occurring in 1992 and 1993 and thus influenced data in the 5-year period of 1989-93. This may have been due to a combination of factors including changes in personnel and case ascertainment, mode of diagnosis (clinical, radiological, histological or microbiological), cross contamination, a micro-epidemic situation or the effect of HIV. It does not seem to have been related specifically to major site or gender (Figure 5), further investigation is indicated. The past and present success seen in Malta in reducing TB is multi-factorial, the main reasons may include, reduction in poverty, improvement in housing, centralisation of both clinical and pharmaceutical services, standardisation of treatment regimes, investigation, drug treatment, follow-up, compliance, and close contact screening, all of which were and still remain cost free for all. In addition, anti-TB drugs were and remain unavailable on the private market, thus eliminating the problem of unrecorded diagnosis and treatment of cases. It must be noted that no increase in incidence occurred after 2001, when the massive influx of new irregular entrant cases started. Investigating the epidemiology of foreign-born TB was not an objective of the present study, and was specifically excluded to obtain a clearer epidemiological picture prevailing in the local population.

Limitations of the study

Data collection was mainly retrospective, and case numbers and populations were both small, although the data was considered nearly complete and reliable for reasons alluded to above. The cases studied included confirmed, probable and possible cases, thus clinical, radiological, histological and microbiological over diagnosis, may have occurred. This was strongly suspected to have occurred at least in 2003 and involved four cases. DNA fingerprinting in Malta was not performed prior to 2006, thus, the possibility of cross-contamination of samples before this date should be considered. In addition, a number of cases which were diagnosed with TB from smear positive but negative culture results may have actually had an environmental mycobacterium infection. In fact, in recent years, approximately 75 % of positive cultures in smear positive cases were non-tuberculosis in origin.

Further study

The high number of cases which occurred in 1992 and 1993 should be investigated further. As prevalence continues to fall, the proportion of false positive diagnoses may increase, moreover the impact of imported TB with often drug resistance, on the native population and the increase of non-tuberculous mycobacterial infections will require particular attention and continued epidemiological monitoring.

Conclusion

It has been shown that trends in TB epidemiology, in small populations with very low levels of TB, can still be investigated using 5-year aggregate data. Trends in TB incidence in the native population in Malta, continues to fall, albeit at a slower rate, while TB is being diagnosed more often in progressively older patient cohorts. TB elimination in Malta, at least in the native population, despite rising national incidence, still remains an achievable goal.

Key points

- Epidemiological portraits were produced using 5-year aggregate data.
- An alternative methodology (compared to analysis of yearly data) concerning TB epidemiological dynamics in small populations with very low incidence, approaching the elimination phase has been described.
- It was possible to show falling trends for 5-year age-groups, birth cohorts, major site, and gender among a whole native population with very low TB incidence.

Acknowledgements

The authors wish to acknowledge the assistance and work of all contributors, past and present including the Chest Unit, Department of Medicine, Infectious Disease Unit, Health Promotion and Disease Prevention Directorate, National Statistics Office, and Chest Clinic.

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Review Article

A review on the investigation of peripheral neuropathy at Mater Dei Hospital

Erika Cefai, Maria Mallia, Josanne Aquilina

Introduction

The term peripheral neuropathy encompasses a wide range of disorders. The underlying causes of peripheral neuropathy are diverse. It is very difficult to ascertain the incidence of peripheral neuropathy with any degree of certainty, but it is a manifestation of several common multisystem disorders, whose incidence is on the rise, such as diabetes and Human Immunodeficiency (HIV) virus infection. Worldwide, the population prevalence is about 2,400 per 100,000 (2.4%), rising with age to 8,000 per 100,000 (8%).[1] Peripheral neuropathy can significantly impact an individual's quality of life especially if undiagnosed and untreated.

Investigation of peripheral neuropathy is expensive and time consuming, and is best performed in a stepwise approach. Even in the best of circumstances, an aetiological diagnosis is not always achieved. At present, the existing guidelines deal with the treatment of peripheral neuropathy but there are none on how patients with peripheral neuropathy should be investigated.

Aims of the audit

The aims were to assess how patients in Mater Dei Hospital were investigated for peripheral neuropathy and whether a definite diagnosis was ultimately reached.

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Methodology

Patient Population and Data Collection

Approval was obtained from the data protection officer at Mater Dei Hospital. 536 EMG results from the year 2011 were randomly selected from the database of the Neuroscience department. These were reviewed and the patients with a neurophysiological diagnosis of peripheral neuropathy were identified. The investigations performed within a year, before or after, the EMG date for these patients were studied. Demographics, source of referral, indication for EMG and diagnostic data were collected for each patient, using PACS, Isoft Clinical Management, Electronic Case Summary, and patient's records. All the data was inputted in a tabulated format using Excel and then analysed.

In this audit, Complete blood count (CBC), Renal profile, Calcium, Liver profile, Fasting blood glucose (FBG) or haemoglobin A1c (Hba1c), Thyroid function tests, vitamin B12, urinalysis for microscopy and Chest X-ray were considered to be first line investigations. Second line investigations include HIV serology, vasculitic screen, serum protein electrophoresis (SPE) and tumour markers, and ultrasound of the abdomen. Serum Angiotensin Converting Enzyme (ACE) levels, paraneoplastic panel, anti ganglioside antibodies, Cerebrospinal fluid (CSF) analysis, nerve biopsy and genetic testing were considered to be specialised tests [Table 1][2].

Results

118 patients with a neurophysiological diagnosis of a peripheral neuropathy were identified from the first 536 EMG results of the year 2011. From the total of 118 patients with peripheral neuropathy, 116 were selected for further review.

44 patients (37.3%) were female and the remaining 62.7% were male (*n*= 74). The mean age was 59.3 years with a range of 4-86 years.

When looking at the remaining 418 EMG results: 34% (n=182) were reported as normal, 40.7% were reported as mononeuropathy (*n*=218), 0.6% plexopathy (*n*=3), radiculopathy in 0.4% (*n*=2), anterior horn cell disease in 0.4% (*n*=2) and myopathy in 0.4% (*n*=2).

***Table 1**: Summary of investigations for peripheral neuropathy*

History And Examination	First tier	CBC, renal profile, liver profile, calcium, FBG/Hba1c, ESR, TFTs, B12 levels, urinalysis, CXR
	Second tier	Vasculitic screen, HIV serology, SPE, tumour markers, US abdomen
	Third tier	ACE levels, paraneoplastic panel, anti-ganglioside antibodies, CSF analysis, nerve biopsy and genetic testing

The commonest indication for the 536 EMG tests was mononeuropathy (53.9%, *n*= 290) followed by peripheral neuropathy in 24.4% (*n*=131). The commonest mononeuropathy diagnosed was carpal tunnel syndrome (41%). In a number of cases more than one indication was selected for the EMG. Peripheral neuropathy was most commonly combined with carpal tunnel syndrome (3.7%).

With regards to the peripheral neuropathy cohort, the main source of referral was the department of Neuroscience (61%, *n*=72). The other two major sources of referral were the department of Medicine with 16.1% (*n*= 19) and the Orthopaedics department with 13.6% (*n*= 16). 47.4% of EMGs booked from the department of medicine were from the diabetes clinic. Of note 6 patients, that were included in this audit, were referred from the paediatrics department (5.1%). The remaining 5 were booked from the Geriatrics department, Gozo general hospital, pain clinic and the Department of Surgery.

Peripheral Neuropathy Cases

When looking at the indications for those 116 cases with an eventual neurophysiological diagnosis of peripheral neuropathy, in 64.4% the main indication was in fact peripheral neuropathy. In 16.1% the indication was mononeuropathy, 13.57% had a combined indication, and the remaining 5.83% were requested for suspected cervical myelopathy, trauma, myotonic dystrophy, myopathy and critical illness neuropathy.

Investigations

Co-morbidities that are associated with peripheral neuropathy were reviewed for all the 116 patients. At the time of request of EMG, the commonest documented co-morbidity detected was diabetes in 40.7% of cases followed by malignancy in 9.3% and drugs in 5.9%. Other relevant known co-morbidities at time of request included advanced chronic kidney disease (3.4%), hepatic cirrhosis (2.5%), nutritional e.g. vitamin B12 deficiency (2.4%), infectious diseases e.g. HIV (1.2%), endocrine (1.2%) and vasculitis (1.2%). In 44.1% no relevant co-morbidities were identified. The neurology department was involved in 58.1% of peripheral neuropathy cases (*n*=68). In the majority of cases this occurred prior to the EMG test.

All the investigations performed on the 116 patients 1 year before and 1 year after the EMG's were searched. When looking at the first line tests that form part of the peripheral neuropathy work-up: a complete blood count was found in 94.8% of cases, renal profile in 93.1% of cases, serum calcium in 67.2%, FBG/Hba1c in 78.4%, LFTs in 88.8%, ESR in 62.1%, TFTs in 83.6% and vitamin b12 levels in 60.3%. Urinalysis was available in 38.8% of patients and a chest x-ray was taken in 54.3% of patients. A proportion of these investigations were performed after the EMG was done as seen in figures 1 and 2.

With respect to the second line investigations anti-nuclear antibody levels were taken in 41% of patients with 58.3% being taken prior the EMG. Anti-nuclear cytoplasmic antibody levels were taken in 23% of patients only. 63% of these were available up to 1 year prior to EMG. Serum protein electrophoresis and tumour markers were taken in 46% and 44.4% of patients respectively. 53.3% of SPE results and 44.4% of tumour marker results were taken before the EMG. An ultrasound abdomen was requested in 22.2% of patients with 57.6% being done prior the EMG.

In terms of specialised tests, anti-ganglioside antibodies were taken in 18.5% of patients, ACE levels in 7% and the paraneoplastic panel in 18.8%. CSF analysis was performed in 16 patients (13.7%) and a nerve biopsy was taken in 6 patients (5.15%). Genetic studies were done for a total of four patients.

***Figure 1**: Results of first tier of investigations 1 year before/after EMG*

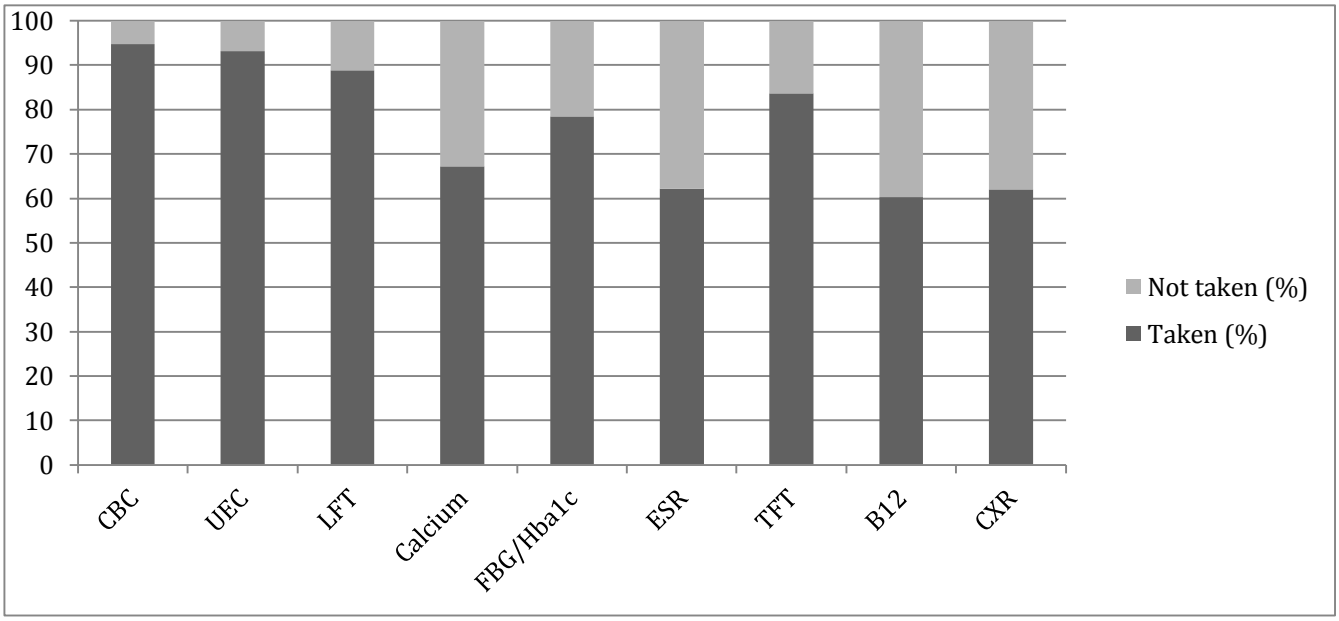


***Figure 2**: First line investigations done prior or after EMG*

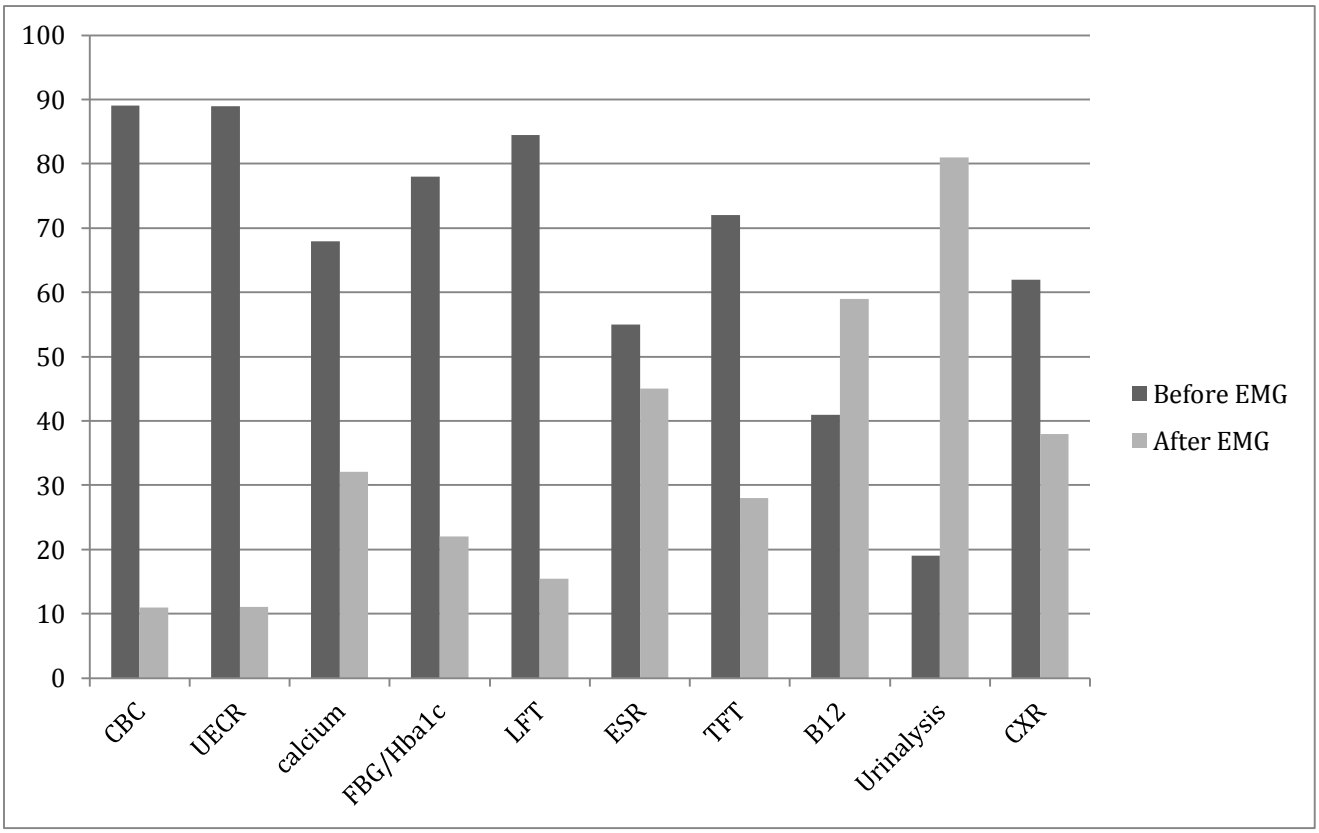
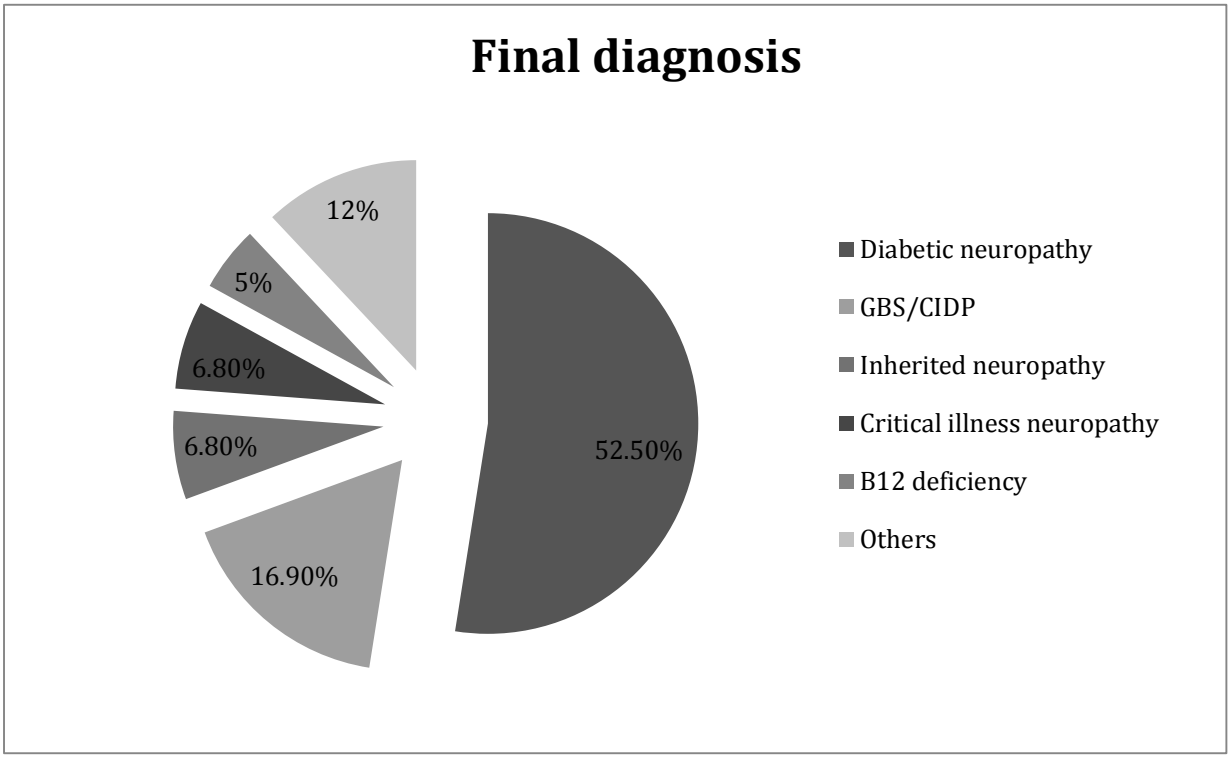


