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MRCP clinical exam in Malta

Stephen Montefort

The Membership of the Royal College of Physicians of the United Kingdom (MRCP UK) is awarded to trainees in Medicine near the end of their Basic Specialist training, following a rigorous exam. This is a major stepping-stone to Higher Specialist training which is remembered by most internal medicine physicians practicing in Malta, and indeed elsewhere around the world since the MRCP diploma is considered very prestigious and carries significant weight towards advancing ones medical career. All these physicians also remember the trials and tribulations both financial and psychological, that they experienced until they finally completed this milestone. This difficult exam is compounded by the fact that one also had to travel to one of various UK centres in the past, making this endeavor even more arduous. Since 2008, to the great benefit of local candidates, the written parts of this exam have been carried out biennially at the Malta Medical School since this was just a matter of organizing a venue, invigilation and secure delivery of papers to and from the UK. Organising the clinical part of the exam, the Practical Assessment of Clinical Examination Skills (PACES), was a completely different and much more challenging task, but one which I set myself as a major goal since becoming the Academic Head of the Department of Medicine in October 2012. PACES is the largest international postgraduate clinical skills assessment in the world with almost 5000 candidates sitting the exam per year.

After securing the support of the Dean and the Executive Administrator of the Medical School, together with the Mater Dei Hospital CEO, contact was made with the examination department of the Royal College of Physicians in August 2013, regarding about the possibility of Malta becoming one of international centres organizing PACES. The reception was very enthusiastic but slow. It was only in March 2015 that Professor Andrew Elder, the then newly appointed Chair of the Clinical Examining Board for the MRCP(UK) PACES examination and Dr. Donald Farquhar, the MRCP assistant International director, visited our medical school to see for themselves whether the Malta

Medical School could become a PACES international centre. Meetings were held with the Dean, the organizing committee, prospective examiners, medical school and hospital administrators. The venue in the laboratory section of the Faculty of Health Sciences was also inspected. The delegation also met Mr. Chris Fearne, the then Parliamentary Secretary for Health who also promised his support toward the organization of this exam. The College delegation was satisfied and it was decided that we should go ahead with our plans for hosting this exam. The most contentious issue was whether local candidates would be allowed to sit for their PACES exam in Malta since the great majority practice in the same hospital where the exam would be carried out. After discussing various pros and cons, it was decided that sufficient measures could be put in place so that these candidates could be examined in a fair and proper manner. It was thus decided that at each session, ten places will be 'ring-fenced' for Maltese candidates. It was also agreed that when these local candidates sat for the exam, they would always be examined by UK examiners, and if paired with a local examiner, the UK examiner would lead during that encounter.

A 'mock' Pathfinder PACES exam was held on the 17th October 2015 in which 15 prospective Maltese candidates sat for the exam. They were examined by 6 visiting UK examiners and the 3 established Maltese PACES examiners who had previously examined in UK centres. Five trainee Maltese examiners received their training during this session and they were all deemed to have attained the required standard to examine candidates in future sessions of PACES, both locally and in the UK.

The first formal session took place at the Faculty of Health Sciences, Mater Dei Hospital between the 1st and 3rd April 2016 where 44 doctors, including 6 Maltese doctors sat for the exam. The rest of the candidates were from Egypt, Iraq, Qatar, Oman and Saudi Arabia. Six more Maltese examiners also received their training during this 3 day session and were also formally

recruited as PACES examiners. The feedback from the Chairman of the examining board, examiners and even some of the visiting candidates was very favourable regarding venue, choice of patients and surrogates, as well as the actual running of the examination process. This has encouraged us immensely and we look forward to hosting the exam in future. Indeed, the next PACES exam is slated for December 2016, and it is envisaged that this exam will be held locally twice a year.

Attaining the status of an international centre for the PACES exam for the Malta Medical school has not only meant that we have been deemed to be of the required high standard to organize such a prestigious examination, but it is also of great help to our local budding physicians to be able to sit for such an important exam in familiar surroundings without having to leave our shores.

Cover Picture:

‘Atlantic Waves’ (inspiration from B. Alexander)

Oil on canvas

By Pierre Mallia

Pierre Mallia is Professor of Family Medicine and Patients’ Rights. He is coordinator of the Bioethics Research Programme, Chairman of the Medicine and Law Unit, and Chairman of the D.H. Health Ethics Committee. He is President of the Malta College of Family Doctors and is coordinating an Erasmus+ project on End-of-Life care in collaboration with seven other countries. He is married to Beatrix and has three children: Daniel (15), Francesca (13), and Kristina (11). He is an amateur painter/artist, stamp collector and likes Astronomy and fishing amongst other things.

The cost of blood in paediatric oncology patients

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Abstract

Introduction: Consumption of blood products is significant aiming to treat low cell counts and improve quality of life however 9% to 44% of the total consumption in centres abroad are unjustified. We reviewed thresholds at which blood products were administered and costs incurred by administering blood products at the local paediatric oncology ward at Mater Dei hospital and assessed whether they were inkeeping with local guidelines.

Methods: Patient files were analyzed retrospectively for demographics, disease, type and amount of blood products used from January to May 2013. The costs involved were obtained from the Blood Bank at Mater Dei Hospital. The standards used were the protocol by HBB regarding administration on KURA and 'Supportive care protocols' in paediatric oncology and haematology.

Results: Nine children were given blood products. Red cell products (RCP) use ranged from 0-10 units. and platelets derived products ranged 0-12 units per patient. haemoglobin levels and platelet counts before transfusions ranged from 3.1 to 8.6g/dL and 9 to $60 \times 10^9/L$ respectively. The total cost for the department was €17,950 while the total amount spent for tests done prior to ordering products was €3,276 out of 22 RCP requests for transfusion only once were RCPs transfused above the standard 7g/dL. Platelets were requested 26 times. Documentation regarding the reason for administration was lacking in patient files.

Conclusion: The use of blood products is dependent on patient needs and is not influenced by prices. Thresholds at which platelets and RCP are administered vary according to the clinical scenario. Rising costs and shrinking donor pools require blood products to be used judiciously.

Introduction

Malta has offered blood product transfusion services since the nineteen thirties, then at the Central Civil Hospital. New premises for the Donation Area of the National Blood transfusion Service (NBTS), opened in 2007, are now available for people to donate blood.¹ Despite the consumption of blood products being significant costs for unjustified blood transfusion account from 9% to 44% in centers abroad.²

Transfusions provide a treatment and improve the quality of life for patients suffering from chronic diseases.³ Alternatives to transfusions may prove to have adverse or suboptimal effects making transfusions best practice in anaemia, thrombocytopenia, and in the context of a haematological malignancy. In these situations, specialised blood products may also be required.⁴ In 2000/1 the UK average cost of blood products (adult red blood cells, adult fresh frozen plasma, adult platelet concentrate, adult cryoprecipitate, paediatric products) had a 256% increase compared to 1994/5. This cost is burdened by a shrinking donor pool, an ageing population and more

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specialised rigorous treatments.⁵⁻⁷

Attempts at comparing the complete cost of blood transfusions by centres has been difficult. Costs are usually compared between red cell products (RCP) as these are the commonest units used. Intangible costs for the centre and society are also generally not included.⁸

What are the current available alternatives to blood transfusions? "Supportive Care protocols of Paediatric Haematology and Oncology" provide guidelines on the management of blood products at Rainbow ward.⁹ From them local guidelines have been established, namely the 'Guideline on administration of blood components'.¹⁰ Cytomegalovirus (CMV)-negative (-ve) platelets are used in newly diagnosed leukemics until CMV status is known, or CMV negative recipients. Apheresis platelets arise from a single donor and are preferred from pooled platelets as they reduce the exposure to multiple donors preventing future transfusion reactions due to alloimmunisation. Irradiated RCP are used in recipients with allogeneic bone marrow, peripheral blood stem cell transplants or harvesting, Hodgkin's disease etc. Graft-versus-host disease is therefore prevented by inactivating lymphocytes in donor components.¹⁰

Aims

To research the amount, cost and cell indices at which blood products are used in Rainbow Ward at Mater Dei Hospital, between the months of January and May 2013 including:

- red cell products,
- CMV-ve red cell products,
- pooled platelets,
- irradiated pooled platelets,
- apheresis platelets.
- irradiated apheresis platelets

Method

Authorization from the Data Protection Officer at Mater Dei Hospital was obtained to review the files of patients admitted to Rainbow ward between the months of January to May 2013. Patient files were analysed retrospectively for:

- age,
- gender,
- disease,
- type and amount of blood products used.