***Figure 3**: Final diagnoses of peripheral neuropathy cases*



Medical notes of all 116 patients were reviewed in search for a documented diagnosis. Each patient fit in 1 of 3 possibilities: no data (no documentation at all was found relevant to the final diagnosis), no diagnosis (patient was investigated but a final diagnosis was not achieved) and diagnosis present (aetiological diagnosis documented in the medical report). Results showed 11 cases with no data, 46 with no diagnosis and 59 patients with a diagnosis. Diagnoses were diabetic neuropathy (*n*=31), Guillaine-Barre syndrome/ Chronic Inflammatory Demyelinating Polyneuropathy (*n*=10), hereditary neuropathies (n=4), critical illness neuropathy (*n*= 4), B12 deficiency (*n*=3), monoclonal gammopathy associated neuropathy *(n*=3), vasculitic neuropathy (*n*=2) and drug-induced neuropathy (*n*=2) [Figure 3].

Discussion

A definite diagnosis of the aetiology of peripheral neuropathy is not always possible. The most common generalized polyneuropathy is diabetic sensorimotor polyneuropathy together with alcohol related neuropathy.[3] Thus, history taking is still paramount in the work up of this condition as it can give important clues as to what the cause may be e.g. concomitant diabetes, alcohol abuse and family history of neuropathy.

Neuropathic pain can cause distress and significantly affect the patient's quality of life. Apart from symptomatic treatment, one should aim to direct the treatment to the underlying cause. This reinforces the need to obtain a diagnosis whenever it is possible. In the challenging cases where the cause is not apparent from the history it is best to adopt a methodological approach. Different tiers of investigations ensure that the diagnostic process is efficient, rational and cost effective.

In this audit, 22% (N=118) of all the EMG's reviewed were confirmed to be peripheral neuropathy. Of note 9 patients in total were referred from the diabetes clinic. As expected, the majority (61.4%) were referred from the Neuroscience department. Four paediatric cases were identified from the cohort. This would explain the low mean age observed (59.3 years). Peripheral neuropathy was the indication for the test in 78% of cases. This implies that in the remaining 22% of cases the diagnosis was incidental.

Diabetes mellitus was the commonest co-morbidity documented in the cohort. Despite this, a FBG and/ or an Hba1c were not taken in 21.4% of patients. An Hba1c is still indicated in known diabetics because it can help assess diabetic control. Diabetic neuropathy is the commonest cause of neuropathy in Western countries with up to a third of the direct costs of diabetes attributed to neuropathy-related morbidity.[4] It may be present in up to 66% of type 1 and 59% of type 2 diabetics making it one of the commonest complications of diabetes.[3] The EMG can be normal in a diabetic patient with peripheral neuropathy symptoms due to small fibre neuropathy. In this audit 26.7% of the patients were confirmed to have diabetic peripheral neuropathy.

Baseline investigations such as a complete blood count or renal profile grouped in this study as the first tier were not taken in all the patients during the 2 year time limit preset for this audit. In this audit 39.7% of our cohort remained without an aetiological diagnosis. In the subset of patients that remained without a diagnosis (*n*=46) only 8 patients (16.3%) had completed the first tier of investigations over the 2 year period. In the remaining 38 patients several investigations were missing: urinalysis missing in 71% (*n*=27), ESR missing in 45% (*n*=17), vitamin B12 levels missing in 40% (*n*=15), calcium levels missing in 37% (n= 14), FBG/HBa1c levels missing in 26% (*n*=10) and 21% did not have a chest x-ray taken (*n*=8). A complete blood count was the only investigation available for all these patients. Irrespective of whether these tests would have been abnormal or not they are still needed for the investigation of peripheral neuropathy. The fact these core investigations were missing could reflect the lack of a systemic approach adopted when investigating patients with peripheral neuropathy.

It is estimated that about 20% of patients seen at peripheral neuropathy clinics are idiopathic despite intensive evaluation.[5-6] Chronic idiopathic axonal polyneuropathy is an entity met in the literature relevant to this condition. It is a diagnosis of exclusion, with uncertain prevalence. The cause is not known and is probably heterogeneous, but a possible association with impaired glucose tolerance or metabolic syndrome has been suggested. One study found a closer association with hypertriglyceridaemia (a feature of the metabolic syndrome) rather than with impaired glucose tolerance.[7-8] This raises the issue whether we should include a lipid profile and an oral glucose tolerance test as part of the second tier of investigations. It is possible that an inherited neuropathy was missed in those 46 patients that remained without a diagnosis. However these are rare and have an estimated prevalence of one in every 2500 individuals.[9]

The audit was limited by the fact that we could not access results of investigations done within the private sector and this could have biased our data. Other clinical data such as co-morbidities was not necessarily documented in the sources of information that we used. Thus we could have underestimated the prevalence of co morbidities in our cohort.

Specialised tests were performed in a significantly lower proportion of the patients. This was expected as these tests are not indicated in all cases with peripheral neuropathy. It was interesting to note that genetic testing was performed in 4 patients. One was inconclusive whilst the other diagnoses were Facioscapulohumeral dystrophy, Charcot-Marie Tooth disease and Myotonic dystrophy.

Conclusion

This audit has shown that there are a significant proportion of cases of peripheral neuropathy that remain without an aetiological diagnosis. Using a stepwise approach which involves a good history and examination followed by the recommended investigations can help make this process more efficient and facilitate the path towards achieving a final diagnosis. Ultimately not all patients will have a diagnosis despite being properly investigated. On the other hand, not all patients will require all the investigations available and this could be for numerous reasons such as the diagnosis can be clear from the history or the patient may refuse specialised tests.

In a significant proportion of patients in this audit the cause of peripheral neuropathy was identifiable from the history, examination and the first tier of investigations e.g. B12 deficiency. In these situations where the cause and management is clear specialist referral is not necessary. Of note, 20 out of the total 31 diabetic neuropathies were still being diagnosed by or referred to neurologists. On the other hand, it is wise to keep an open mind when investigating peripheral neuropathy even in known diabetic patients.

This audit highlights the significance that a thorough history, examination and baseline investigations can have in achieving a diagnosis for peripheral neuropathy. Such baseline investigations are readily available even to general practitioners in the community. This will help avoid unnecessary specialist referrals. Red flags that warrant referral to a neurologist are an uncertain cause, severe symptoms, rapid progression as well as the presence of weakness or motor symptoms.[1]

A re-audit, using a standard proforma based on the investigations mentioned, will be done in a prospective fashion so as to see whether its implementation can lead to an improvement in the diagnostic yield of peripheral neuropathies.

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Original Article

The efficacy of lymph node fine needle aspiration cytology

Jason Attard, Jonathan Galea, Alexandra Betts

Abstract

Introduction: Fine needle aspiration cytology (FNAC) of lymph nodes is a safe, easy, cheap and quick diagnostic tool, which involves the examination of a random sample of cells from a lymph node.

Aim: To assess the distribution of diagnostic categories and the efficacy of lymph node fine needle aspiration cytology at our institution. These were compared to the literature.

Methodology: All of lymph node FNAC cases taken between the 1st January 2012 and the 31st December 2013 were retrieved from our Laboratory Information System. A total of 300 cases were retrieved and then placed into one of six categories; Category 1: Non-diagnostic, 2: Reactive, 3: Probably reactive but lymphoma cannot be excluded, 4: Non-Hodgkin lymphoma, 5: Hodgkin lymphoma, and 6: Metastasis. These were then correlated with the histology of the lymph node excision specimens.

Results: The proportion of diagnoses placed under categories 1, 2, 3, 4, 5 and 6 represent 14%, 53%, 4.3%, 5.7%, 1.7% and 21.3% of the total respectively. The overall efficacy of FNAC showed a sensitivity of 84.5%, specificity of 99.3%, a false negative rate of 10%, a false positive rate of 0.7%, accuracy of 93.1%, positive predictive value of 98.8% and negative predictive value of 89.9%.

Conclusions: FNAC of lymph nodes is a very useful and effective tool in triaging patients with lymphadenopathy.

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Keywords

Lymph node, fine needle aspiration, cytology, efficacy

Introduction

Fine needle aspiration cytology (FNAC) is a safe, easy, quick, cheap technique for diagnosing benign as well as malignant enlarged lymph nodes.[1-2] This technique involves taking a random sample of cells from a potentially pathological lymph node using a needle.[3] The indications for lymph node FNAC are: for the diagnosis of reactive lymphadenopathy, metastatic and lymphoid malignancy, staging and monitoring for relapse or the effects of treatment.[1] Lymph node FNAC is excellent in the diagnosis of metastatic malignancy, reducing the need for diagnostic excision biopsy in many patients.[4-5] The diagnosis of lymphoid neoplasms on FNAC remains controversial and is often followed by tissue biopsy.

In this study, we present our lymph node FNAC experience encompassing all diagnostic categories.

Materials and methods

All lymph node FNAC cases taken between the 1st January 2012 and the 31st December 2013 were retrieved from our Laboratory Information System via the Cognos search engine by inputting the specimen type using SNOMED codes. The reports were then reviewed and categorised as follows:

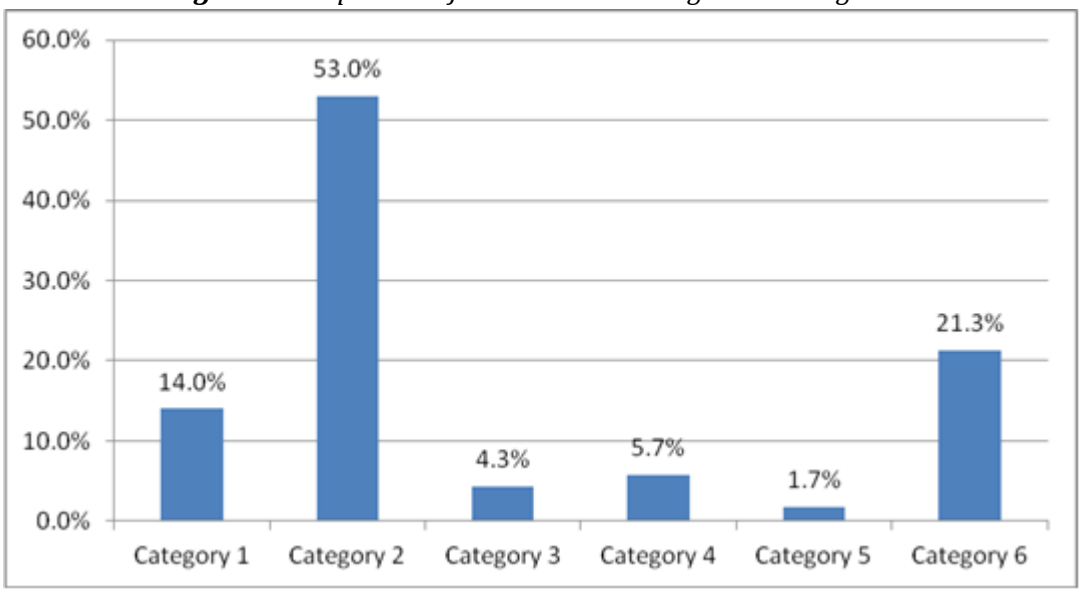
Category **1**: Non-diagnostic
Category **2**: Benign reactive lymphoid hyperplasia
Category **3**: Although favouring a reactive process, lymphoma cannot be excluded
Category **4**: Suspicious for non-Hodgkin lymphoma
Category **5**: Suspicious for Hodgkin lymphoma
Category **6**: Metastatic malignancy

The cytological findings were then correlated with the histological findings of the lymph node excision specimens when these were subsequently submitted to the histopathology department. The aim was to assess the overall efficacy of the test.

Results

A total of three hundred (300) lymph nodes were sampled by FNA in the period under review. The diagnoses designated under categories 1, 2, 3, 4, 5 and 6 represented 14.0%, 53.0%, 4.3%, 5.7%, 1.7% and 21.3% of all lymph node FNACs respectively (see figure 1).

Figure 1: *Proportion of cases in the six diagnostic Categories*



Category 1: Non Diagnostic

In our study, 73.8% (32 out of 42) of all of cases categorised as non-diagnostic did not have follow up histology. One case (2.38%) was followed up by core biopsy; however the two core biopsies submitted were composed of fibrous connective tissue and skeletal muscle with no evidence of lymphoid tissue on histology. This biopsy was therefore considered inadequate for diagnostic purposes. In four cases (9.52%), subsequent histology showed benign lymphoid hyperplasia. Three cases of Hodgkin lymphoma and three cases of metastatic carcinoma (each representing 7.14%) were diagnosed on histology of the subsequently excised lymph nodes.

These results are summarised in Table 1.

Cases in this FNAC diagnostic category are inadequate and hence histologic correlation is not appropriate. We have therefore opted to exclude this category from our efficacy statistics.

Category 2: Benign lymphoid hyperplasia

In our study, 78.6% (125) of cases were not followed up by histology. From a clinical perspective and for the purpose of this study, these are assumed to represent reactive lymph nodes. The 21.4% cases which did have subsequent histology can be divided into two groups, namely true negative cases (52.9%) and false negative cases (47.1%). The false negative cases were 6 cases of non-Hodgkin lymphoma, 1 case of Hodgkin lymphoma and 9 cases of metastatic carcinoma.

These results are summarised in Table 2.

Category 3: Although favouring a reactive process, lymphoma needs to be excluded

Six cases in this category showed benign lymphoid hyperplasia on subsequent histology whilst two cases were diagnosed as non-Hodgkin lymphoma and four cases as Hodgkin lymphoma on subsequent histology. One case did not have follow up histology.

The thirteen cases in this diagnostic category were excluded from the overall efficacy statistics in view of the higher degree of uncertainty inherent in the cytologic diagnosis.

Category 4: Suspicious for non-Hodgkin lymphoma

There were seventeen cases in this category. Two cases did not have follow up histology however they were confirmed with ancillary tests; using cell block and immunohistochemistry. Fourteen cases were confirmed to be cases of non-Hodgkin lymphoma on follow up histology. One case was a false positive and was diagnosed as a pilomatrixoma on subsequent histology.

Category 5: Suspicious for Hodgkin lymphoma

All five cases diagnosed on FNAC were confirmed on subsequent histology.

Category 6: Metastatic malignancy (see Table 3)

Of these, twenty two cases did not have a follow up histology. From a clinical perspective and for the purpose of this study, these are assumed to represent metastasis to lymph nodes. Fifteen cases were confirmed using ancillary tests. Twenty seven cases were confirmed on subsequent histology.

These results are summarised in Table 5.

The overall efficacy of lymph node fine needle aspiration cytology is summarised in table 4.

Table 1: *Category 1: Non Diagnostic*

Number of patients	Histopathological report	Number of patients
42 (14%)	No follow up histology	31(74%)
	Non diagnostic histology	1(2%)
	Benign lymphoid hyperplasia	4(10%)
	Hodgkin lymphoma	3(7%)
	Metastatic carcinoma	3(7%)

Table 2: *Category 2: Benign Reactive Lymphoid Hyperplasia*

Number of patients	Histopathological report	Number of patients
159 (53.0%)	No follow up histology	125(79%)
	Benign lymphoid hyperplasia	18(11%)
	Non-Hodgkin Lymphoma	6(4%)
	Hodgkin Lymphoma	1(1%)
	Metastatic carcinoma	9(5%)

Table 3*: Category 6: Metastatic malignancy*

Number of patients	Histopathological report	Number of patients
64 (21.30%)	No follow up histology	22(34%)
	Metastatic carcinoma*	42(66%)

*Of these, 27 cases had follow up histology and 15 cases were confirmed using cell block and immunohistochemistry.

Table 4: The overall efficacy of lymph node FNAC

True negative	143
False negative	16
True positive	87
False positive	1
Sensitivity	84.5%
Specificity	99.3%
False positive rate	0.7%
False negative rate	10.0%
Accuracy	93.1%
Positive Predictive Value	98.8%
Negative Predictive Value	89.9%

Discussion

The proportion of cases in the different categories and the efficacy of FNAC at our institution were compared to those reported in the literature (summarised in Tables 5 and 6).

Category 1: Non Diagnostic

A non-diagnostic diagnosis occurs when the specimen is found unsatisfactory either because of low cellularity or due to difficulty in assessment e.g. obscuring blood.

After a literature review, we could not find a standardised system for assessing the adequacy of a lymph node aspirate and in practice this appears to be based on the cytologist's interpretation. The adequacy rate of lymph node FNAC in our institution (14%) compares well with that reported in the literature (5.6% –21.7% [2, 7]). The wide variability depends on the size and location of the lymph node, and on the operator's and cytologist's experience.

Table 5*: Comparison of the relative frequency of the different categories*

	C1	C2	C3	C4	C5	C6
Our results	*14%*	*53%*	*4.3%*	*5.7%*	*1.8%*	*21.3%*
Mitra et al	5.6%	-	2.8%	13.7%		
Nasuti et al	12%	13%		17%		52%
Gilani et al	21.7%	-	-	-	-	-
Jing et al	8%	-	-	-	-	-
Steel et al	10.9%					
Rammeh et al	20.6%	-	-	-	-	-
Lioe et al	15.9%	52.7%	6.1%	25.1%		
Stani J	-	23.5%	-	-	-	-

Table 6: *Comparison of the efficacy of fine needle aspiration cytology of lymph nodes*

	Sensitivity	Specificity	False negative	False positive	Accuracy	Positive Predictive Value	Negative Predictive Value
Our results	*84.5%*	*99.3%*	*10%*	*0.7%*	*93.1%*	*98.8%*	*89.9%*
Gilani et al	91.7%	100%	4.3% [1]	11% [2]	93.5%	100%	77.8%
Jing et al (for metastasis)	77.5%	100%	-	-	82.2%	100%	53.7%
Steel et al	-	-	3.4%	0.9%	-	-	-
Thierauf et al	85%	87%	5%	15%	-	64%	92%
Hall et al (for melanoma)	97%	98%	-	-	-	-	-
Lioe et al	85.4%	100%	12.5% [3]	0%	94.4%	100%	91.8%
Marti et al (for metastasis)	86%	100%	29%	0%	91%	100%	78%
Fung et al (for metastasis)	75%	100%	-	-	95.6%%	100%	79%

[1] Micrometastasis on histology.
[2] The patients had undergone preoperative neoadjuvant chemotherapy, with no residual tumour present.
[3] The false negative rate fell to 3.5% after excluding lymphomas.

Category 2: Benign lymphoid hyperplasia

A diagnosis of benign lymphoid hyperplasia is conferred when the cytology specimen is cellular, is not obscured by blood or other material and is composed of a polymorphic population of lymphoid cells. The proportion of cases in this category in our institution is considerable, amounting to 53% of all cases. This is higher than reported by Nasuti et al and Stani (13% and 23.5% respectively) [6, 15], and comparable to Lioe et al (52.7%). [14] The high percentage of cases in category 2 in this study could possibly be accounted for by a lower clinical threshold to perform fine needle aspiration cytology at our institution.

Category 3: Although favouring a reactive process, lymphoma needs to be excluded

In this category, the cytological picture is cellular and unobscured and is composed of a relatively monomorphic population of small to intermediate-sized lymphocytes. This category is reserved for those cases where the cytological picture is equivocal and has overlapping features. One of the limitations of fine needle aspiration cytology of lymph nodes is in differentiating between reactive lymphoid proliferations and lymphoma, especially low grade lymphoma.[5] The proportion of cases in this category (4.3%) lies in between that observed in the study by Mitra et al (2.8%) and Lioe et al (6.1%).[2, 14]

Category 4: Suspicious or diagnostic of non-Hodgkin lymphoma

The cytological picture of this category is characterised by a cellular, unobscured monomorphic population of intermediate-sized to large atypical lymphoid cells and with variable mitosis. At our institution, non-Hodgkin lymphoma holds an overall specificity of 94.1% and sensitivity of 66.7%. This rises to 72.7% if the cases in categories 1 and 3 are excluded.

Category 5: Suspicious for Hodgkin lymphoma

In this category, the diagnosis relies on the identification of Reed-Sternberg or Hodgkin cells, on a background of small monomorphic lymphocytes, eosinophils and other inflammatory cells, in the absence of tingible body macrophages. At our institution, Hodgkin lymphoma holds a specificity of 100% and sensitivity of 38%. If the cases in categories 1 and 3 are excluded, the sensitivity rises to 83%. According to Chhieng et al.[10], Hodgkin lymphoma has a high false negative rate due to typical scarcity of Reed-Sternberg or Hodgkin cells in aspirates, the presence of fibrosis (in the nodular sclerosis type), sampling error and misinterpretation of the diagnostic cells.

Category 6: Metastatic malignancy

In this category, the cytological diagnosis relies on the presence of single cells or clusters of malignant cells with a morphology which is alien to that of the normal lymphoid milieu. This often occurs on a background of a normal lymphoid FNAC specimen. The overall specificity at our institution was 100%. The overall sensitivity was 84%, which rises to 88% after excluding the cases in categories 1 and 3. Our data compares well with that in the reported literature which shows a specificity of 100% across all studies and a sensitivity which ranges from 75 to 86%.[8, 16-17] The lower specificity in some cases can be explained by the small size of metastatic deposits. [17]

There overall efficacy of lymph node fine needle aspiration cytology is tabulated in table 4.

This study has a number of limitations which were taken into consideration:

- This is a retrospective study.
- A number of lymph node FNAC cases were submitted by the clinicians as a lesion or mass in the head and neck region. These were thus encoded using the 'Head and neck cytologic material' SNOMED code and were not included in this study.
- This study assumed that all lymph nodes classified as benign reactive lymphoid hyperplasia, which did not have a subsequent diagnosis of lymphoma within one year, were truly reactive.
- This study assumed that all lymph nodes classified as metastatic malignancy were truly involved.
- Lymph node excisions performed in the private sector following a FNA performed at our institution could not be assessed.
- The lymph node excised may not be the same lymph node that was sampled by fine needle aspiration.
- The numbers in categories 3,4,5 are small. These can introduce a wide margin of error in statistical comparisons.

In spite of these limitations, this study has been able to demonstrate the clinical usefulness of this test.

Conclusion

The overall efficacy of lymph node FNAC diagnosis compares very well with that quoted in the literature. This test's greatest strength lies in triaging reactive from neoplastic lymph nodes, principally high grade non-Hodgkin's lymphoma and metastasis. Its weakness lies in sampling issues and differentiating between certain patterns of reactive lymphoid hyperplasia and low grade non-Hodgkin's lymphoma. Our comparatively high rate of cases in the benign category could possibly be explained by a higher index of suspicion among our clinicians with a consequent lower threshold to biopsy. The proportion of cases with a non-diagnostic cytology result could be possibly

brought down by ensuring that operators and cytologists are properly trained and retrained. Fine needle aspiration cytology of lymph nodes remains a very important and valid tool in the management of patients with lymphadenopathy.

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Original Article

Depressive illness in institutionalised older people in Malta

Paul Zammit, Anthony Fiorini

Abstract

Introduction: Depression in older persons is associated with being placed in a nursing home. Depression is linked to increased medical morbidity in nursing home residents.

Methods: 150 patients living in two nursing homes in Malta were included in the study. The geriatric depression scale was used to identify depression. Data for risk factors for depression and management of residents for this pathology was also collected.

Results: 67.3% (*p* value <0.01) were found to be depressed. 12% of the total population had major depression while 55.3% had minor depression. Only 40% of those diagnosed with depression in this study had been so diagnosed prior to the study. Significant associations included low Barthel scores, loneliness, being currently in pain, taking several medications, being widowed and having osteoarthritis. The study also showed that those residents already diagnosed with depression were being treated inappropriately with low prescription levels of antidepressants (40.6%).

Conclusion: Results show that depression in nursing home residents is highly prevalent and under diagnosed. There is also a lack of proper treatment in those identified with depression. There is a need for further research to develop intervention and management strategies for depression that is specifically tailored to meet the needs of the frail nursing home population.

Keywords

Depression, nursing homes, elderly

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Introduction

Several independent studies have shown that major and minor depression is widespread in the nursing home population. A study[i] had observed that, 'Depression is the most common, treatable psychiatric disorder found in elderly nursing home residents'. This statement is understandable when consideration is given to the inactivity, decline in functional competence, loss of personal autonomy, and inevitable confrontation with the process of death and dying that are associated with a nursing home placement. In addition, some nursing home residents have already had previous episodes of depression in their lives or are admitted to the facility already with low mood or with other chronic forms of this illness. Such circumstances provide a population and environment conducive to the development and persistence of depressive illness.

There are other described characteristics of depression affecting older persons, thus making a diagnosis difficult. [ii] Proper diagnosis and adequate treatment give good therapeutic results among older persons. The consequences of undiagnosed and untreated depression are high both for the older person as well as for carers and staff. From the rehabilitation point of view, persistent depression among individuals with physical dependency following an acute event such as a cerebrovascular accident (CVA) is associated with failure to improve in physical functioning. Depression is linked to increased medical morbidity in nursing home residents, a relationship that also has been suggested for medical inpatients. Due to this loss in activities of daily living (ADLs), the need of increased nursing time and other health care facility services is greater for depressed than non depressed residents, and financial costs are higher as well.

Studies have found that depression prevalence in this population is higher than in the community and ranges from 35% to 80%.[4] Associated factors with one being depressed in a nursing home include pain, functional limitations in ADLs, visual impairment, the effect of a stroke, loneliness, lack of social support, negative life events and perceived inadequacy plus lack of care among others.[5] Besides, when depression is successfully diagnosed in older persons the medications given are often inappropriate.[6]

In addition, a study[7] showed increased mortality in nursing home residents with major depressive disorder. It is apparent that depression in long term care facilities

is a condition that has negative medical, social, and financial consequences.[8]

Methodology

In Malta there have been no studies on depression in older persons living in nursing homes. The main hypothesis was to see if depression is widespread but unrecognised in nursing home residents in Malta. Management in those residents identified as being depressed was assessed along with significant associations. The collection of data was through subject interview and review of the medical records. Parameters included descriptive statistics such as age, gender and marital status. The Barthel ADL index was taken to judge the level of independence. Medical data collected included the presence of the physical symptom of pain, common medical pathologies and the number of medications the subject was on.

All residents had a consent form explained to them and full confidentiality was emphasized. The geriatric depression scale (GDS) developed by Yesevage[9] was the tool used to identify depression. Prior to this a mini-mental state examination (MMSE) developed by Folstein[10] was carried out to exclude from the study all those who were cognitively impaired. This was done because the GDS has a low sensitivity in severely demented subjects.

The study was done in the two largest nursing homes in Malta. The largest had a capacity of 1100 residents and the second had a capacity of 200 residents. The total number of subjects included in the study was 150 in total. These were chosen randomly from the two homes and the interview was done by one doctor. No patient refused to do the interview. Data was analysed using SPSS version 13.0.0.

Exclusion criteria

Residents who had communication difficulties had to be excluded from the study as they were unable to do the interview. Residents with cognitive impairment (MMSE less than 21) were also excluded as the reliability of the GDS decreases markedly with MMSE scores of 20 or less.

Results

From 150 subjects, 113 were female and 37 male. Mean age was 80.3 years (Standard deviation (SD) 6.7, range 60-96). Mean MMSE scores was 26.9. The mean Barthel index score was 12.9 (SD 6.6 range 0-20). 96 (64%) were widowed. There were 25 (16.7%) who were still married whilst 29 (19.3%) remained single. The mean number of medical pathologies for each resident was 3.2 (SD 1.5, range 0-7). The most common pathology was diabetes (41.3%). 37 (24.67%) were suffering from osteoarthritis (OA) and 14 (9.33%) had a recent fracture. The mean number of medications each subject was on was 6.5 (SD 3.1, range 0-15). 46 (31.7%) admitted feeling lonely. 51 (34%) of residents admitted suffering from pain regularly.

Depression

Mean GDS score was 12.5 (SD 5.9, range 1-26). 101 (67.3%) had GDS scores suggestive of depression. According to GDS scoring (GDS over 11) there were 18 (17.8% of those depressed) with major depression and 83 (82.2% of those depressed) with minor depression (GDS less than 11). When enquired directly 52 (34.6%) felt depressed. When the GDS was done 41 (78.8%) of these actually had an element of depression. There were a number of risk factors which were positively associated with depressed residents. Those with a p value <0.05 by using one way ANOVA can be seen in Table 1.

Only 15 (10%) of the 150 subjects interviewed were seen by a specialist regarding depression. Of those seen, 10 (66.6%) had depression according to the GDS. None of the residents were ever seen by a psychologist. There were a total of 43 residents (28.7%) on some kind of anti-depressant. Of these, 35 (81.4%) were found to be depressed. 37 (86%) were on selective serotonin reuptake inhibitors (SSRIs) while only 6 (14%) were on a tricyclic antidepressant.

Discussion

The results show that the population of subjects living in nursing homes in Malta had a high degree of depressive disease. A major difference when one compares this study in Malta with the prevalence of depression in other countries is that it is higher. Only a study in Taiwan[4] had a higher prevalence of depression while other studies on this subject had a lower one.[5,11,12] The prevalence of major depression in other countries was found to vary from 12.4% in the USA[13] to 16% in the Netherlands.[14] In Malta the results regards major depression were similar at 12%. Thus, the major difference was the much higher prevalence of minor depression.

There were various risk factors in the subjects studied which were positively associated with depression (Table 1). These risk factors compared favourably with similar studies done in Europe.[5,15] Studies also found depression in nursing homes to be associated with heart disease, stroke[16] and Parkinsonism[5] but this was not found in this study.

There may be various reasons for these risk factors being associated with depression. Having low Barthel scores means one is dependent and disabled so the number of activities a subject can do is limited which may increase the risk of depression. When a person is lonely or widowed means he might be left with a sense

of emptiness and solitude resulting from inadequate levels of social relationships. This would increase the risk of depression. Pain is a disabling symptom that can affect the quality of life of a person physically as well as psychologically. A person who is in pain, especially if chronic, will have the mood affected adversely and may lead to a depressive disorder. Residents who feel unsatisfied living in a nursing home may feel that their needs are not adequately met or listened to and this may have caused their depression.

Residents suffering from OA and fractures were at increased risk of being pain which may have been the cause for their depression. Another reason could be the fact that these two conditions tended to increase dependency which was significantly correlated with depression in this study.

Having a large number of co-morbidities and having depression may be due the fact that these subjects may have been worried about their precarious health. Having medical conditions may cause an alteration in their lifestyle (e.g. change in food habit if one has diabetes) which may also cause low mood. These subjects tend to take a higher amount of medications which may be the reason why the latter was associated with depression. The more medication one takes, the higher the potential risk of side-effects which may also be a reason for the lower mood of these subjects.

28.6% of the total number of residents was or were on an anti-depressant. Of the 101 who were found to be depressed, 35 (34.6%) were on an anti-depressant. These levels were quite low and these might have been for a number of reasons. One of the reasons might have been failure to make a diagnosis of depression. This was evident from the fact that only 41 of the 101 depressed residents (40.6%) had this diagnosis in their medical records. Another reason might have been the fact that clinicians were reluctant to treat the depressed residents. As regards non pharmacological treatment this can be said to be nonexistent as none of the subjects were ever seen by a psychologist. Review by a psychiatrist was also low with only 9.9% being seen.