Exclusion criteria included:

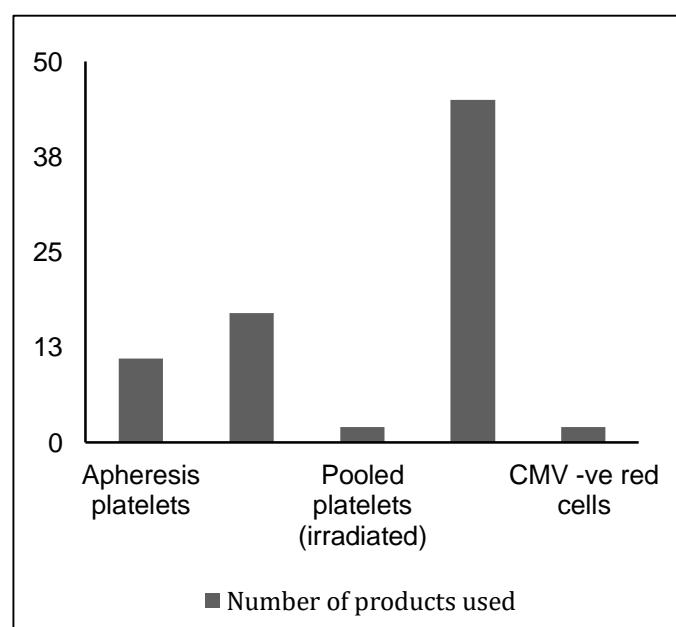
- patients transfused outside Rainbow ward,
- patients who were above 16 years of age,
- patients receiving transfusions outside the set time frame.

The cost of each blood product was obtained from the blood bank at Mater Dei Hospital. Blood products used in this study were divided into: RCPs, CMV-ve RCPs, pooled platelets, irradiated pooled platelets, apheresis platelets and irradiated apheresis platelets. The currency used was the euro. Patient details were anonymised.

Results

Nine children were transfused between January and May 2013, with a range of 0-10 units of RCPs and 0-12 therapeutic doses/units of platelets. The total amount spent for tests used to order blood products was that of 3276 euro, as provided by the Blood Bank at Mater Dei Hospital. 47 units of RCP and 30 platelet blood products were used in all (Figure 1). The haemoglobin range before transfusing RCP ranged from 3.1-8.6g/dl. RCP transfusions occurred 22 times, with only one instance where RCP were transfused above 8g/dl. RCP was the commonest blood product used whereas irradiated platelets were the least used (Figure 1).

Figure 1: Number of units used according to blood product



Platelet counts before transfusion ranged from $9-60 \times 10^9/\text{liter}$. Platelets were transfused on 26 occasions, with eleven instances of platelet indices above $20 \times 10^9/\text{L}$.

The total cost over the five month period for the department was 17,950 euro. The greatest cost per condition was for acute lymphoblastic

leukaemia (ALL)-1 – 5375 euro whilst the lowest cost was for ALL-4 at 125 euro. Patients' duration of treatment ranged from weeks to months.

ALL was the commonest condition treated, accounting for four out of nine patients. It was also the most costly per patient due to more frequent use of apheresis platelets (Table 2).

Table 1: Data regarding patients and products

Number of patients	9
Age Range	2-13 years
Mean Age	4 years 8 months
Total Units of RCPs	47
Range of RCP used	0-10 units
Total price of RCPs	5750 euro
Total number of platelet products used	30 units
Range of platelet products used	0-12 units
Total price of platelet products	12200 euro
Range of total cost per patient	125-5375 euro
Mean total cost per patient	1994 euro
Range of haemoglobin on transfusing RCP	3.1-8.6g/dl
Range of platelet count on transfusing platelets	$9-60 \times 10^9/\text{l}$

Table 2: Amount spent on blood products per patient

Condition treated	Cost per blood product (euro)						
	RCP	CMV -ve red cells	Apheresis platelets	Pooled platelets	Pooled platelets irradiated	Irradiated apheresis platelets	Total amount spent
ALL-1	1250	125	3500	500	0	0	5375
ALL-2	625	0	0	250	250	0	1125
ALL-3	375	0	0	0	0	0	375
ALL-4	125	0	0	0	0	0	125
Aplastic anaemia	375	0	1400	250	0	0	2025
Burkitt's lymphoma	250	0	0	250	0	0	500
Nephroblastomatosis	1125	0	2100	1000	0	0	4225
Retinoblastoma	0	0	0	250	0	0	250
Yolk sac carcinoma	1500	0	700	1750	0	0	3950
Total product used	5625	125	7700	4250	250	0	17950

Table 3: Prices for blood products before and after 2015 in Malta¹¹

Blood product	Prices according to year (euro)	
	2006-2014	2015
Red cell concentrate	125.00	166.10
Pooled platelets	250.00	346.27
Single donor platelets	700.00	714.90
Fresh frozen plasma	70.00	119.78

Limitations

1. It was unclear at times whether the products requested were actually used due to missing documentation in patient files.
2. The indication for blood product administration was not included.
3. Cycles of chemotherapy and radiotherapy were not noted.
4. Protocol by HBB regarding administration on KURA on administration of blood products specifically for paediatric patients were set up by the haematology working group at Mater Dei Hospital.¹⁰
5. Documentation of transfusion having occurred was not documented at times

Discussion

95% of red cell transfusions ($n=21$) were performed with a hemoglobin of less than 8mg/dl. Supportive care protocols recommend transfusions occurring at thresholds of 7mg/dl but patients who are symptomatic, suffering from aplastic anemia or bone marrow failure syndromes have higher thresholds.¹¹

43% ($n=13$) of platelet transfusions occurred at levels above $20 \times 10^9/l$. Protocols recommend routine transfusion occurring at levels less than $10 \times 10^9/l$ and less than $20 \times 10^9/l$ if suffering concurrent illness/bleeding/on anticoagulants. However prior to a potentially hemorrhagic event such as a lumbar puncture or change of central line platelet transfusions are recommended if levels are less than $50 \times 10^9/l$.¹¹

Over five months 17,950 euro was spent on blood products with an average cost of almost 2000 euro per patient.

Included also was the total cost of the process used to choose blood products for patients. The first process involves "Type and Screen" (T&S). This step checks blood group and antibody detection. If no antibodies are present, compatibility testing is performed by a "Spin and Read" (S&R), which is carried out at room temperature. If the samples indicate an antibody is present compatibility testing is performed by an IAT cross-match. If the S&R or IAT cross match is negative the blood product can then be issued. T&S are performed on each unit of RCP requested, whereas S&R or IAT crossmatch are performed on RCP that are issued but not necessarily transfused. 3276 euro were spent on these processes.¹³ On average almost

2000 euro was spent per patient in the five month period (Table 1).

Prices for blood products have remained stable in Malta from the year 2006 to 2014. These prices were changed owing to increasing costs in the production of blood products¹¹. This rise reflects the rise in costs shown in other countries however it does not account for other costs such as hospital care, nursing etc.

Conclusion

The use of blood products is dependent on patient needs and is not influenced by prices. Thresholds at which platelets and RCP are administered vary according to the clinical scenario. In view of rising costs and shrinking donor pools these resources should be used judiciously. Better documentation would ascertain whether platelet products were used adequately.

Acknowledgements

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References

1. Balzan C. Blood transfusion and blood banking in Malta: a historical perspective. MMJ. 2012 1(24):39.
2. Hess JR, Hiippala S. Optimizing the use of blood products in trauma care. Crit Care. 2005;9 Suppl 5:S10-4. Epub 2005 Oct 7. doi: 10.1186/cc3780. Pubmed PMID: 16221314. PMCID: PMC3226118.
3. Denton TA, Diamond GA, Matloff JM, Gray RJ. Anemia therapy: individual benefit and societal cost. Seminars in Oncology. 1994 [cited 2016 Mar 17];(21):29–35. Available from: https://www.researchgate.net/publication/14995990_Anemia_therapy_individual_benefit_and_social_cost
4. Forbes JM, Anderson MD, Anderson GF et al. Blood transfusion costs: a multicenter study. Transfusion. 1991;31:318–23. PubMed PMID: 2020994.
5. Varney JS, Guest FJ. The annual cost of blood transfusions in the UK. Transfus Med. 2003 Aug;13(4):205-18. PubMed PMID: 12880391.
6. Toner RW, Pizzi L, Leas B, Ballas SK, Quigley A, Goldfarb NI. Costs to hospitals of acquiring and processing blood in the US: a survey of hospital based blood banks and transfusion services. Appl Health Econ Health Policy. 2011;9(1):29-37. Doi: 10.2165/11530740-000000000-00000.
7. Adams RLC, Bird R. Quality use of blood products. Aust Prescr 2014;37:132-6.
8. Van Hulst M, De Wolf JT, Staginnus U et al. Pharmacoeconomics of blood transfusion safety: review of the available evidence. Vox Sanguinis 2002; 83: 146–55. PubMed PMID: 12201844.

Original Article

9. Sibson K, Bate J, Chisholm J, Ajitsaria R, Patel S, Evans R, Cheng D, King W, Dannat M, Henry L, Taj M, Anderson A, Marshall L, O'Sullivan M. Supportive care protocols Paediatric Haematology & oncology. 4th ed. Cheng D, Tattermusch S, editors. United Kingdom: NHS Foundation Trust; 2014 Jun 1. [cited 2016 Mar 15]. Available from: <http://www.londoncancer.org/media/66356/scp2011version5-0august.pdf>.
10. Mater Dei hospital blood bank. Guideline on the administration of blood components. c2015. [cited 2016 Mar 16]. Available from: kura.gov.mt.
11. Great Ormond Street Hospital for Children NHS trust, The Royal Marsden NHS Foundation Trust, The University College London Hospital NHS Trust. Supportive Care Protocols Paediatric Haematology & Oncology United Kingdom. 2011 Aug. 197p.
12. Debattista N. (nevile.debattista@gov.mt) RE: follow up on audit. Email to: Baldacchino I. (ian.baldacchino@gov.mt) 23 Apr 2015.
13. Debattista N. (nevile.debattista@gov.mt) RE: breakdown or prices. Email to: Baldacchino I. (ian.baldacchino@gov.mt) 27 Apr 2015.

Male patients commencing FOLFOX/ FOLFIRI chemotherapy in 2014, descriptive statistics

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Abstract

Background: Metastatic colorectal cancer is an incurable illness; however the advent of chemotherapy has significantly improved survival and symptom control. FOLFOX and FOLFIRI are used at SPBOH as the standard of care for patients with metastatic disease. No statistical data is available on that cohort of patients; this study aims to establish a population data-set for patients on FOLFOX/FOLFIRI.

Methods: This retrospective cross-sectional study included all patients on FOLFOX and FOLFIRI in 2014. Only male patients were included, data was retrospectively extracted from the ward's logbook and ISOFT clinical manager. Cycle 1, 6 and 12 dates were documented. Data was analysed using clinically reliable statistical tools, all reported *p*-values were statistically significant at <0.05 .

Results: From a total of 108 patients, 4 patients were excluded from the analysis. The average age of patients was 65.2 years. The average length of 12 cycles was 24.5 weeks. 19% of patients had cycles longer than 7 months whereas only 10% lasted more than 8 months on treatment. 41% of patients dropped out before completing the full course with a complication and mortality rate of 17%. Patients on FOLFIRI were more likely to have their chemotherapy changed and were also more likely to have received previous treatment.

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Conclusion: Although chemotherapy increases survival in metastatic colorectal cancer we have to appreciate that many patients do not proceed smoothly with their treatment. Many of those patients are middle aged independent individuals, after-all the physician must draw the line at the appropriate time and focus on palliative care rather than continuing ineffectively with chemotherapy.

MeSH Terms

Antineoplastic Combined Chemotherapy Protocols, Colorectal Neoplasms, data interpretation, statistical, Malta

Introduction

With a global incidence of 1.2 million cases annually, colorectal cancer stands as one of the most common and lethal malignancies. It is the fourth most common cause of death in men and the third in women, killing an estimate of 608,700 patients each year.¹ In the developed world, death rate from colorectal cancer has been decreasing, mainly due to screening and the detection and treatment of early stage disease. Population based screening programmes are usually not affordable in many parts of the world because of the expense of colonoscopy.² Loco-regional data is lacking, however in the United States, around 2/5 of colorectal cancer patients present with stage I and II local disease, around 2/5 with regionally advanced stage III disease and 1/5 with metastases.³

Metastatic colorectal cancer is an incurable illness, however in the advent of chemotherapy survival and symptom relief has significantly improved. Chemotherapy for metastatic colorectal cancer has developed in a stepwise fashion over the past decades. 5-FU was the first chemotherapeutic agent shown to be effective. Subsequently the regimen of 5-FU/cisplatin/folinic acid, was shown to increase survival in metastatic colorectal cancer from 5 to 11 months.⁴ More so two cytotoxic chemotherapies exhibited considerable efficacy when added to the 5-FU/folinic acid backbone. It is

combined with Oxaliplatin in the FOLFOX infusional regimen and with Irinotecan in the FOLFIRI regimen. Multiple clinical trials have shown that the FOLFIRI and FOLFOX regimens are equivalent in terms of efficacy. For first line therapy, oncologists typically choose between FOLFOX and FOLFIRI based on the side effect profile of both regimens.⁵⁻⁶

To prolong survival and improve quality of life, palliative chemotherapy is administered to patients with locally advanced or metastatic cancer. As a result of this established benefit, the 1990 National Institutes of Health Consensus Panel on Colorectal Cancer recommended routine 5-FU-based adjuvant chemotherapy for patients with node-positive (stage-III) colon cancer. This was originally recommended for 12 months, and later on revised to 6 months because of proven equivalence in survival benefits.⁷⁻⁹

As the only provider of systemic chemotherapy treatment in Malta, Sir Paul Boffa Oncology Hospital (SPBOH) serves the whole population of Malta and Gozo and caters for a wide array of cancer patients. FOLFOX and FOLFIRI are used at SPBOH as the standard of care for patients with metastatic as well as adjuvant colorectal cancer treatment. It is important to note that the initiation of adjuvant/palliative chemotherapy is just the first step in survival improvement. Because the completion of chemotherapy is associated with increased survival, it is essential to complete the chemotherapy cycles once initiated.⁷ Little is known about the actual completion rate of such a therapy in our community, and we were unable to identify other regional studies that assessed the completion of chemotherapy for colorectal cancer in actual practice. This study aims to form a population-based assessment for patients who were started on FOLFOX and FOLFIRI.

Methods

This retrospective cross-sectional study was done at Sir Paul Boffa Oncology Hospital. SPBOH is the only provider of systemic chemotherapy treatment in Malta. It serves the whole population of Malta and Gozo and hosts a wide array of cancer

patients. Permission was granted by foundation school audit and quality Improvement committee, Malta. All male patients who were started on FOLFOX or FOLFIRI in 2014 were included in the study. Data consisting of the patient's age, chemotherapy type and cycle, frequency of admission, tumour type and mortality were retrospectively extracted from the ward's logbook, computer registry and ISOFT clinical manager. The patients' admission dates for cycles 1, 6 and 12 dates were documented. A full course of modified de Gramont FOLFOX or FOLFIRI chemotherapy consists of a total of 12 cycles administered every fortnight. All patients who were intended to complete 12 cycles of adjuvant or palliative chemotherapy were included in the analysis. Patients who were on neo-adjuvant treatment and patients on maintenance chemotherapy for more than 12 months were excluded. Data was analysed using SPSS statistical tool. We first described the characteristics of all study cases and then used chi-square tests to compare the initiation and completion rates of adjuvant chemotherapy by characteristics. Multiple logistic regression was used to identify factors associated with the initiation and completion of chemotherapy. All reported *P-values* were two sided and were considered to be statistically significant at less than 0.05 levels.

Results

During 2014 SPBOH had a total of 1350 male admissions for chemotherapy, 874 of those admissions were for the infusion of either FOLFOX or FOLFIRI, 647 and 227 respectively. During this period a total of 108 patients were newly started on either treatment. Only patients who were on FOLFOX or FOLFIRI were included. Four patients were excluded from the analysis because they were on neo-adjuvant therapy or maintenance chemotherapy for more than 12 cycles.