In other countries the situation is similar to the above. Studies in the United States show that from 45% to 53% of the depressed residents were not on any form of treatment.[6,17] In the United Kingdom a study showed a worse result with only 19% of depressed older residents being on any form of treatment.[18] In Germany few residents were treated and only 11% were on anti-depressants. It found that review by a psychiatrist was low at 20% which was similar to this study. Only 4% were ever seen by a psychologist.[19] In Australia results were similar to Malta. A study found that only 33% of depressed residents were on anti-depressant treatment.[20]

It was positive to note that the majority of residents who were on an anti-depressant were on the newer SSRIs (86%) and only 14% were on the older tricyclics. This may have been due to the increased awareness of the side-effects of the latter. These findings in Malta were similar to other countries. The general trend was for SSRIs to be given rather than for other anti-depressants such as tricyclics as the former are better tolerated with less side-effects.[20- 21]

Conclusion

Depression appears to be a major health problem among nursing home residents in Malta. The results of this study emphasize the major importance of optimal medical treatment and care for residents in pain, those having a high number of medical co-morbidities in general, those having had a fracture in the past, those taking a large number of medications and OA sufferers. Furthermore, special attention and care must focus on psychosocial factors on those already diagnosed with depression, aspects of loneliness and the widowed. The absence of treatment given to those residents with depression was an important factor. Given that the number of residents involved in the study was high with consequent significant results, there is a need for further research to develop intervention and management strategies for depression that is specifically tailored to meet the needs of the frail nursing home population.

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Original Article

The male to female ratio at birth following the Scottish Independence Referendum, September 2014

Victor Grech, Julian Mamo

Abstract

Introduction: Human male live births exceed female live births by approximately 3%. This sex ratio is conventionally expressed as M/F (male divided by total live births). Many factors have been implicated as influencing this ratio, such as stress. This phenomenon occurred following the Quebec sovereignty referendum of 1995. This study was carried out in order to ascertain whether the Scottish referendum of September 2014 had any effect on the M/F ratio in Scotland.

Methods: Monthly live births by gender for Scotland were obtained from Scottish Office of National Records for the period January 2004 to July 2015. They were analysed for any significant period changes as witnessed in Quebec in 1995.

Results: There were 661166 total births (338850 male and 322316 female births), with an overall M/F of 0.5125 (95% CI: 0.5113-0.5137). There were no changes in M/F in the first five months after the referendum. However, there was a non-significant rise in M/F toward the end of 2014 which continued during much of 2015. The rise in M/F reached its peak in May-June 2015, 8-9 months after the referendum (M/F 0.5199 compared to M/F of 0.5124 for aggregated May-June values 2004-14).

Discussion: There was no significant drop in M/F in the Scottish population in relation to the Scottish referendum. This may be due to a type 2 error since this study was less powered (12 times smaller) than the Quebec study. The non-significant rise may have potentially been caused by increased coital rates as observed after the birth of Prince William in 1982 and for Hong Kong in relation to Dragon years. It will be interesting to analyse the rest of the UK data when this becomes officially available.

Key words

Scotland, Sex Ratio, Birth Rate/*trends Infant, Newborn

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Introduction

Human male live births exceed female live births by approximately 3%. This sex ratio is conventionally expressed as M/F, signifying male divided by total live births. Many factors have been implicated as influencing this ratio, such as stress from violent events[1] and toxins,[2] both of which tend to be associated with a reduction in the ratio three to five months after the event, potentially due to excessive male foetal losses in stressed and already pregnant women.[3] This is in accordance with the Trivers-Willard hypothesis which theorises that natural selection has favoured females who are likelier to lose male foetuses when stressed.[4]

Even non-violent political events have been shown to be associated with a reduction in the ratio and this includes the Quebec referendum of 1995 proposing sovereignty from Canada.[5] This study was carried out in order to ascertain whether the Scottish referendum of September 2015 was associated with any effect on the M/F ratio in Scotland.

Methods

Complete monthly live births by gender for England and Wales for 2015 and for the previous 10 years were not published and were not forthcoming from the UK Office for National Statistics. The equivalent data for the Scottish population for January 2004 to July 2015 were made available directly from Customer Services, National Records of Scotland, Ladywell House, Edinburgh (Ms. Rose Almond – personal

communication) as an Excel spreadsheet, with the proviso that data for 2015 is still preliminary and unpublished.

Linear logistic regression was used in order to assess time trends in the occurrence of boys among live births, and to investigate whether there were changes in the trend functions after distinct events. Segmented regression (so-called "broken stick") regression analysis was carried out. This involved considering the male proportion among all male (m) and female (f) births: pm = m/(m+f). Important and useful parameters in this context are the sex odds: SO = pm/(1- pm) = m/f, and the sex odds ratio (SOR), which is the ratio of two sex odds of interest, i.e. in exposed versus non-exposed populations. Dummy coding was used for single points in time and for time periods. The simple and parsimonious logistic model for a trend and a jump in 2006 has the following form (LB = live births):

Boyst ~ Binomial(LBt,π t):

$$\log\ \text{odds}(\pi_t) = \text{intercept} + \alpha * t + \beta * d_{timeperiod}(t)$$

Statistical analyses were carried out with R 2.15.1, MATHEMATICA 8.0, and SAS 9.3 (SAS Institute Inc: SAS/STAT User's Guide, Version 9.3. Cary NC: SAS Institute Inc; 2012). The quadratic equations of Fleiss were used for the calculation of 95% confidence intervals for ratios.[6] A *p* value ≤0.05 was taken to represent a statistically significant result.

Results

This study analysed 661166 total births (338850 male and 322316 female births), with an overall M/F of 0.5125 (95% CI: 0.5113-0.5137). There were no changes in M/F three to five months after the referendum in September 2014. However, there was a non-significant rise in M/F in the following year with a peak in May-June 2015, i.e. 8-9 months after the referendum (figures 1 to 3). This can be seen when comparing May-June 2015 M/F (0.5199) with the aggregates for the same two months over the period 2004-2014 (0.5124*: p=ns,* figure 4).

Figure 1: *Sex odds ratio (SOR) for Scotland January 2004-July 2015. Jump November 2014, p=0.36.*

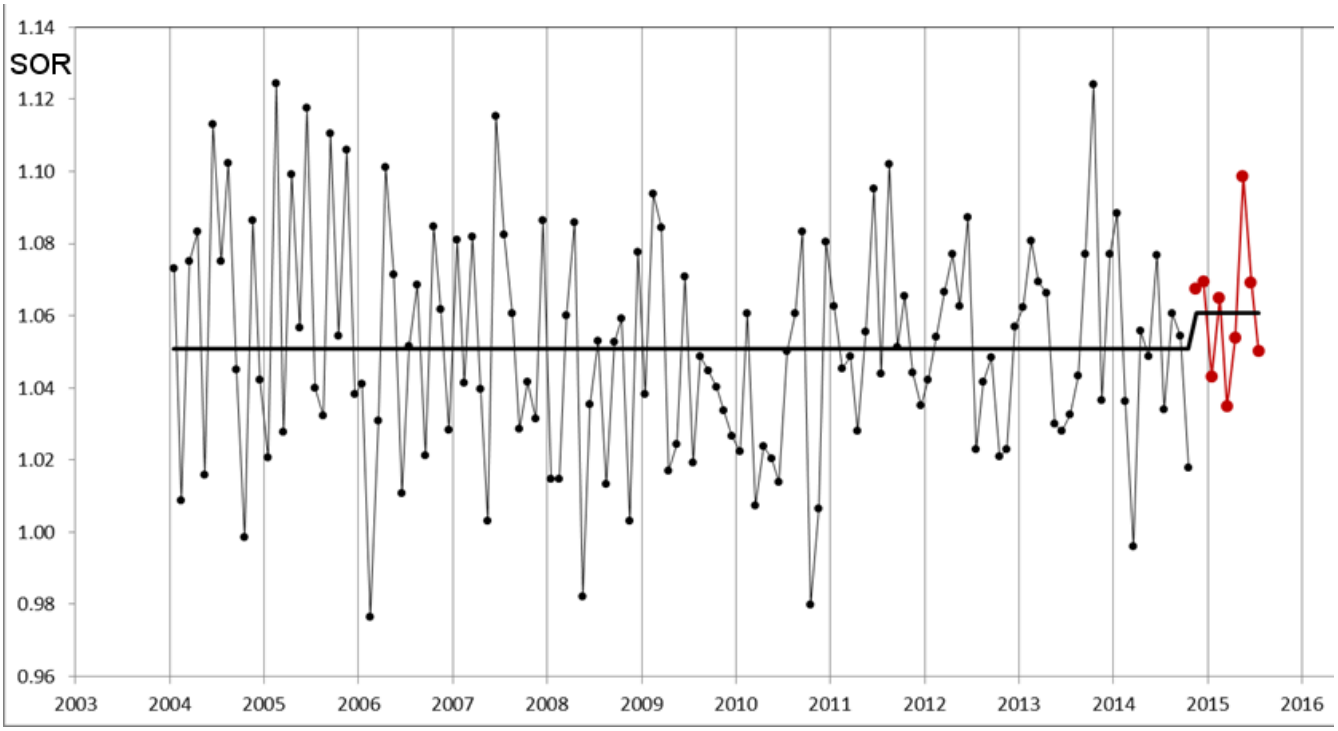


Figure 2: *Sex odds ratio (SOR) for Scotland January 2004-July 2015. Jump December 2014, p=0.43.*

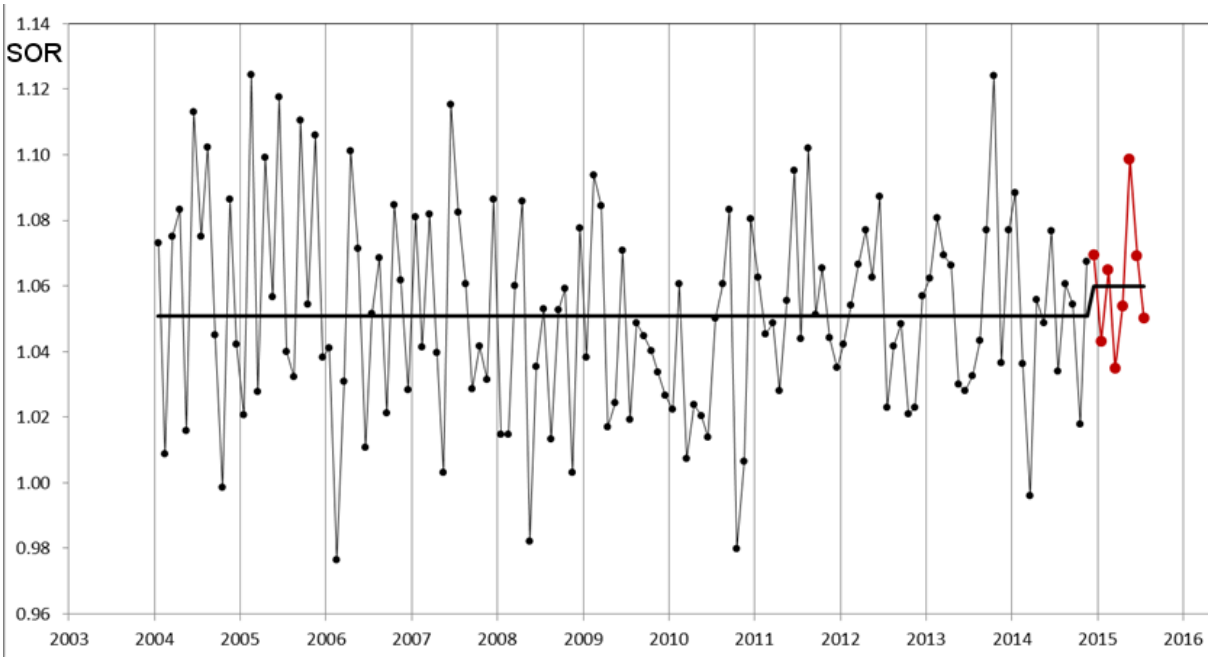


Figure 3*: Sex odds ratio (SOR) for Scotland January 2004-July 2015. Jump January 2015, p=0.53.*

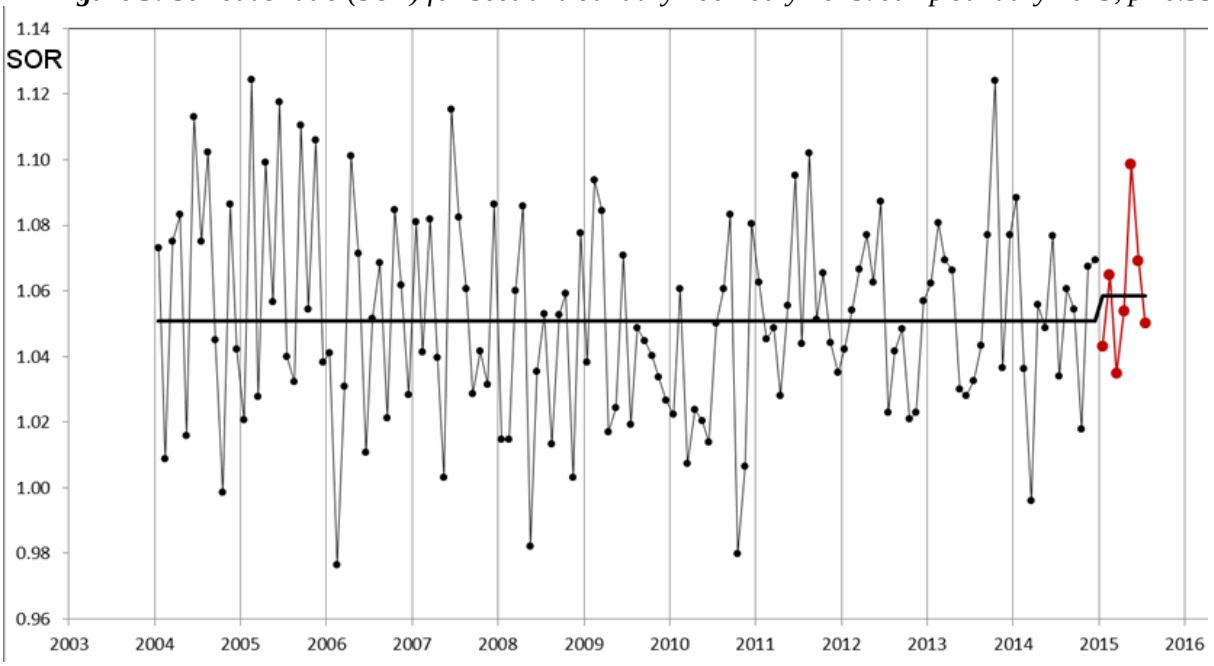
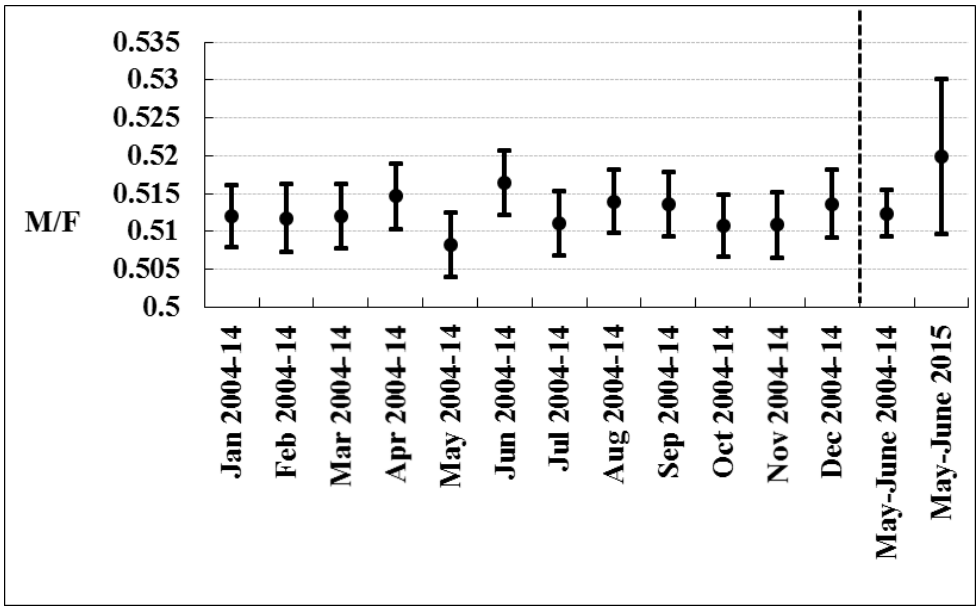


***Figure 4**: Monthly aggregate M/F for 2004-14, and for May-June aggregate for 2014-14 and May-June totals for 2015.*



Discussion

This study failed to find a drop in M/F in relation to the Scottish referendum seeking secession from the Union. This is in contrast with the Quebec sovereignty referendum of 1995 which was associated with in a drop in male births three months after referendum, followed by a rapid rise.[5] This may be due to a type 2 error since this study was less powered, with a sample size 12 times smaller than the Quebec study which analysed 8099600 live births.[5]

The rise (albeit non-significant) may have potentially been caused by increased coital rates. M/F follows a U-shaped regression on cycle day of insemination, suggesting that female conceptions result most often from conceptions around ovulation, with male conceptions occurring more frequently at the beginning and end of the menstrual cycle.[7,8] These findings have been confirmed by more recent meta-analysis.[9] The rise in M/F in May-June 2015 may thus have been due to higher coital rates associated with the emotions linked to this particular event, transiently skewing M/F toward more male births.

This is not without precedent. It was recently shown that in the UK, M/F transiently rose in association with a Royal birth, that of Prince William in 1982. This event was associated with a sharp and significant rise in M/F in the following year only.[10]

These contentions are further reinforced by a recent study that showed that male births rose in Hong Kong in relation to Dragon years, since such years are considered auspicious for baby's births, in accordance with the Chinese Zodiac. The putative mechanism may be similar, with possible increased coital activity, since parents actively seek to conceive a child in Dragon years.[11]

It will be interesting to analyse the rest of the UK data when this becomes officially available.

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An unexpected cause of palmar paraesthesia in a soldier: A case report

Matthew Psaila, Kirill Micallef Stafrace

Abstract

Introduction: Athletes presenting with neurological symptoms merit thorough assessments that in most cases will include investigations with one or more imaging modality. Imaging is especially useful in atypical presentations of neurological pathology (both acute and chronic) as was the instance in the presented case report.

Case presentation: The case of a 22-year-old male soldier is presented who presented with a two week history of paraesthesia involving his right hand. After being assessed by the military medical officer, a presumptive diagnosis of cervical radiculopathy was made and appropriate treatment was prescribed. Symptoms persisted despite treatment and following an inconclusive cervical X-Ray, a magnetic resonance scan was booked that confirmed the diagnosis of multiple sclerosis. The patient was admitted to hospital and started on intravenous methylprednisolone and beta-interferon therapy with resolution of his symptoms.

Conclusion: This case highlights the usefulness of imaging in confirming diagnosis, especially in atypical presentations of pathology afflicting the neurological system. Atypical symptoms, lack of response to standard therapy and inconclusive initial radiological investigations, should prompt the physician to carry out further detailed imaging modalities. The choice of the latter will need to reflect the working differential diagnoses. With reference to the presented case, imaging plays a role not only in diagnosis but also in assessing response to treatment and disease progression.

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Keywords

Multiple sclerosis, palmar paraesthesia, magnetic resonance scan, neurological symptoms

Introduction

Neurological symptoms necessitate thorough assessments and investigations (where applicable) to identify underlying pathologies, to guide treatment and possibly halt further progression. In sports however, the simple act of participation in physical activity may be linked with the onset of neurological symptoms.[1] The latter could possibly be preempted by pre-participation screening.[2] Soldiers who undertake regular intensive military training are at a relatively high risk of injury including the involvement of the neurological system.[3]

To this effect, Schoenfeld and colleagues,[3] audited cervical radiculopathy in the United States military and identified an incidence rate of approximately two per 1000 person-years, with female gender, higher military ranks, white race and service-type all reflecting risk. In the presented case, symptoms were atypical for a diagnosis of cervical radiculopathy, however, when all the medical and occupational factors where considered, the latter diagnosis featured most prominently in the differential diagnosis. Conservative management was employed with a multimodal approach involving biomechanical, pharmacological and imaging components.[4] The negative initial imaging modalities led to the use of more detailed radiological tests which eventually confirmed the diagnosis.

Case Presentation

Background

The case of a 22-year old Maltese infantry soldier is presented, who had attended for review by a military medical officer. The soldier participated regularly in physical training that comprised strength and endurance training as well as military based training that included weighted route marching and combat training. The patient had a negative medical history and had not sustained significant debilitating physical injuries throughout his military career.

History of presenting complaint

The patient disclosed to the medical officer that over the past two weeks he had been complaining of tingling and numbness throughout his right hand. This

sensation involved both palmar and dorsal surfaces of his hand and was not associated with hand muscle weakness. This was the first time he experienced such a sensation in his right hand, however, on further questioning, he did recall experiencing tingling in his right lower leg and foot in the previous year. The latter was milder in intensity and resolved spontaneously after five days and therefore he did not seek medical advice having presumed that it was training related and that it was nothing serious.

On further questioning, his symptoms were present throughout the day and were not preceded by trauma. He did not complain of any neck, elbow and wrist pain and there were no specific aggravating or relieving factors. The patient did not consume any medications for his symptoms and was still managing (although struggling) to continue with his work-related duties as well as some physical training. Systemic enquiry was negative and he had a negative family history.

Examination

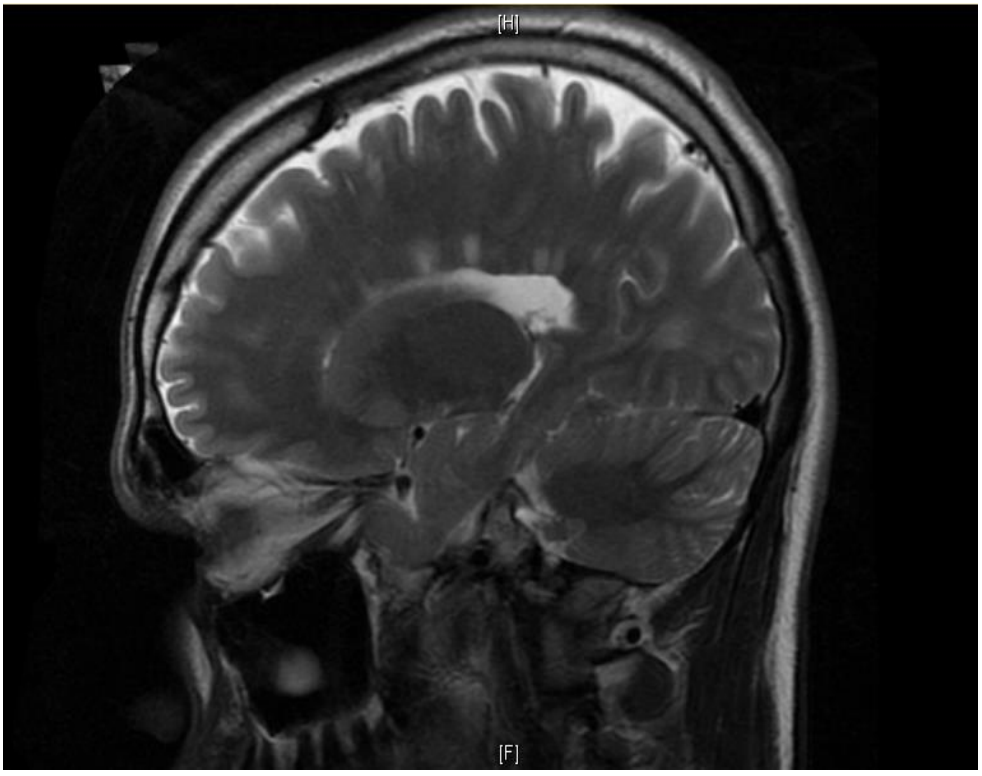
The patient had a regular pulse, was normotensive at rest and had a normal cardiovascular, respiratory and gastrointestinal system examination. Neurological examination of his right hand revealed decreased (when compared to the left side) appreciation of pain and light touch sensation on the palmar and dorsal surfaces of his right hand in a distribution that did not conform to a specific dermatomal pattern. Joint position and vibration sense was normal. The rest of his neurological system, including cranial nerves and right lower limb, were completely normal.

Since his duties at work are mainly clerical, entailing long hours of working on a computer with possibly an incorrect neck posture, a presumptive diagnosis of cervical radiculopathy with involvement of the right cervical sixth and cervical seventh dermatomes was made by the reviewing medical officer. He was prescribed diclofenac sodium, vitamin-B complex and advised regarding his posture when using his computer. Elastic kinetic taping of his paraspinal muscles was suggested by the patient's physiotherapist to improve sensory biofeedback.

Follow-up

A cervical spine X-Ray was taken to assess cervical spine alignment as well as exclude bony pathology. When reviewed after one week, the patient was still complaining of a right sensory deficit in his right hand that had not worsened but did not improve with the advised treatment. The X-Ray was reported as normal. At this stage the patient was referred for a Magnetic Resonance Imaging (MRI) scan to visualize the cervical spine, spinal cord, nerve roots and surrounding connective tissue. This scan identified a small high intensity lesion within the spinal cord at the level of the sixth cervical nerve root. The rest of the spine, as well as disk spaces, were intact.

Figure 1: *Magnetic resonance imaging scan of the head and brain*



An MRI of the head was also undertaken that identified multiple lesions of high signal intensity in both periventricular regions, corpus callosum, splenium and pons (Figure 1). When considering the patient's presentation and objective clinical assessment together with the history of a similar episode the year previously afflicting his right lower limb, a diagnosis of MS was made as per the revised 2010 McDonald criteria for diagnosis of MS.[5] No additional data is recommended in the criteria for the diagnosis of MS to be made, however, the authors list that imaging, for the identification of lesions typical of MS, is desirable.[5] With reference to the lesions identified on MRI, the McDonald criteria specify that there needs to involvement of at least two of the four regions of the central nervous system that are typically affected in MS, that is, the periventricular, juxtacortical, infratentorial and spinal cord. As per final MRI report, lesions were identified in only one of the regions listed in the criteria.

After being diagnosed with MS, the patient was reviewed by a neurologist and admitted to a neurological ward, where he was started on intravenous methylprednisolone and intramuscular beta-interferon therapy. His symptoms resolved gradually over a span of five days and he was discharged home with an out-patients follow up at the MS clinic.

Discussion

MS is a chronic neurological condition of presumed autoimmune etiology characterized by central nervous system demyelination.[6] The MS international federation has recently updated the Atlas of MS, with the revised number of people with MS worldwide in 2013 measuring 2.3 million, increasing from the 2.1 million people estimated to be diagnosed with MS in 2008.[7] According to epidemiology studies in the United Kingdom, the incidence of MS is 203 per 100,000 and peaks between the ages of 40 and 50, being almost twice as common in females.[8] This incidence rate contrasts with earlier epidemiological data from Malta, where an incidence rate of two cases per 100,000 per year was identified.[9] The last survey in Malta was conducted in 2005 by the MS society of Malta, with an estimated 100 people diagnosed with MS at the time.[10]

In the presented case, initial symptoms were incorrectly attributed to cervical radiculopathy, despite the lack of evidence from the clinical examination that revealed purely sensory neurological deficits that did not correlate to a dermatomal pattern.The presentation described in the above case, with atypical neurological signs and symptoms, is a common presentation of MS as opposed to MS presenting with signs and symptoms mimicking peripheral nervous system involvement, which is a very uncommon presentation.[11] In fact, only five cases of MS mimicking cervical radiculopathy were ever presented in the literature, one with solely sensory deficits[12] and four with both sensory and motor deficits.[13] No cases of MS presenting with signs and/or symptoms mimicking lower limb peripheral nervous system involvement have been described in the literature.

MRI is the imaging modality of choice in MS, having a sensitivity of between 35% and 100% and specificity of 36% to 92%.[14] Unfortunately there is no single radiological gold standard test to diagnose MS in view of the inability of conventional MRI to clearly distinguish between inflammation, edema and demyelination.[15] The McDonald 2010 criteria are aimed to target this weakness, incorporating novel MRI techniques in patients with a history of clinically relapsing disease, to diagnose MS in adults.[16] This has improved the sensitivity to 84% and specificity to 80%. Novel MRI techniques include silent gadolinium-enhancing and non-enhancing lesions in baseline brain MRI.[7] However, care needs to employed as such enhancing lesions may reflect normal structures, including blood vessels.[17] Bilello and colleagues[18] have challenged the latter diagnostic difficulty through the use of a computer-assisted detection software to analyze magnetic resonance images over time, potentially improving diagnostic sensitivity.[18] The latter will also aide in recognition of MS, monitoring of progression and treatment response. Earlier recognition of MS will in turn allow for earlier institution of treatment, which is being increasingly recognized as a being key in minimizing long-term disability.[19]

Conclusion

Management of athletes presenting with neurological symptoms will, in the majority of cases, necessitate thorough assessments and investigations to identify the underlying pathology. However, symptoms may accompany the simple act of participating in physical activity without an obvious underlying cause. Imaging in the presented case was employed to investigate neurological symptoms and was targeted to the identified differential diagnosis, starting with simple tests, such as an X-Ray, and progressing to MRI scans after the initial tests were inconclusive. In the above case, the MRI scan was instrumental to confirm the diagnosis. With reference to the discussed MacDonald 2010 criteria, despite the advances in diagnosing MS, the practicality of employing these standards in daily clinical practice needs to be evaluated further. With specific reference to Malta, a repeat of the survey conducted in 1999 to update present local epidemiological data regarding number of persons diagnosed with MS, would be desirable, since available published data is outdated.

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Case Report

A Rare Case of an Idiopathic Extraocular Muscle Abscess

Maria de Bono Agius, Mario Vella

Abstract

Diplopia has a diverse range of ophthalmological, neurological, autoimmune, neoplastic and infectious causes. However it is very rare for an extraocular muscle abscess to occur. A skeletal muscle abscess usually occurs in the thigh and trunk muscles and is most commonly caused by *Staphylococcus aureus*.[1]

The purpose of this case report is to describe this condition we came across in our eye casualty department in a healthy teenager who presented with painful diplopia and this was due to a lateral rectus muscle abscess.

Complete resolution of the diplopia occurred by 6 weeks from starting treatment. The possible aetiologies and possible complications of such a condition are then discussed.

An idiopathic extraocular muscle abscess is a rare condition which should be included in the differential diagnosis of a patient presenting with painful double vision.

Keywords

extraocular muscle abscess; idiopathic; painful diplopia; Staphylococcus aureus

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Introduction

Our 16 year old patient had an idiopathic right lateral rectus muscle abscess. All cardinal signs of an abscess including rubor, calor, dolor, tumor, function laesa and swinging fever were present.

Case

A healthy 16 year old female presented to the Ophthalmic Casualty in the evening complaining of a 4 day history of headache and nausea. She also complained of increased swelling of her right eye and painful eye movements. She gave no past ophthalmic history of note.

On examination she had a visual acuity of 6/6 both eyes (OU), normal colour vision OU, normal pupil reaction OU and a normal posterior segment OU.
Diplopia was elicited in right more than in left gaze with generalized painful eye movements. Prism cover test gave readings of 8 prism dioptres (PD) base out (BO) at 1/3m and 12 PD BO at 6m.

On closer examination, there was increased conjunctival hyperemia over the Lateral Rectus area of her right eye as well as a moderate ptosis from a swollen right upper eyelid.

Her vital parameters were checked and all was normal except for a temperature of
102.2°F. She was referred for an Otolaryngology consultation and this proved to be normal.

She was started on the following antimicrobial therapy: intravenous Co-amoxiclav 1g bd
and intravenous Metronidazole 500mgs tid. An MRI Orbits was done and this showed the
presence of a lateral rectus muscle abscess in the right eye. (See Fig. 1).

Improvement of her symptoms was observed after the first few days of treatment.
She was changed over to oral therapy after 6 days since she was not tolerating adequate
food intake and was then discharged home on Ciprofloxacin 250mgs bd x 3 weeks.

A repeat orthoptic test at 6 weeks showed negligible diplopia and a control MRI orbits at
4 months showed complete resolution of the lateral rectus abscess (see Fig. 2). To date, the patient has remained disease free with no residual motility dysfunction.