The average age of patients was 65.2 years (ranging from 31-82) (64-67 95% confidence interval). 83% of patients were ≤ 70 years old. The main bulk, 65 patients, were between the ages of 60-70 years. Only 17 patients were > 70 years old. (Table 1, 2) (Graph 1)

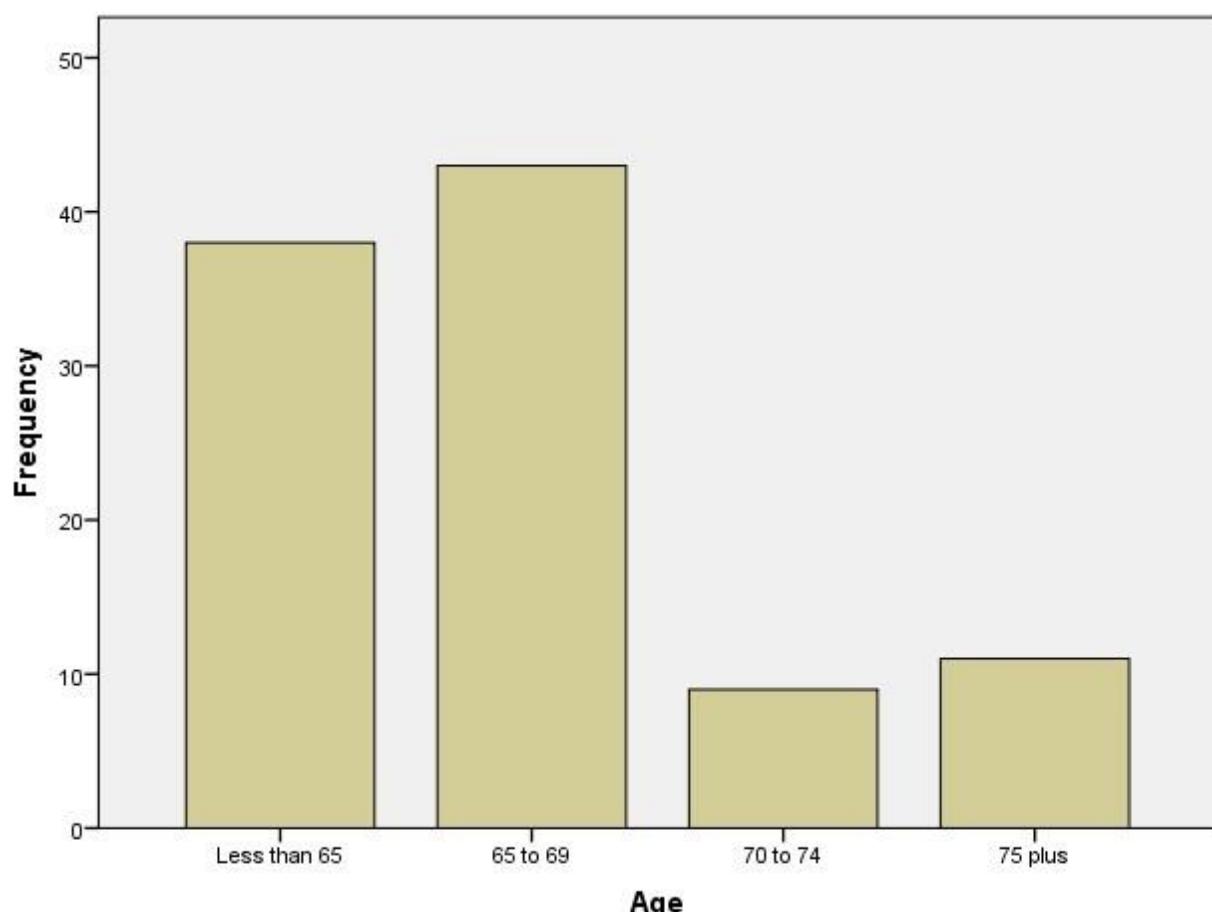
Table 1: Age statistics

		Age	
	Mean Difference	95% Confidence Interval of the Difference	
		Lower	Upper
age	65.198	63.63	66.77
Mean		65.20	
Median		67.00	
Mode		67	
Std. Deviation		7.942	
Minimum		31	
Maximum		82	

Table 2: Age statistics

Years	Frequency
Less than 65	38
65 to 69	43
70 to 74	9
75 plus	11
Total	101

Figure 1: Age Distribution



88 patients were on FOLFOX and 16 on FOLFIRI. Of those 12 patients had upper GI primary malignancies, 88 had lower GI malignancies and only 3 had other types.

91 patients did not receive previous treatments, 6 were previously treated with FOLFOX, 3 with FOLFIRI and 4 received other kinds of treatment. 89 patients (82%) did not have a change in Chemotherapy during the 12 cycles. However, the treatments of 14 patients (13%) were

altered; 5 patients were changed to FOLFOX, 7 changed to FOLFIRI and 3 were changed to other treatment regimens.

43.8% ($n=7$) of patients on FOLFIRI had their chemotherapy changed whereas only 9.1% ($n=8$) of patients on FOLFOX had a change in treatment. Patients on FOLFIRI were more likely to have their chemotherapy changed χ^2 (1) = 13.176, $p<0.001$. (Table 3)

Table 3: Chemotherapy regimen and whether or not it was changed

			Chemotherapy changed		Total	
			Yes	No		
Chemotherapy Regimen	FOLFOX	Count	8	80	88	
		% within Chemotherapy Regimen	9.1%	90.9%	100.0%	
	FOLFIRI	Count	7	9	16	
		% within Chemotherapy Regimen	43.8%	56.2%	100.0%	
Total		Count	15	89	104	
		% within Chemotherapy Regimen	14.4%	85.6%	100.0%	

Patients on FOLFIRI were also more likely to have received previous treatment χ^2 (1) = 24.312, $p<0.05$. Only 5.7% ($n=5$) of patients on FOLFOX received previous treatment; whereas 50% ($n=8$) of patients on FOLFIRI received previous treatment. (Table 4) Nonetheless, no statistically significant correlation between the types of chemotherapy and whether the patient will complete his chemotherapy cycles were found.

The average length of 12 cycles was 171.5 days or 24.5 weeks. The average length of cycles 1-6 and 6-12 were 11.6 and 12.9 weeks respectively. The mean difference between cycles 1-6 and cycles 6-12 is 1.6 weeks (1-2.3 95% confidence interval). 19% ($N=20$) of patients had cycles longer than 7 months whereas only 10% ($N=11$) lasted more than 8 months on treatment.

14.5% of patients ($N=15$) dropped out before completing 6 cycles, and 27% ($N=28$) of patients

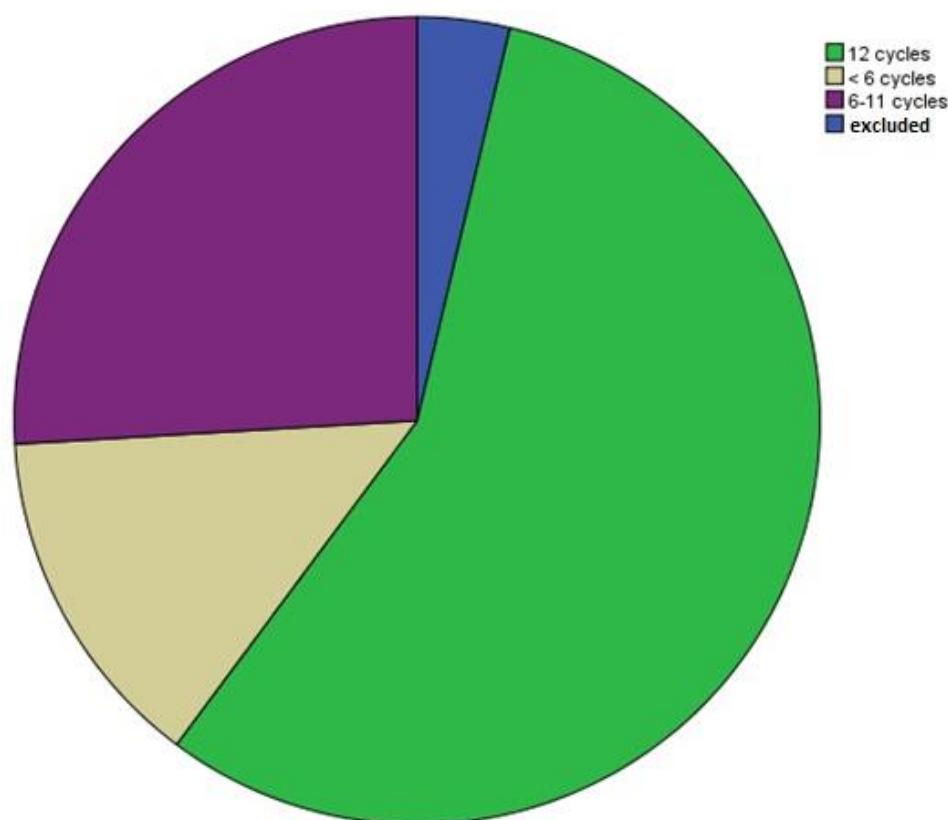
before finishing the full course. Therefore only 59% ($N=61$) continued for the whole 12 cycles. (Graph 2)

No statistically significant correlation was found between whether patients will complete chemotherapy and the presence of previous treatment, the type of chemotherapy, the presence of previous treatment, the primary tumour site or the age of the patients.