Figure 1a: *MR Orbits; with contrast showing a right lateral rectus muscle abscess*

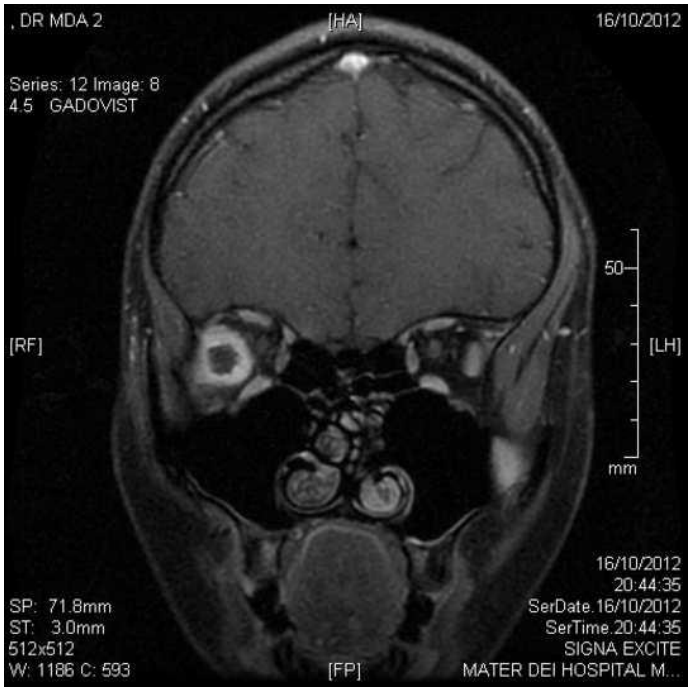


Figure 1b: *MR Orbits; with contrast showing a right lateral rectus muscle abscess*

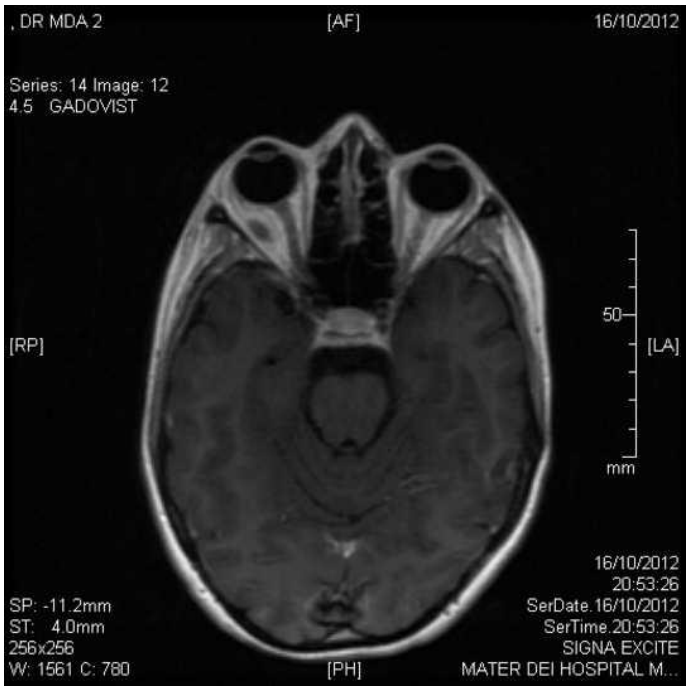


Figure 2a: *MR Orbits; with contrast showing resolution of the right lateral rectus muscle abscess*

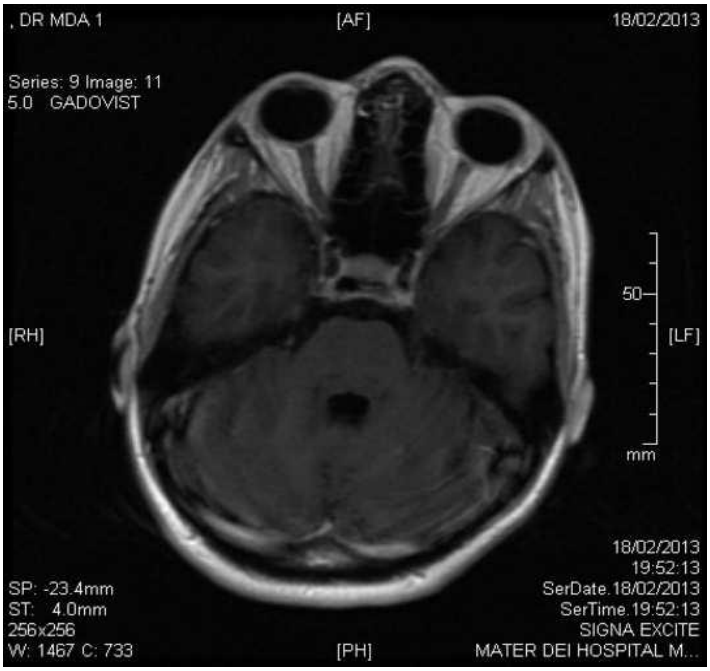
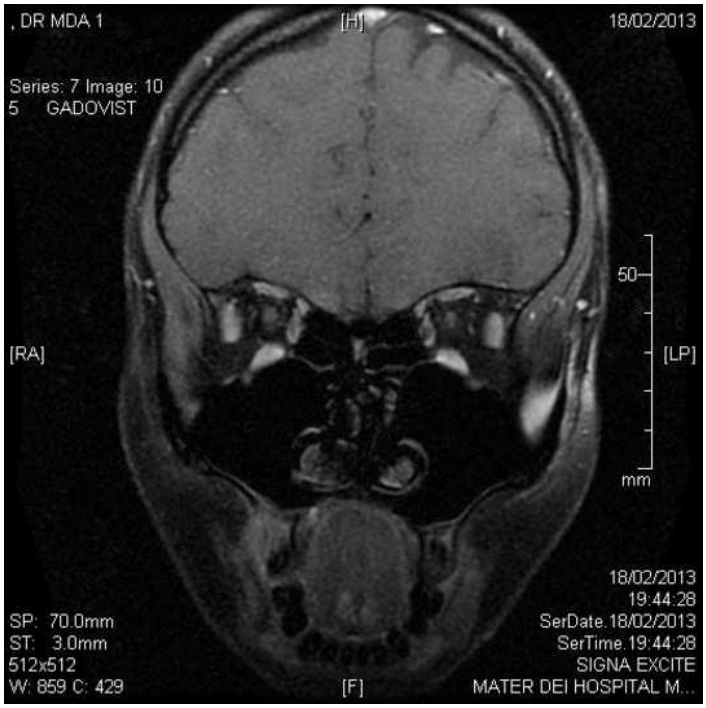


Figure 2b: *MR Orbits; with contrast showing resolution of the right lateral rectus muscle abscess*



Discussion

There have been no case reports of an isolated abscess in an extraocular muscle in Malta. The pathogenesis of an extraocular muscle abscess remains unknown however potential causes are: haematogenous spread from bacteraemia, local spread example from dacryocystitis, midfacial or dental infection, post-trauma or post-surgery.[6] Blood cultures should be taken to help in the management of the patient. The aetiology of such an abscess is usually *Staphylococcus aureus* followed by parasitic infestation with *Cysticercus cellulosae* which is the encysted larva of the pork tapeworm, *Taenia solium.*[2,4]

In our case, antibiotics were started following a normal Otorhinolaryngology review – however in view of the fever, an infective aetiology was still high on the

cards and this was proven the following morning when the MR Orbits was carried out. Intracranial extension can be rapid from orbital cellulitis and thus it was important for the antibiotics to be started sooner rather than later. Ultrasound-guided drainage was not necessary in our case due to rapid improvement in the patient's symptoms and signs. Should the patient's symptoms have worsened, then this would have been necessary to help both culture the organism as well as provide drainage of the abscess.[5]

Both CT and MRI can be used as investigative tools in this circumstance. However since MRI gives no radiation exposure and is better to study soft tissues, it was the modality of choice. In fact if one had to compare the information gathered on an extraocular muscle abscess between MRI and CT, the former demonstrates a more clear delineation of the extent of inflammatory changes than does CT, and it also demonstrates the abscess as a collection distinct from surrounding structures on at least one repetition rate. With CT, unless an abscess contains air or is of low attenuation, it often blends with the surrounding structures and is difficult to differentiate from them.

Possible differential diagnoses include:

- Inflammation – idiopathic orbital inflammatory disease
- Infections - orbital cellulitis
- Structural lesions (ex. dermoid cyst)
- Vascular neoplastic lesions (ex. capillary haemangioma, lymphangioma)
- Lymphoproliferative diseases (ex. lymphocytic granuloma)
- Neurogenic tumors (ex. neuroblastoma, plexiform neurofibroma)
- Mesenchymal tumors (ex. rhabdomyosarcoma)
- Metastatic carcinoma.[3]

Possible complications from such a condition can be:

- Intraocular Complications:
  - Fibrosis of Lateral Rectus muscle with permanent restriction of movement
  - Optic Neuropathy
  - Central Retinal Artery Occlusion
- Intracranial complications include meningitis, cavernous sinus thrombosis, and intracranial, epidural, or subdural abscess formation.

The role of biopsy is probably limited to atypical cases or those unresponsive to therapy, particularly to exclude neoplasia.

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Review Article

Optimisation of Anticoagulation in Patients with Atrial Fibrillation

Ankita Prasad, Patrick Pullicino

Abstract

Atrial fibrillation is a common cardiac arrhythmia associated with debilitating complications, one of which is stroke. Anticoagulants (warfarin and the non-vitamin K antagonist oral anticoagulants) are recommended for stroke prophylaxis, their utilisation however requires stroke risk reduction to be balanced against hemorrhage risk. Current review of the literature suggests that despite the presence of risk stratification tools such as the $CHADS_2$ and the newer CHA_2DS_2-VASc, clinicians often find it challenging to anticipate the risk-benefit ratio of anticoagulation. This results in both the underuse and overuse of anticoagulation in patients as well as uncertainty over whether to use anticoagulation in paroxysmal AF. This review looks at optimising anticoagulation by improving the assessment of bleeding risk and by improving the assessment of stroke risk. The percutaneous occlusion of the left atrial appendage is an emerging alternative to oral anticoagulation therapy.

Key words

anticoagulation, atrial fibrillation, stroke

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Abbreviations

AF: Atrial Fibrillation, $CHADS_2$: Congestive heart failure, hypertension, age ≥75 years, diabetes mellitus, previous stroke/transient ischaemic attack score, CHA_2DS_2-VASc: Congestive heart failure, hypertension, age ≥75 years, diabetes mellitus, previous stroke or transient ischemic attack, vascular disease, age 65 to 74 years, female sex score, CMBs: cerebral microbleeds, ECG: Electrocardiography, ICH: intracerebral haemorrhage, LAA: left atrial appendage, MRI: Magnetic Resonance Imaging, NOACs: non-vitamin K antagonist oral anticoagulants, NT-proBNP: N-terminal pro-brain natriuretic peptide OAC: oral anticoagulants, PAF: Paroxysmal Atrial Fibrillation

Introduction

Atrial fibrillation (AF) is the most frequent sustained cardiac arrhythmia in clinical practice.[1] In 2010 it was estimated that globally 33.5 million individuals had AF, and the prevalence is estimated to be increasing worldwide.[2] AF patients have a five-fold increase in their risk of ischemic stroke and strokes in AF patients have a higher chance of being fatal or disabling.[3] Oral anticoagulants are recommended for stroke prophylaxis but stroke risk varies in AF and risk reduction effect must be balanced against haemorrhage risk. Not all patients with AF have a stroke risk high enough to warrant anticoagulation. It may be difficult for the clinician to decide whether to anticoagulate a specific patient and anticoagulation is not always appropriately managed.[4] To use anticoagulants properly it is also important to look for occult intermittent AF in specific circumstances. When intermittent AF is detected, there is uncertainty about which patients should be anticoagulated.[5] This review will explore these key areas in which anticoagulation therapy may be optimised in AF patients.

Anticoagulants, stroke risk reduction and haemorrhage

The main anticoagulants, warfarin and the non-vitamin K antagonist oral anticoagulants (NOACs) - Dabigatran, Apixaban and Rivaroxaban, recommended for the use of stroke prophylaxis, have all been found to be effective in preventing stroke but are all associated with an increased risk of bleeding.[6] Successful use of anticoagulant treatment therefore needs to be able to achieve a balance between decreasing the risk of stroke

and increasing the risk of bleeding.[7]

The risks of stroke and bleeding in AF patients depend on individuals' vascular risk factors and clinical risk stratification schemes have been developed to assess the risk of stroke and bleeding.[8] These include the $CHADS_2$ (Congestive heart failure, hypertension, age ≥75 years, diabetes mellitus, previous stroke/transient ischaemic attack) score (Table 1) and the newer CHA_2DS_2-VASc (congestive heart failure, hypertension, age ≥75 years, diabetes mellitus, previous stroke or transient ischemic attack, vascular disease, age 65 to 74 years, female sex) score (Table 2) to assess the risk of stroke and the HAS-BLED tool (Table 3) to assess the risk of bleeding.[4]

***Table 1**: Assessment of Stroke (CHADS2) in Atrial Fibrillation Patients*

$CHADS_2$ Risk	**Score**
Congestive Heart Failure	1
Hypertension	1
Age > 75	1
Diabetes	1
Stroke or TIA	2

***Table 2**: Assessment of Stroke (CHA2DS2-VASc) in Atrial Fibrillation Patients*

CHA_2DS_2-VASc Risk	**Score**
CHF or LVEF ≤ 40%	1
Hypertension	1
Age ≥ 75	2
Diabetes	1
Stroke/TIA/ Thromboembolism	2
Vascular Disease	1
Age 65 – 74	1
Female	1

***Table 3**: Assessment of Bleeding Risk (HAS-BLED) in Atrial Fibrillation Patients*

HAS-BLED Tool	**Score**
Hypertension	1
Abnormal liver function	1
Abnormal renal function	1
Previous Stroke	1
History of predisposition to bleeding	1
Labile INR	1
Elderly (> 65)	1
Drugs (Antiplatelets or NSAIDs)	1
Harmful Alcohol intake	1

Under the $CHADS_2$ tool AF patients are considered low risk for stroke if the score is 0 and high risk if the score is ≥ 2.[9] Under the newer CHA_2DS_2-VASc tool, AF patients are considered to have a low risk of stroke if they are below 65 with no risk factors other than their sex (this equates to a CHA2DS2-VASc score of 0 for men or 1 for women) and high risk if they have a CHA2DS2-VASc of ≥ 2,[9-10] (this means any woman over 65 or men with any added risk factor) Anticoagulation is indicated in any patient with a history of stroke.

Underuse of anticoagulants and optimisation

The underuse of oral anticoagulants in patients with a high risk of stroke can result in the occurrence of preventable ischemic stroke.[11] A recent study found that use of anticoagulants is poorly associated with the stroke risk. The international Global anticoagulant registry in the field (GARFIELD) study examined the use of warfarin and NOACs and found 38% of patients classified as having a high risk of stroke ($CHADS_2$ score ≥2) did not receive anticoagulant therapy. Similarly when risk was assessed using the CHA_2DS_2-VASc score, 40.7% of the patients with a high risk of stroke did not receive anticoagulant therapy.[12]

Underuse of anticoagulants is often due to an over-estimation of bleeding risks. The ESC and NICE guidelines recommend that the bleeding risk of patients with AF should be assessed using the HAS-BLED score.[13] The HAS-BLED score offers better prediction of bleeding compared with other bleeding risk scores such as HEMORR2HAGES (Table 4) and ATRIA (Table 5) but the effectiveness of HAS-BLED has largely been based on the prediction of bleeding events that were not considered major, i.e. gastrointestinal bleeds as opposed

to intracerebral haemorrhage (ICH).[14] A recent study showed that patients are prepared to accept 4.4 systemic major bleeds for every stroke prevented, so that the stroke risk reduction cannot be balanced against non-intracerebral bleeds.[15] The estimation of bleeding risk is difficult as many of the known factors that increase bleeding risk, overlap with stroke risk factors. Given that the prediction of bleeding risk can be challenging and that the HAS-BLED score does not directly address the bleeding event of greatest concern (ICH), an alternative approach to predicting the risk of bleeding such as brain MRI maybe necessary.[14] MRI can show cerebral microbleeds (CMBs) that are small areas of brain haemorrhage that may increase the risk of future intracerebral haemorrhage in AF patients.[16-17.] A recent meta-analysis of CMBs found the risk of ICH to increase up to 8 fold in ischemic stroke patients with CMBs compared to those without.[18]

There is limited data on cohorts exposed to OAC therapy but the presence of CMBs have been found to increase the risk of warfarin associated ICH. A case control study comparing warfarin users with ICH and warfarin users without ICH, found the number of CMBs were much higher in the ICH group (79.2% vs. 22.9%).[19] Assessing the microbleeds location and underlying cause of the ICH can help decide whether to restart anticoagulation after an ICH.[19] In patients on warfarin there is an increased risk of ICH with lobar microbleeds compared with deep CMBs.[20] Cerebral amyloid angiopathy and a high risk of recurrence are associated with lobar ICH in the aged population, whereas deep ICH are often associated with hypertension. Controlling the blood pressure can permit the resumption of anticoagulation in the case of deep ICH, whereas the presence of multiple lobar microbleeds on MRI will prevent the resumption.[19]

Findings such as these have prompted the recommendation that MRI screening for anticoagulation therapy should be necessary in patients with AF $\geq$ 60.[20] Larger prospective cohort studies such as the ongoing CROMIS-2 study are expected to establish whether brain MRI has the capacity to predict an individual's ICH risk and improve the personalised management of AF patients.[18] The use of MRI in such a way may have significant appeal, despite the economical and logistical issues, particularly for clinicians whose concern for haemorrhagic risk takes precedence over the benefit of stroke prevention when prescribing anticoagulants.[14] In patients in whom the risk of bleeding is too high, the percutaneous occlusion of the left atrial appendage (LAA) is an emerging alternative to oral anticoagulation therapy for stroke prevention as the LAA has been recognised as a major site of clot formation in non-valvular AF patients.[21] Haemorrhagic change in an ischaemic infarct should not be a reason not to anticoagulate.