10 patients passed away before completing their planned chemotherapy cycles, 8 patients had significant thrombotic complications like deep venous thrombosis, pulmonary embolism and arterial embolism. Most complications occurred before finishing 6 cycles. Treatment was discontinued for the rest of the patients mainly because of poor response to chemotherapy and disease progression.

Table 4: Chemotherapy regimen and presence of previous treatment

		Previous treatment	Total	
		FOLFOX/ FOLRIRI or OTHER	NONE	
CHEMO				
	FOLFOX	Count	5	83
		% within CHEMO	5.7%	94.3%
				100.0%
	FOLFIRI	Count	8	8
		% within CHEMO	50.0%	50.0%
				100.0%
Total		Count	13	91
		% within CHEMO	12.5%	87.5%
				100.0%

Figure 2: Number of chemotherapy cycles

Discussion

This study provides a national overview for the use of FOLFOX/ FOLFIRI amongst Maltese patients with colorectal cancer and the proportion of patients who complete the prescribed therapy. The average age for patients in our study was 65.2; we had a significantly lower proportion of patients older than 70 years than those younger. These findings contradict with the natural prevalence of the disease, as colon cancer is predominantly a disease of the elderly population with an expected increase in prevalence with age¹¹; nonetheless this may be explained by the patients and oncologists choice and preferences for a less aggressive approach to palliative care among the elderly; however, data were not available to statistically test these assumptions.

Physicians may be reluctant to endorse such aggressive therapy for elderly because of the uncertainties regarding the risk–benefit trade-offs. However this is not consistent with best practice guidelines, as neither guideline recommends age as a factor to consider in treatment decisions.¹² Moreover in our study elderly patients (>75) were as likely to complete the course of treatment as the younger patients.

The overall rate of treatment completion in our study was 59% (N=61). This equilibrates with those found in other international studies. One prospective study conducted in Houston Texas in 2011 found that overall completion rate of adjuvant chemotherapy among patients with colon cancer was 62.2%. Patient's age at diagnosis, comorbidity score and marital status were significantly associated with the rate of initiation and completion of adjuvant chemotherapy.⁷

Take gastro-oesophageal cancer as an example, a recent study found that the overall rate of treatment completion was 52.7% and ranged from 50–60% for patients with good performance status but was under 35% for patients aged 55 years or older with poor performance status. Treatment completion was not associated with site of cancer, pre-treatment stage, sex, comorbidities or histology. Likewise, rates of adjuvant chemotherapy in patients with epithelial ovarian cancer approximate 46.5%; age and more than two comorbidities were identified as significant predictors.¹³ Our finding showed that no significant correlation was found

between whether patients will complete chemotherapy and the presence of previous treatment or the primary tumour site and is consistent with previous research.

FOLFOX and FOLFIRI are the most commonly used infusion treatments at SPBOH comprising of around 70% of all chemotherapies administered in the hospital. The average duration of cycles is satisfactory with around 70% finishing within 24 weeks. Although underrepresented in our study sample, patients on FOLFIRI were much more likely to have been given previous treatments and have their chemotherapy changed. Nonetheless both regimens had equal completion rates with no statistically significant difference between them.

From our whole sample it is noted that only 16 patients were started on FOLFIRI whereas all the rest were on FOLFOX. This could explain the higher initiation rates for FOLFOX or a likely more tolerable side effect profile. Nonetheless FOLFOX can cause significant peripheral neuropathy and approximately 18% of patients develop grade 3 neuropathy. Other quoted side effects in literature include cold related transient paraesthesia, allergic reactions, coronary artery spasm, neutropaenia, thrombocytopaenia, diarrhoea and mucositis. On the other hand, FOLFIRI shares most of the side effect profiles apart from the neuropathy caused by Oxaliplatin. The Irinotecan part of FOLFIRI can cause severe diarrhoea and approximately 13% of patients develop grade 3-4 diarrhoea, in addition it may lead to asthenia and is associated with a cholinergic syndrome characterized by rhinitis, increased salivation, lacrimation, diaphoresis and flushing.⁹⁻¹⁰

A significant number in our sample did not complete their treatment 41% (N=43). 10 patients were deceased; all of those patients had evidence of disease progression. 15 other patients had disease progression with expansion of the metastatic deposits, this heralded the chemotherapy futile and patients were sent for palliative care. 8 patients experienced significant complications like deep venous thrombosis, pulmonary embolism and arterial embolism; however of those only two patients stopped chemotherapy. In the other 16 patients the reason for discontinuation of chemotherapy was not clear from the data available. Other plausible explanations for why patients may

not have completed their treatment include the increasing financial or mobility barriers to care, preference changes, presence of comorbid conditions or mainly the debilitating chemotherapy-induced side effects.⁷

It is imperative to emphasize that systemic chemotherapy in metastatic colorectal cancer is usually not curative. However it is important to note that because the completion of chemotherapy is associated with increased survival, it is essential to complete the chemotherapy cycles once initiated. Nonetheless, in countries that do not have sufficient funds to administer chemotherapy, it is appropriate to forego chemotherapy and focus on palliative care. It must also be noted that, where available, a multidisciplinary approach and resection of oligometastatic disease and systemic treatment may cure some patients with metastatic colorectal cancer.⁷

Clinicians and patients should consider all this information aided by evidence based data and the extensive national statistics highlighted in this study to base treatment decisions. Afterall by balancing potential benefits, the probability of treatment completion, toxicity of treatment, quality of life and overall patient preferences an informed treatment approach can be undertaken.

Conclusion

As referring physicians, we have to appreciate that a large proportion of referred patients for adjuvant or palliative chemotherapy do not proceed smoothly with their treatment. Many of those patients are middle aged fully functional individuals. Although chemotherapy increases survival in metastatic colorectal cancer, many patients do not complete the whole chemotherapy regimen due to debilitating side effects or disease progression. Both chemotherapies are found to be comparatively equivalent, however FOLFOX is usually preferred due to a more tolerable side effect profile, FOLFIRI is usually reserved as second line treatment, as a test for efficacy. After all, the physician must be confident to draw the line at the appropriate time and rather focus on palliative care.

References

1. Jemal A, Bray F, Center MM, Ferlay J, Ward E, Forman D. Global cancer statistics. CA Cancer J Clin. 2011 Mar-Apr;61(2):69-90.
2. Burt RW, Cannon JA, David DS, Early DS, Ford JM, Giardello FM, et al. Colorectal cancer screening. J Natl Compr Canc Netw. 2013 Dec 1;11(12):1538-75.
3. American Cancer Society [Internet]. Colorectal cancer facts & figures 2011-2013. C 2011 – [cited 2016 Jan 15]. Available from: <http://www.cancer.org/research/cancerfactsfigures/colorectal-cancer-facts-figures/colorectal-cancer-facts-figures-2011-2013-page>
4. Scheithauer W, Rosen H, Kornek GV, Sebesta C, and Depisch D. Randomised comparison of combination chemotherapy plus supportive care with supportive care alone in patients with metastatic colorectal cancer. BMJ. 1993 Mar 20; 306(6880): 752-755.
5. Tournigand C, André T, Achille E, Lledo G, Flesh M, Mery Mignard D, et al. Folfiri followed by folfox6 or the reverse sequence in advanced colorectal cancer: A randomized gercor study. J Clin Oncol. 2004 Jan 15;22(2):229-37
6. Colucci G1, Gebbia V, Paoletti G, Giuliani F, Caruso M, Gebbia N, et al. Phase iii randomized trial of folfiri versus folfox4 in the treatment of advanced colorectal cancer: A multicenter study of the gruppo oncologico dell'italia meridionale. J Clin Oncol. 2005 Aug 1;23(22):4866-75.
7. Hu CY, Delclos GL, Chan W and Du XL. Assessing the initiation and completion of adjuvant chemotherapy in a large nationwide and population-based cohort of elderly patients with stage-III colon cancer. Med Oncol. 2011 Dec;28(4):1062-74.
8. Adjuvant Therapy for Patients with Colon and Rectum Cancer. NIH Consens Statement Online 1990 Apr 16-18 [cited 2016 Jan 02];8(4):1-25
9. WHO [Internet]. Union for International Cancer Control – [cited 2016 Jan 28]. Available from: http://www.who.int/selection_medicines/committees/expert/20/applications/MetastaticColorectal.pdf?ua=1
10. de Gramont A, Figer A, Seymour M, Homerin M, Hmissi A, Cassidy J, et al. Leucovorin and fluorouracil with or without oxaliplatin as first-line treatment in advanced colorectal cancer. J Clin Oncol. 2000 Aug;18(16):2938-47.
11. Horner MJ, Ries LAG, editors. SEER cancer statistics review [Internet]. Bethesda, MD, National Cancer Institute; 1975–2006 [cited 2016 Jan 29]. Available from: http://seer.cancer.gov/archive/csr/1975_2006/
12. MacMillan Cancer Support [Internet]. Cancer services coming of age: learning from the improving cancer treatment assessment and support for older people project – [cited 2016 Jan 04]. Available from: https://www.gov.uk/government/uploads/system/uploads/attachment_data/file/213205/DH_Macmillan_Age-UK_Report_Final.pdf
13. Oliver G, Tom C and Richard H H. A population-based observational study on the factors associated with the completion of palliative chemotherapy among patients with oesophagogastric cancer. BMJ Open. 2015;5:e006724

Maltese doctors: views and experiences on end of life decisions and care

Jurgen Abela, Pierre Mallia

Abstract

Background: End of life (EoL) decisions are important and challenging for doctors.