***Table 4**: Assessment of Bleeding Risk (HEMORR(2)HAGES) in Atrial Fibrillation Patients*

HEMORR(2)HAGES	**Score**
Hepatic or renal disease	1
Ethanol abuse	1
malignancy	1
Older age	1
Reduced platelet count or function	1
Rebleeding risk	2
Hypertension	1
Anaemia	1
Genetic factors	1
Excessive Fall risk	1
Stroke	1

***Table 5**: Assessment of Bleeding Risk (ATRIA) in Atrial Fibrillation Patients*

ATRIA	**Score**
Anaemia	3
Severe renal disease	3
age $\geq$ 75 years	2
Previous haemorrhage	1
hypertension	1

Overuse of anticoagulants and optimisation

The overuse of anticoagulant therapy in low risk patients puts this population at an unnecessary risk of complications associated with bleeding.[9] The Global Anticoagulant Registry in the FIELD (GARFIELD) study which focused on the use of warfarin and NOACs, found when risk was assessed with the $CHADS_2$ score, 42.5% of low risk patients were on anticoagulant therapy and when risk was assessed with the CHA_2DS_2-VASc score even though fewer patients appeared to be on anticoagulant therapy (38.7%) the risk of overuse remained.[12]

Barnes et al.[9] found in their study that only 3.4% of low risk patients ($CHADS_2$ score of 0) were receiving inappropriate therapy with warfarin for stroke prophylaxis in AF, when procedure-based indications were considered. However the value of 3.4% in this study was achieved by utilising the total number of non-valvular AF patients involved in the study as the denominator. Whereas the earlier studies referred to in the paper such as Meiltz et al.'s study,[22] used the total number of patients with a $CHADS_2$ score of 0 as the denominator .The use of a larger denominator by Barnes et al.[9] may render the results misleading and thus the overuse of anticoagulants in low risk AF patients can still be seen as a problem.

The underuse and overuse of anticoagulants suggest that, the $CHADS_2$ and CHA_2DS_2-VASc tools are often not followed appropriately. Furthermore the tools have a limited capacity for the prediction of stroke as shown by their low c statistic scores (0.549 to 0.638).[7] A c-statistic of 1.0 offers perfect discrimination whereas a value of 0.5 means a tool is no better than random chance at making a prediction.[23] In light of this, biomarkers have been suggested as prognostic tools.

Elevated troponin and NT-proBNP levels are each independently associated with the rates of stroke and the addition of the biomarkers to the $CHADS_2$and CHA_2DS_2VASc clinical risk tools improves the prognostic ability of the tools [24]. The level of natriuretic peptides in AF can be associated with atrial dysfunction, which is an established risk factor for thrombus formation in AF. Currently no established explanation exists for the association between stroke and elevated troponin levels but the availability of troponin measurements in most hospitals means it a promising prognostic tool.[7]

The addition of both cardiac biomarkers to the $CHADS_2$ and CHA_2DS_2VASc scores, improves the c statistic more compared to the individual addition of the biomarkers.[25-26] In the future there may be a role for a multi marker strategy to improve risk stratification. It is important to note however that the results from these trials were derived from clinical trial populations and therefore it may not be possible to immediately extrapolate the findings to the general AF population until further trials are performed.[27] BNP levels show considerable variability and despite being a significant risk factor in a study population it is less likely that an isolated result in any patient will be a significantly robust stroke risk marker.

Use of Anticoagulation in Paroxysmal AF and Optimisation

The utilisation of anticoagulation in paroxysmal AF also poses problems. The terminology surrounding the different patterns of AF have been inconsistent in the past, however recent guidelines have proposed a consensus definition for the different types of AF.[28] Paroxysmal AF has been defined as episodes of AF that spontaneously end within 7 days. Persistent AF has been defined as episodes lasting more than 7 days and permanent AF has been defined as AF without any intervening periods of sinus rhythm.[29] The minimum duration of an AF episode that is acceptable as a risk factor for stroke is still unsettled,[5] however guidelines state anticoagulation should be considered after 48 hours of AF[29] Current guidelines recommend that the pattern of AF should not determine whether a patient is given anticoagulation or not. Patients with each type of AF should receive oral anticoagulant therapy dependant on the presence of individual stroke risk factors. [10] Previous data comparing the stroke risk of paroxysmal and permanent AF is believed to be restricted due to methodological problems, such as the use of small sample sizes or differing rates of anticoagulation in patients with differing patterns of AF.

Recent larger trials have found the stroke risk to be higher in non-paroxysmal AF compared to paroxysmal AF. A recent study found that within each CHA_2DS_2-VASc category the outcome rates of embolic events were lower in paroxysmal AF compared to persistent and permanent AF.[28] It is proposed that the electrical abnormalities and pathophysiological changes that predispose patients to thrombus formation and stroke are more pronounced in patients with permanent rather than paroxysmal AF. Thus the pattern of AF can be seen as a marker of increased susceptibility of stroke.[30]

In the above study patients with a CHA_2DS_2-VASc score of ≥ 2 and paroxysmal AF still had a minimum stroke risk of 2%, confirming recommendations that patients with a high clinical risk score of stroke should be anticoagulated regardless of the pattern of AF.[28] To optimise anticoagulation therapy in AF patients it is recommended that in patients where it is not clear whether a patient would benefit from anticoagulant therapy, the pattern of AF should be taken into account.

In low risk patients with paroxysmal AF the benefit of anticoagulation may not outweigh the risk of bleeding.[28] Similar recommendations have been made by Steinberg et al.[31] who prompt for further research regarding more thorough stroke prevention in patients with persistent AF compared to paroxysmal AF.

The detection of PAF itself is challenging due to its short, unpredictable and often asymptomatic nature.[32] There are a variety of strategies and devices available to detect PAF which include intermittent, event-triggered and continuous monitoring through both external and implanted devices. Although it has been established that prolonged ECG monitoring detects more paroxysmal AF the optimum method and duration for detection remain unclear.[33] This is an area which would aid from further research and help to further the optimisation of anticoagulation therapy in AF patients.

Conclusion

Optimal utilisation of anticoagulation in AF patients is challenging. The overuse and underuse of anticoagulation suggests uncertainty exists regarding when anticoagulation is appropriate. The current clinical risk stratification tools are still suboptimal at predicting the risks of stroke and of bleeding and this reduces the ability to accurately balance the risks of anticoagulation in an individual. The presence of novel promising risk stratification tools (biomarkers and MRI) and new techniques for risk assessment may help to manage anticoagulation better in the future. In our current state of knowledge, it is important to apply the CHADS2 or CHA2DS2VASC as well as the HAS-BLED scores as faithfully as possible to gauge the potential risk of stroke and bleeding. Gauging the risk of intracerebral haemorrhage is more of an art but patients with prior cerebral haemorrhage and multiple microbleeds should not be anticoagulated. In these patients and in patients with contraindications to anticoagulants, LAA occlusion should be considered.

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Case Report

Orbital Pseudotumour Masquerading as Wegener's Granulomatosis

Matthew Fenech, Thomas Fenech

Abstract

A twenty-two year old female patient presented with new onset bilateral hard orbital masses and progressively worse tear lake problems. Computed tomography of the orbits revealed poorly differentiated bilateral orbital masses. Laboratory investigation revealed ANCA positivity. Routine biochemical investigations were all within normal limits. CXR was also normal. Biopsy of the orbital masses revealed non-specific histological findings. An initial diagnosis of Granulomatosis with Polyangitis (GPA) was postulated. Oral steroids were given followed by a rapid response to steroid therapy. The working diagnosis of GPA was abandoned and a diagnosis of idiopathic orbital inflammation (IOI), or orbital pseudotumour was made owing to the benign, non-infective, inflammatory pathology with no evident systemic or local cause. Tailoring off of steroids resulted in repeated flare ups, resulting in the initiation of methotrexate therapy. The patient is in remission and is currently on combined steroid and methotrexate treatment. IOI is a diagnosis of exclusion and a rapid response to steroids serves as a diagnostic aid but is not in itself diagnostic.

Key words

Orbital Pseudotumour, Granulomatosis with Polyangitis, ANCA, Steroids

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Background

Idiopathic orbital inflammation (IOI) or orbital pseudotumour is an uncommon, benign, non-infective, inflammatory pathology involving the orbital tissues. It is a diagnosis of exclusion after systemic and local causes have been thoroughly excluded, characterised by polymorphous lymphoid infiltrate with varying degrees of fibrosis. MR orbit is the single most important investigation. A diagnosis is usually clinched when a rapid response is seen to oral or systemic steroids. The pathological process underlying IOI remains unresolved, some postulating it is primarily an autoimmune process.

Case Presentation

A twenty-two year old female patient presented with bilateral orbital masses and persistent tear lake problems. There was associated proptosis but no involvement or impairment of any of the extra-ocular muscles movements. Humphrey Visual Field examination did not reveal any visual field defect. There was an extremely toxic tear lake secondary to the severe dacryoadenitis spilling inflammatory debris onto the front of the eye.

Masses were present in both lacrimal glands, especially on the right side, spilling down into the inferior part of the right orbit. Masses were woody hard with gross inflammation of the ocular surface overlying it. There was no corneal guttering or scleritis.

Serial MR Orbits were performed. The first revealed significant right preseptal and post-septal orbital change, which appeared to include and emanate from the region of the right lacrimal gland. The left lateral gland also appeared mildly prominent. A biopsy of the right lower orbital mass revealed fibroconnective tissue with a patchy chronic inflammatory infiltrate and no identifiable fat. The infiltrate included ill-formed lymphoid-follicles and a loose scattering of lymphocytes and histiocytes with only rare plasma cells and eiosinophils. Occasional multinucleate giant cells were seen. There was no frank necrosis but ample nuclear dust was visible. There was no vasculitis and no evidence of underlying neoplasia. Findings were deemed to be non-specific but likely to be due to Granulomatosis with Polyangitis (GPA).

Laboratory investigation revealed elevated ANCA titres. Further breakdown of such titres revealed elevated P-ANCA patterns with grossly elevated Anti-Myeloperoxidase but insignificant Anti-protease 3 antibody levels. CRP, ESR, C3, C4 and anti-nuclear antibodies were never elevated and were always found within normal limits.

CXR revealed no evidence of pulmonary pathology.

The patient was started on IV steroids followed by oral steroids as an initial diagnosis of GPA was suspected. Rapid response to steroids was seen in the form of radiological and symptomatic improvement. Due to the non-specific histological findings and lack of systemic involvement, a diagnosis of GPA was abandoned and a diagnosis of IOI was adhered to.

Investigations

Routine laboratory and haematological investigations were normal including serum ACE, T3, T4 and TSH. CXR performed revealed no pathology. Serum ANCA levels were elevated. Further breakdown of such titres revealed P-ANCA patterns which are indicative of Anti-Myeloperoxidase antibody at 42.4, while Anti-protease 3 antibody was less than 2.0.

Imaging modalities used included computed tomography (CT) and magnetic resonance imaging (MRI). Usually, CT is the preferred imaging modality in IOI because of its good inherent contrast of orbital fat, muscle, bony structures and adjacent paranasal sinuses. MRI showed diffuse involvement of the lacrimal glands with associated infiltration of orbital fat. There were bilateral poorly-defined orbital masses. Both pre-septal and post –septal changes were seen. On T2-weighted imaging areas were hypointense in appearance with restricted diffusion. Such infiltrative changes favoured a diagnosis of IOI.

A decision was made to opt for a second opinion from specialists at the Moorfield's Eye Hospital London. A decision was made to perform biopsies of the left orbital mass in order to exclude an underlying malignancy or possible GPA, after the images form the MRI performed at Mater Dei Hospital were reviewed. Biopsy is not usually indicated for IOI but serves as a good diagnostic tool if a diagnosis has not been concretely established. Unfortunately, the histopathological spectrum of IOI is typically nondiagnostic.

Differential Diagnosis

IOI is diagnosed by a thorough clinical history and evaluation to rule out other causes of orbital disease. One must take note of similar episodes in the past and the onset of symptoms. Symptoms are rather acute in IOI but generally more subacute or chronic in other pathologies. Trauma, infection and risk factors for immunological compromise must be excluded.

Infection was considered. The orbit is a common site for specific infections, usually spreading from adjacent sinuses or the face. It may also be a result of direct trauma. The patient was afebrile and routine investigations were unremarkable.

Thyroid orbitopathy must also be excluded. Laboratory investigations including T3, T4 and TSH were unremarkable. Onset of symptoms was rather acute, while in Graves' disease, a slower, more insidious course is usually apparent. Examination did not reveal any eye lid retraction, eyelid lag, extra-ocular myopathy. There was a mild element of proptosis. Radiological findings however were not consistent with thyroid orbitopathy. There was no evident enlargement of extraocular muscles, while conversely, orbital fat volume was reduced.

Wegener's Granulomatosis or Granulomatosis with polyangitis (GPA) was initially diagnosed secondary to the elevated serum ANCA levels. GPA is a necrotising granulomatous inflammation and vasculitis, effecting the respiratory and renal systems. Ophthalmic symptoms are usually acute in onset and may be unilateral or bilateral. Systemic work-up of our patient revealed no impairment of pulmonary or renal function. Further breakdown of ANCA levels revealed a grossly elevated P-ANCA level reactive against myeloperoxidase while a c-ANCA level reactive against proteinase 3 which was within normal limits. The anti-Proteinase3: Myeloperoxidase ratio was not elevated, making the serum ANCA level testing non-diagnostic. Furthermore, radiological changes were not classical of GPA, bar the mass lesions bilaterally. That being said, classical findings of GPA are present in less than a third of patients while ANCA is only found in 50-65% of patients with the limited form of GPA. A diagnosis of GPA was abandoned but ultimately could not be completely excluded.

The possibility of neoplasm must also be considered. Although this was excluded at biopsy.

Treatment

Corticosteroids are usually the mainstay of treatment usually providing rapid improvement of symptoms.

Such was the case with our patient. IV steroids were initiated after the biopsy was performed. IV steroids were given for 2 days followed by oral steroids, starting at a dose of 80mg per day, tailoring down accordingly over several months. Prednisolone treatment was stopped completely after 17 months. There was a significant resolution in both symptoms and radiological evidence. Methotrexate once weekly and 10mg Folic Acid daily were started after

prednisolone was stopped.

The patient is currently still on methotrexate and undergoing regular follow up blood investigations. She is symptom free but occasionally still suffers from flare ups, consisting of orbital pain, a sensation of heaviness and conjunctival injection. Flare ups are less frequent and less severe ever since the prolonged use of methotrexate.

Outcome and Follow-up

Recurrence rates are high. Regular patient follow up is necessary to assess disease progression as well as treatment efficacy. Steroid therapy should be accompanied by close monitoring to assess for steroid related complications.

Stopping steroids typically results in a relapse rate of 60-80%, irrespective of the initial response to steroids. Response to steroids at relapse is typically not as dramatic as the initial response, commonly resulting in the use of other agents.

In our patient, follow up revealed near complete regression of masses bilaterally, with some residual disease on the right eye. There was no progression of orbital fat infiltration.

Serum ANCA levels also showed regression on follow up, further excluding the unlikely diagnosis of GPA.

Discussion

Idiopathic orbital inflammation (IOI) is a non-malignant, non-infectious orbital inflammation with no local or systemic cause. The disease may be confined to a single orbital structure, but more commonly effects multiple structures.[1] Any structure may be effected, with orbital fat, lacrimal glands and extraocular muscles being most commonly effected.[2]

Onset is usually unilateral and acute, progressing over a few hours or days. That being said, bilateral disease is not uncommon and onset may be subacute or even chronic.[3] There is no gender, age or racial predilection, presenting universally with a mixture of infiltrative and inflammatory signs and symptoms.[4]

Examination may reveal proptosis, chemosis, tenderness, peri-orbital swelling and impaired extra-ocular muscle function. Ultimately, presentation varies depending on the location and degree of inflammation, fibrosis or mass effect. [5]

The pathogenesis of IOI remains elusive and unclear. An immune-mediated response has been implicated as the most likely underlying cause. Infectious aetiologies have also been implicated, most commonly upper respiratory tract infections and Streptococcal pharyngitis. IOI is also strongly related to several rheumatological conditions including Crohn's disease, ankylosing spondylitis, rheumatoid arthritis, systemic lupus erythematosis and myasthenia gravis.[6]

Laboratory investigation is usually followed by imaging studies. Classically, orbital pseudotumours may present as diffuse or localised orbital masses which is classically poorly demarcated and enhancing with contrast. The lacrimal gland is the most commonly involved structure usually showing diffuse enlargement with poorly defined margins. Other CT findings include diffuse infiltration of orbital fat, extraocular muscle enlargement, uveoslceral thickening and optic nerve thickening.[7] MRI is more valuable in demonstrating soft tissue changes in IOI *(Figure 1, Figure 2)*. T1 – weighted images show intense contrast enhancement of abnormal soft tissues.