Aim: To better understand, describe and quantify this aspect of care.

Methodology: A national cross-sectional validated survey was mailed to all doctors of the country.

Results: The response rate was 39.3%. The respondents had been practicing for 19.72 years (95% CI: 18.3 – 21.0). 86% of respondents declared that their religion was important in EoL care. 42.9% (25.6% disagreed, 31.5% neutral) agreed with the right of a patient to decide whether or not to hasten the end of life. 48.6% agreed (34% disagreed, 17.4% neutral) that high quality palliative care nearly removes all requests for euthanasia. 60.4% agreed (23.9% disagreed, 15.7% neutral) that physicians should aim to preserve life.

Each doctor cared for an average of 10.5 EoL (95%CI: 8.45-12.64) patients in the prior 12 months. 32.1% of doctors withdrew or withheld treatment in the care of these patients. Of the remaining 67.9%, 36.6% agreed with such practices. 50.3% had intensified analgesia at EoL with the possibility of hastening death. Only 6% had sedated patients at EoL. Lastly, 11.9% received request for euthanasia whilst 90.2% of doctors would never consider euthanasia.

Significant correlations were observed between considering euthanasia, importance of religion, withdrawing/withholding treatment, doctors' specialty, preservation of life and request for euthanasia. A thematic analysis of comments highlighted the importance of the topic, feeling uncomfortable in EoL care, the religious aspect of care, lack of legal framework and the challenge of symptom control.

Conclusions: The overall majority of doctors is against euthanasia. There is a strong sense of guidance by their religious beliefs when it comes to EoL care. Doctors believe in preserving life as a guiding principle at the end of life, but do not shun intensification of analgesia at the end of life. Different specialties have slightly different views on EoL. Doctors need guidance – legal and moral – on this subject, in the absence of which, their religion and philosophy of life is used to guide them in this rather difficult area of practice.

Introduction

Palliative Care (PC) aims to improve the quality of life of the patient with a limited prognosis through a combined approach addressing the physical, psychosocial and spiritual nature aspects of the patient, including bereavement support to the relatives of the patient.¹ Historically, PC was born out of oncology. Following on a landmark study, PC has expanded to include non-cancer diseases such as heart failure and respiratory failure.² Such palliative approach to managing disease and symptoms is also reflected in the training curricula of various medical disciplines and in the most recent guidelines for the management of certain non-malignant conditions in their end stage.³⁻⁵

A particularly challenging moment in any specialty, not only in palliative care, is the end of life (EoL), due to the fact that ethical issues commonly arise with respect to symptom control, hydration, treatment withdrawal and the management of the dying process. In fact, the ethical challenges of EoL in medical practice are

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reflected in a variety of documents.⁶ Further to this, one should consider the effect that the (occasionally difficult to manage) suffering of the patients has on doctors. In fact, moral distress in doctors has been recently documented and frameworks to address it are being put forward.⁷

The country of Malta has experienced rapid and significant socio-cultural changes. One of the aims of this study was to inform a particular area of medical practice where controversial issues regularly arise. In addition, the authors have a particular interest in ethical issues at EoL. This study is being presented within ENDCARE Malta, an Erasmus + project aimed at supporting the harmonization and EoL practices.

Method

The aim of the study was to describe and quantify the thoughts amongst medical practitioners on EoL decision making. Hence a primarily quantitative methodology was adopted and accordingly, a questionnaire was used. The questionnaire was previously used in similar populations ie doctors, and previously validated as part of the EURELD (European end-of-life consortium) initiative.⁸ The necessary permission was sought and obtained.

The questionnaire was sent by post to all medical practitioners who were listed on the Principal Register of the Medical Council of Malta as on November 2013. Only doctors who had a local address listed on the register were included ($N=1007$).

The questionnaire consisted of four sections, followed by a short comments section. The four sections related to demographic details; details on religion/philosophy of life; thoughts on palliative care and training; and lastly a section on past experiences and views in relation to end of life decisions.

Each questionnaire had a short note included where the aims of the study were explained and consent sought. The participants were asked to fill in the questionnaire and return it back by not more than one month.

Every effort was made to ensure a good response rate.⁹⁻¹⁰ The introductory note was personalized, each participant had a prepaid envelope to return the questionnaire and the questionnaire was not long. However, contrary to existing recommendations, no reminder note was

sent to the doctors. This was done since the author felt that the area being studied was 'sensitive' and consequently felt that a reminder was inappropriate.

The University of Malta Research Ethics Committee approved the study. The data collected was analyzed using SPSS version 22.0 and Excel version 12.3.6. For ease of analysis, the respondents were grouped in umbrella specialties. Hence medicine includes general medicine, neurology, cardiology, renal medicine, respiratory medicine and so on. The same goes for surgery which included amongst others general surgery, ENT and orthopaedics.

Results

396 doctors returned the questionnaire, giving a response rate of 39.3%. Of those that answered, 40 were no longer actively practicing as doctors. As per questionnaire, they were asked to return the questionnaire unfilled. The subsequent analysis of results is consequently limited to those doctors who were actively practicing at the time of the questionnaire ($n=356$)

The results of the questionnaire will be presented in sections as per hereunder:

I. Demographic details

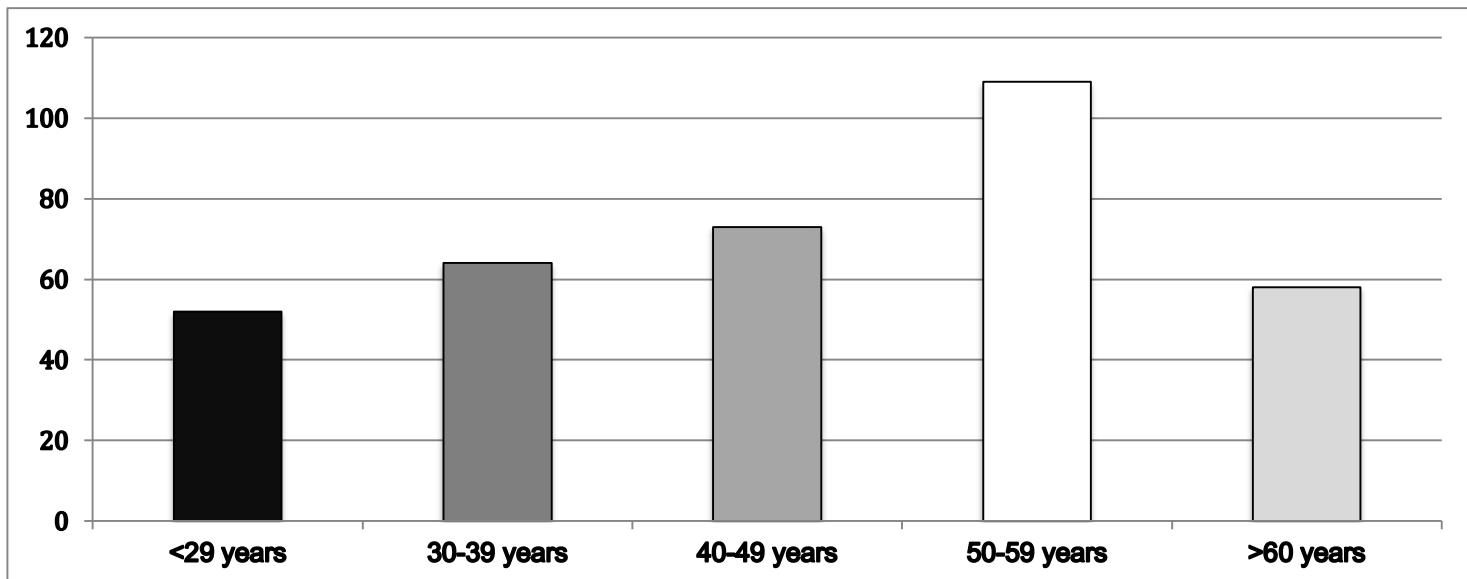
Of the respondents, 59.2% were males, whereas 40.8% were females. Overall, the respondents had been practicing for an average 19.72 years (95% CI: 18.3 – 21.0). The age of respondents is summarized in Figure 1. The distribution of specialties of respondents is summarized in Table 1. The largest specialty was general practice, the results of which have been analyzed in a separate paper.¹¹

II. Respondents and their religion

The respondents were asked to identify their religion/philosophy of life. As expected, the majority of respondents (91.6%) identified the Roman Catholic Church as their religion. The importance of religion in EoL decisions is summarized in Figure 2.

III. Views of respondents on palliative care and EoL care.

The respondents were asked to rate on a 5-point scale whether they disagree/agree with a set of statements. A summary of the responses is found in Table 2.

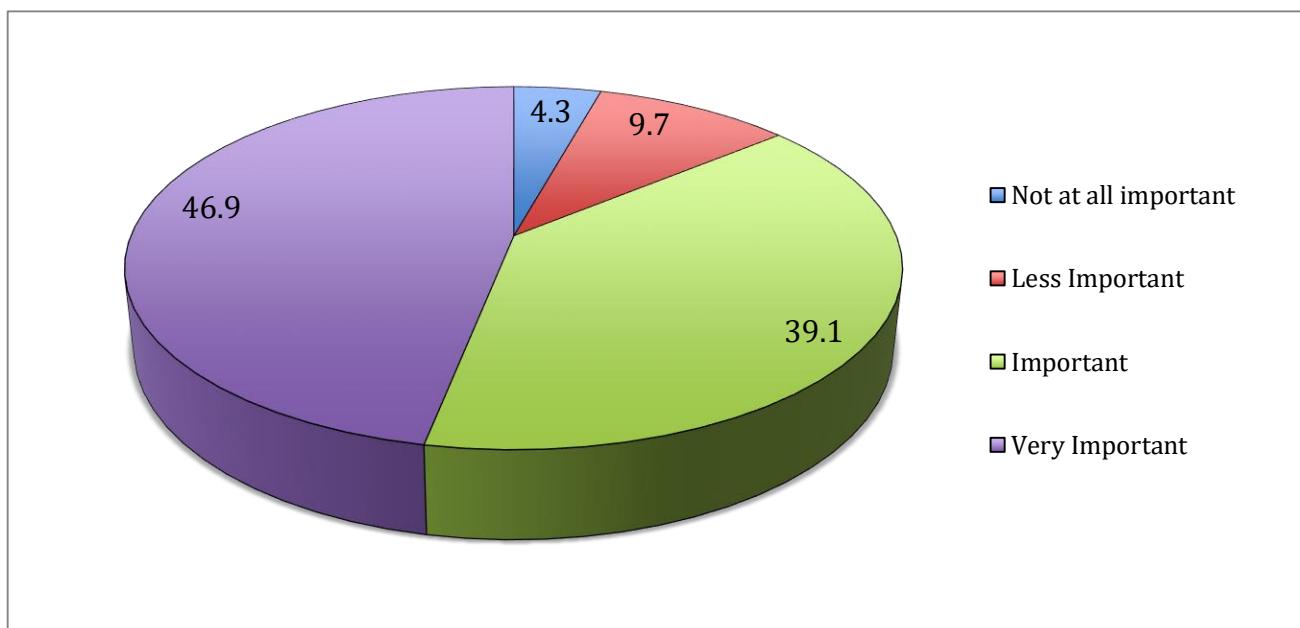
Figure 1: Age distribution of respondents**Table 1:** Respondents and their specialties

Specialty	Number	Percentage of total (N=356)
General Practice	160	44.9%
Medicine *	49	12.4%
Surgery**	45	11.4%
Other***	23	5.8%
Anaesthesia	21	5.9%
Paediatrics	21	5.9%
Gynaecology	18	5.1%
Geriatrics	12	3.4%
Psychiatry	7	2.0%

* Includes general medicine; neurology; cardiology; respiratory medicine; oncology

** Includes general surgery, orthopaedics, ENT surgery, neurosurgery

*** Includes dermatology, radiology, public health,

Figure 2: Importance of Religion in EoL Decisions (% response) ($p<0.001$)**Table 2: Agreement/disagreement on EoL statements**

Statements on EoL	Disagree (%)	Neutral (%)	Agree (%)
Patient has a right to decide whether to hasten his EoL ($p<0.001$)	25.6	31.5	42.9
High Quality PC removes almost all requests for euthanasia at EoL ($p<0.001$)	34	17.4	48.6
Physicians should always aim to preserve life ($p<0.001$)	23.9	15.7	60.4

IV. Respondents and situations of EoL care

The final part of the questionnaire dealt with actual experiences in EoL care. On each question, the respondents were asked whether they ever experienced a particular clinical scenario and if so, how long ago was it.

To start with, respondents were asked how many terminal patients did they care for in the last 12 months. The mean answer was 10.5 patients (95% CI: 8.45-12.64).

They were subsequently asked on whether they ever withdrew or withheld any treatment to their patients. Of all the doctors 32.1% had

withdrawn/withheld treatment. Of these:

- 13.9% had withheld treatment,
- 4.0% had withdrawn treatment and
- 14.2% withheld and withdrew treatment.

Out of the remaining 67.9% who never carried out such practices:

- 13.6% of doctors would withhold treatment;
- 2.0% would withdraw treatment
- 21.0% agree to both
- 31.4% would not withdraw/withhold treatment.

Of those that answered positively to this question, the last time they had a patient in such

situation was a mean 15.8 months ago (95%CI: 7.87-23.91).

The respondents were also asked whether they ever intensified analgesia at EoL with the possibility of hastening death and whether they ever sedated patient at the EoL. The responses to these two questions are grouped together in Figure 3.

Those who responded positively to these two questions reported that they last had a patient needing intensification of analgesia 18.5 months ago (95%CI: 11.53-25.65), whilst with respect to

sedation, the last patient they could recall was 36.3 months ago (95%CI: 11.13-61.3).

When asked whether they ever received a request for euthanasia from patients, 11.9% answered positively. Of these, the last time they received a request was on average 35.6 months ago (95%CI: 15.27-55.92)

Finally, the respondents were asked whether they would consider euthanasia. The response as percentage of total respondents is summarized in figure 4.

Figure 3: Views on Intensification of Analgesia and Sedation at EoL (% response) ($p < 0.001$)