Figure 1*: MR Orbit; Axial T2 Sequence showing regression of orbital inflammation. A(2012), B(2013), C(2014)*

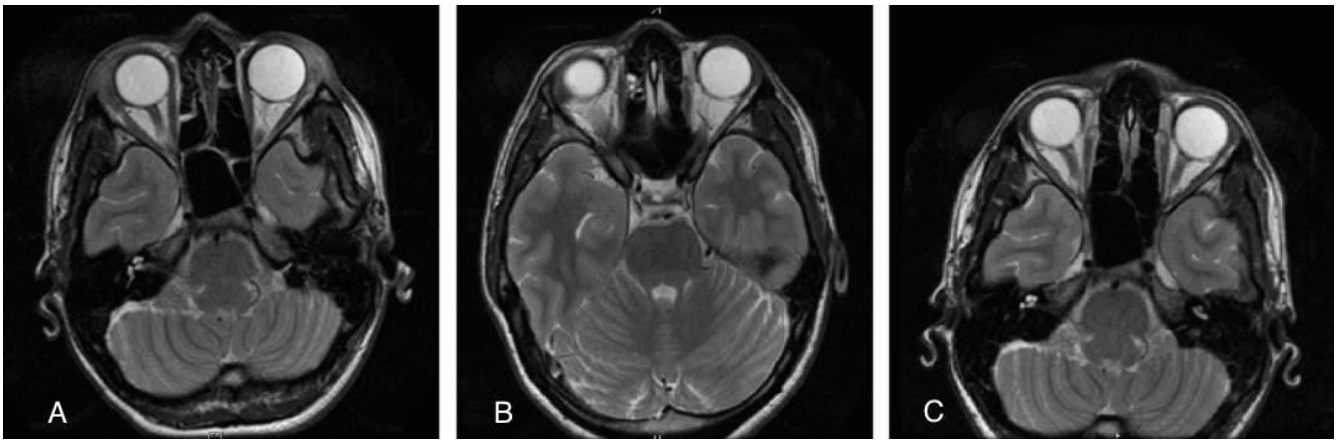
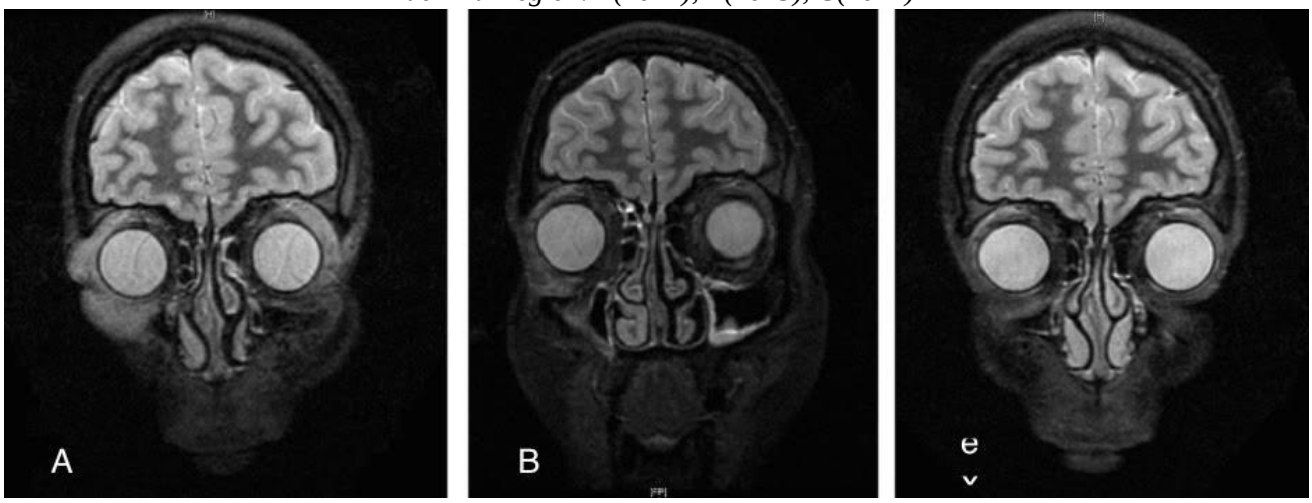


***Figure 2**: MR Orbit; Coronal Stir sequence showing regression of orbital inflammation with some residual disease in the lacrimal region. A(2012), B(2013), C(2014)*



It is not uncommon that as a result of diagnostic uncertainty, a biopsy is performed. Classical IOI reveals an atypical histopathology with a fibro-inflammatory infiltrate.[2]

Before treatment is started, a thorough work up is required. If the work up in negative, treatment for presumed IOI may be initiated. In some patients, symptoms and signs may resolve spontaneously.[5] In patients with mild clinical presentation, clinical progression may be monitored and non-steroidal anti-inflammatories may be started. In more moderate and severe disease, systemic corticosteroids are the cornerstone of management.[3] Typically, 75% of patients show improvement of symptoms and radiological findings within 24-72 hours of imitating treatment. Steroids must be given for several months to ensure remission, ideally starting with a dose of 1-1.5 mg/kg body weight for 1-2 weeks followed by a gradual tapering down of the overall systemic dose.

A rapid response to steroids, although a useful diagnostic indicator, is not diagnostic. Several studies have shown steroid unresponsive IOI. Furthermore, even with treatment, 23% to 56% of patients tend to suffer recurrences, most commonly in cases showing bilateral disease. Recurrence is most likely the result of incomplete resolution of the initial presentation, typically resurfacing when treatment is tapered off.

Unfortunately, in cases which are refractory to both corticosteroids and radiation therapy, further treatment options are limited. Chemotherapeutic agents such as cyclophosphamide, cyclosporine or methotrexate have proven to be helpful.[3]

Following treatment, good visual prognosis may be expected. Response and recurrence rates are dependent on the degree of inflammation, dose and duration of corticosteroid treatment and ultimately the natural history of the disease. The clinical and histological features do not correlate well with the final outcome.[1]

Patient's perspective

The initial period was characterized by anxiety. The diagnosis was not certain and neither was the approach that was to be taken. The need for review by foreign specialists only increased her anxiety and did not help in what had been already difficult period.

Once a diagnosis was made, there was still uncertainty as to the possible response to therapy. She was pleased that steroid proved to be very successful initially but was left very frustrated by the fact that flare-ups did occasionally recur, even though they were not as severe as the initial presentation. A decision was made to start further treatment in the form of methotrexate. This was initially met with further anxiety as doubt on the certainty of the diagnosis began to resurface. However with reassurance and eventual stable response to the methotrexate, anxiety was resolved and she no longer has any issues with her treatment and response.

Learning Points/Take Home Messages

1. IOI is a diagnosis of exclusion.
2. Thorough history and examination is necessary in order to exclude concrete differential diagnosis.
3. Misdiagnosis may have serious implications considering the benign nature of this disease.
4. A rapid response to steroids serves as a diagnostic aid but is not in itself diagnostic.
5. Investment and research is needed to more accurately diagnose IOI. Currently, histological features are non-diagnostic, showing granulomatous and non-granulomatous inflammatory infiltrates.

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Case Report

A large pericardial effusion and bilateral pleural effusions as the initial manifestations of Familial Mediterranean Fever

Emma Louise Schembri, Simon Mifsud, Daniela Cassar Demarco, Bernard Coleiro, Carmel Mallia

Abstract

Familial Mediterranean Fever (FMF) is a condition characterized by recurrent febrile poly-serositis. Typical presentations of the disease include episodes of fever, abdominal pain and joint pains. Chest pain is a less common presentation. We report a case of FMF which presented with a large pericardial effusion and bilateral pleural effusions in a lady who had no positive family history and negative genetic testing.

Keywords

Familial Mediterranean Fever, Pericardial effusion, Pleural effusion

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Case Presentation

A thirty-four year old lady was admitted to the emergency department with a three day history of central pleuritic chest pain associated with dyspnoea and low grade fever (37.6°C). The patient had been in good health prior to this admission but complained of similar symptoms over the previous four years. These symptoms used to last around three to five days and occurred approximately three times a year. Investigations were being carried out to identify the cause of these symptoms prior to her admission. A computed tomography (CT) scan of the thorax revealed small bilateral pleural effusions. Pleurocentesis was performed; however analysis of the pleural fluid was equivocal. In view of the inconclusive result, the patient underwent an open lung and pleural biopsy which revealed normal lung parenchyma and a pleural plaque, respectively.

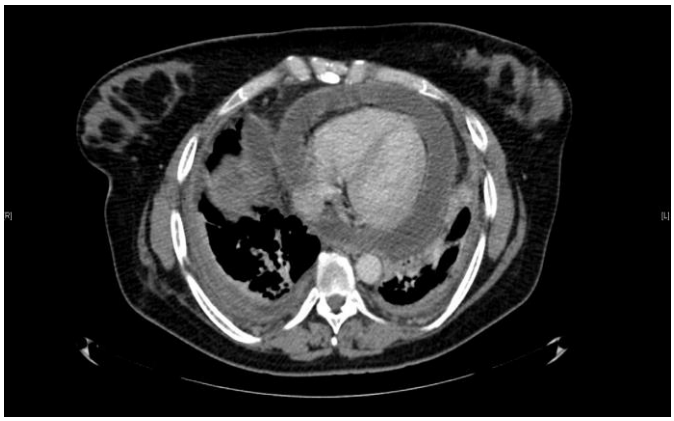
On this occasion, the patient's chest pain and dyspnoea were more severe than usual and hence necessitated medical admission. Physical examination revealed a distressed patient running a temperature of 37.6°C, with a blood pressure of 112/84mmHg. The patient was tachycardic at 130 beats per minute and tachypneoic at 22 breaths per minute. On auscultation of the chest, there was reduced air entry at the lung bases. Heart sounds were reduced in intensity. The rest of the examination was unremarkable.

Peripheral blood investigations revealed a leukocytosis of 18.98×10^9/L (normal values: 4.3-11.4×10^9/L) with a neutrophil shift. Erythrocyte sedimentation rate (ESR) and C-reactive protein (CRP) were both elevated at 75mm 1st hour (normal values: 10-14mm 1st hour) and 228 (normal values: 0-10mg/L) respectively. Serum creatinine and electrolytes were normal. Peripheral blood cultures, TORCH, Epstein-Barr Antigen PCR, Cytomegalovirus Antigen PCR, Mycoplasma IgM Antibody and an auto-immune screen were eventually all negative.

An echocardiogram revealed a large pericardial effusion with no signs of cardiac tamponade or inferior vena cava collapse. This was also confirmed on a CT scan of the thorax, abdomen and pelvis (figure 1). Other findings on CT were an enhancing pericardium suggestive of inflammation, bilateral small pleural

effusions and minimal ascites. These findings were in keeping with the presence of poly-serositis.

***Figure 1**: CT thorax showing the large pericardial effusion and small bilateral pleural effusions.*



Pending blood culture and auto-immune screen results, empirical treatment with intra-venous piperacillin-tazobactam was commenced. This antibiotic therapy failed to improve the patient's symptoms and the inflammatory markers remained elevated. In view of these intermittent, recurrent, self-resolving episodes of febrile pleuritis and pericarditis, a working diagnosis of Familial Mediterranean Fever (FMF) was put forward. Genetic testing for the condition was done.

The antibiotics were stopped and colchicine was prescribed at 1mg daily. There was an immediate good response to colchicine therapy, and this continued to favour a diagnosis of FMF. In view of the large pericardial effusion, the patient was given a single intra-venous dose of methylprednisolone to hasten its resolution. Daily echocardiograms showed a reduction in the pericardial effusion to a size of 8mm following the initiation of colchicine therapy. The patient was completely asymptomatic after seven days when she was discharged on colchicine 1mg daily. A follow up echocardiogram two weeks after discharge confirmed that the pericardial effusion did not re-accumulate. The patient will have regular follow up outpatient appointments.

Discussion

Familial Mediterranean Fever (FMF) is a recurrent febrile poly-serositis inherited in an autosomal recessive manner, affecting mostly individuals of Mediterranean descent. FMF is characterized by brief recurrent, self-limiting episodes of fever, peritonitis, pleuritis, arthritis and myalgia. The most frequent presenting manifestations include abdominal pain (90%), articular involvement (75%) and chest pain due to pleuritis or pericarditis (30-40%).[1]

Pericardial involvement rates in FMF are variable with different studies giving incidence rates of 0.7%,[2] 1.4%,[3] and 27%.[4] These studies have all concluded that pericardial involvement is a manifestation of FMF. The low incidence rates may be due to under-diagnosis whereas the higher rates can be due to the various methods used to define and detect pericarditis and pericardial effusion;[5-6] hence explaining the substantial variability in incidence.

This case describes a large pericardial effusion and bilateral pleural effusions as the major presenting features of FMF without any joint or abdominal involvement. This case is also quite unusual since the condition typically presents in childhood and rarely occurs after the age of thirty.[7] In this case, the lack of a positive family history for FMF made the diagnosis of FMF more challenging. However, the word 'familial' in FMF is a misnomer since only 50% of patients with FMF have a positive family history.[7-9] Thus; a negative family history does not exclude a diagnosis of FMF.

This case highlights the fact that FMF requires a high index of clinical suspicion as early recognition may be clinically difficult in view of its non-specific presentation. In order to help clinicians in differentiating FMF from other periodic febrile illnesses, the Tel-Hashomer Revisited Criteria can be used for the diagnosis of FMF. These criteria are divided into three major and three minor criteria as demonstrated in table 1. A 'definitive' diagnosis of FMF requires the presence of two major criteria or one major and two minor criteria. The diagnosis is considered as 'probable' if only one major and one minor criteria are present.

***Table 1**: Tel-Hashomer Revisited Criteria for the diagnosis of FMF*

Tel-Hashomer Revisited Criteria for the diagnosis of FMF[10]	
Major Criteria	**Patient's Case: Present or Absent**
Recurrent febrile episodes with serositis or synovitis	Present
Amyloid A amyloidosis without a predisposing cause	Absent
Response to continuous colchicine prophylaxis	Present
Minor Criteria	**Patient's Case: Present or Absent**
Recurrent febrile episodes	Present
Erysipelas-like erythema	Absent
FMF in a 1st degree relative	Absent

From the results shown in table 1, this patient had satisfied two major and one minor criteria suggesting a 'definitive' diagnosis of FMF. The Tel-Hashomer

Revisited Criteria can be used as a diagnostic adjunct given the difficulty of diagnosing FMF. A study by Livneh A. et al, concluded that the new set of Tel-Hashomer Criteria were highly sensitive (>95%) and specific (>97%) and were reliable in diagnosing and distinguishing FMF from other periodic illnesses.[11]

The gene responsible for FMF is the MEditerranean FeVer gene (MEFV) located on chromosome 16. The most common mutations are found in exon 2 and 10 of the gene. This patient had no mutations identified in exon 2 and 10 of the MEFV gene. Despite the negative genetic test, one must note that genetic testing only has a 70-80% positive predictive value and the diagnosis of FMF remains clinical.[1, 12] This is of marked importance in the Maltese isles, as no data exists regarding the frequency of the various mutations involved in FMF. This means that FMF is a clinical diagnosis and genetic testing may help confirm the diagnosis but not exclude it. Hence, in such situations the Tel-Hashomer Revisited Criteria are extremely valuable.

Making an early diagnosis of FMF is of utmost benefit to the patient for two main reasons:

1. The avoidance of many unnecessary investigations and possible surgical interventions.[1]
2. Early treatment with colchicine. Colchicine is a tricyclic alkaloid that diminishes the number of FMF attacks,[10] and hence prevents the occurrence of Amyloid A amyloidosis and eventually renal failure.[1, 13-14] Assessment of renal amyloidosis is done via regular urinalysis to check for proteinuria. If proteinuria is detected, more definitive renal studies are required to assess the degree of renal amyloid deposition.[15]

Colchicine is the mainstay of treatment in FMF.[13] However in colchicine resistant cases of FMF other agents have been put forward including corticosteroids, non-biological and biological DMARDs, interferon-alpha[16], anti-TNF agents[17] and interleukin-1 receptor antagonists[18-20]. These immunosuppressive agents may be beneficial in an acute inflammatory episode of FMF but their role in FMF prophylaxis and prevention of amyloidosis is unclear.[17]

Despite the treatment currently available for FMF some patients still have regular flare-ups. This emphasizes the importance of continuous research for further effective FMF treatment. There is ongoing research focussing on colchicine analogues which have a greater therapeutic window and are less toxic than colchicine.[21]

In conclusion, pericardial involvement is a rare but well known manifestation of FMF. Pericardial effusions in FMF usually regress with no permanent defect. Nonetheless, a study by Dabestani et al, demonstrated that there have been cases of pericardial tamponade and constrictive pericarditis secondary to FMF, as well as a higher risk of progression of FMF and amyloidosis in patients with pericardial involvement.[4, 6] This highlights the importance of evaluating patients with FMF carefully and assessing for pericardial involvement. Long term follow up of such cases by both rheumatologists and cardiologists may help prevent the occurrence of complications.

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Corinthia Group Prize in Paediatrics, 2015

The Corinthia Group Prize in Paediatrics for 2015 was awarded to Dr Luke Saliba, who obtained the highest aggregate mark over the combined examinations in Paediatrics in the fourth and final year of the undergraduate course. Whilst offering our congratulations to Dr Saliba, we would also like to congratulate all those who performed admirably during the undergraduate course in Paediatrics. In the accompanying photograph, Dr Saliba is seen receiving a cheque for €233 from Professor Simon Attard Montalto, Head of Paediatrics, in the Boardroom of Medical School. Finally, the Academic Department of Paediatrics and Medical School remain indebted and are extremely grateful to the Corinthia Group for their ongoing support.

Professor Simon Attard Montalto