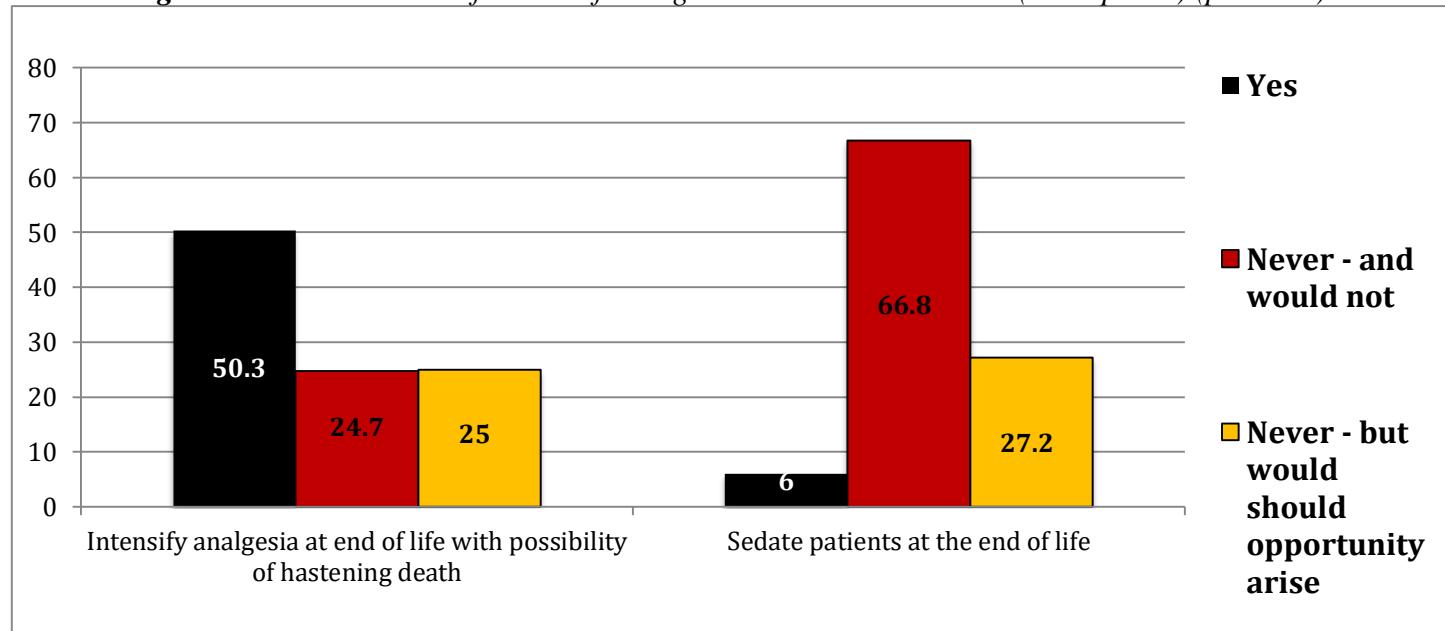
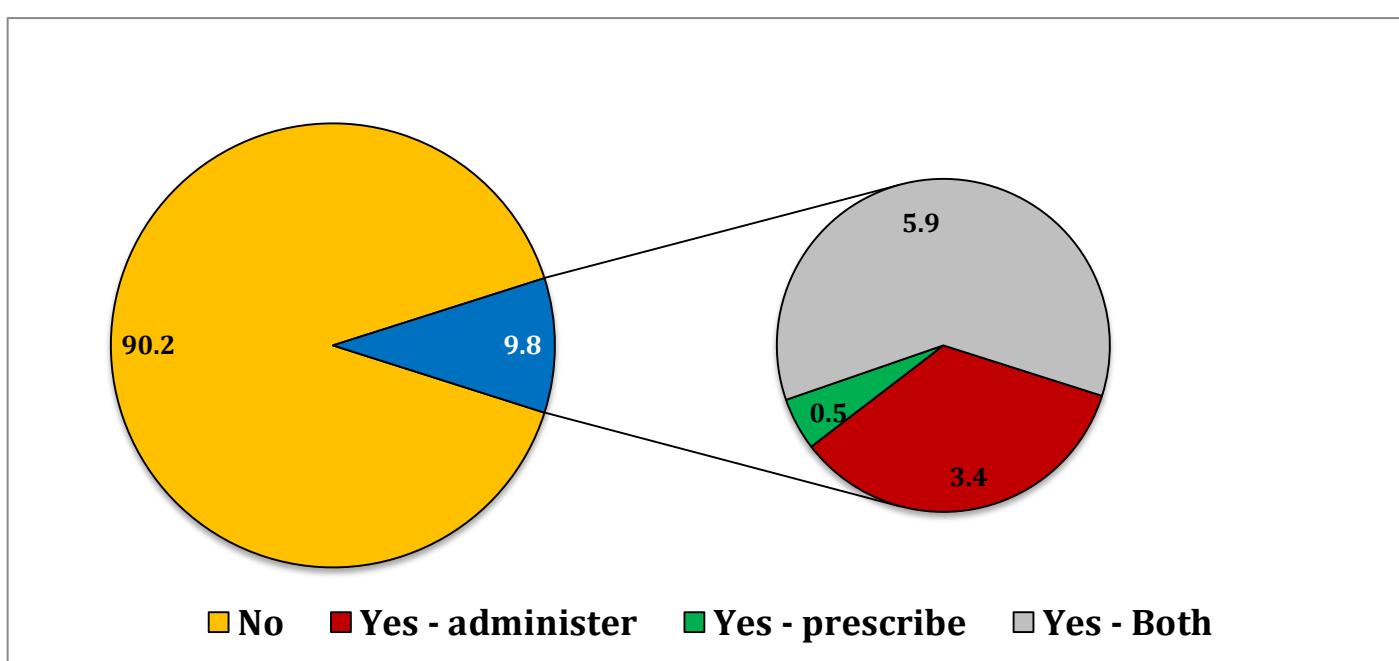


Figure 4: Would you consider euthanasia on explicit request from patients? (% response)



V. Associations

Analysis of possible relations between the various variables was carried out using appropriate non-parametric statistical tools (Chi-squared tests; Wilcoxon signed rank test). There was a significant ($p=0.013$) association between the practicing specialty and the number of requests for euthanasia as shown in figure 5. Another significant association ($p=0.011$) was observed between the practicing specialty and the response to the

statement on whether physicians should always aim to preserve life (figure 6). A very significant relation ($p<0.001$) was observed between the importance given to religion and considering euthanasia and views on withholding/withdrawing treatment (Table 3). Finally significant associations were identified between the importance given to religion and the responses to the broad statements on EoL Care.

Figure 5: Requests for euthanasia and Specialty (% response) ($p=0.013$)

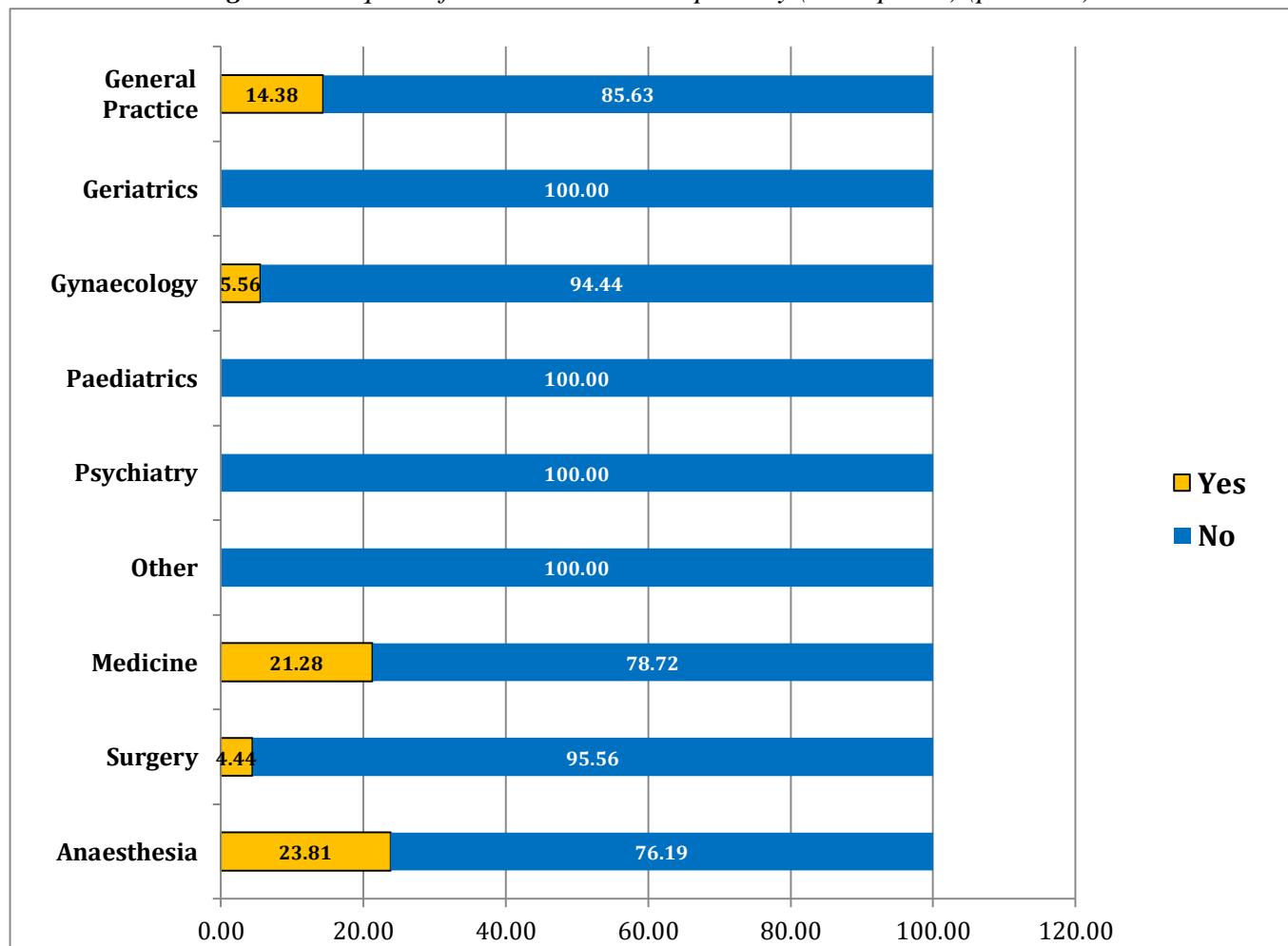


Figure 6: Physicians should always aim to preserve life and practicing specialty ($p=0.011$)

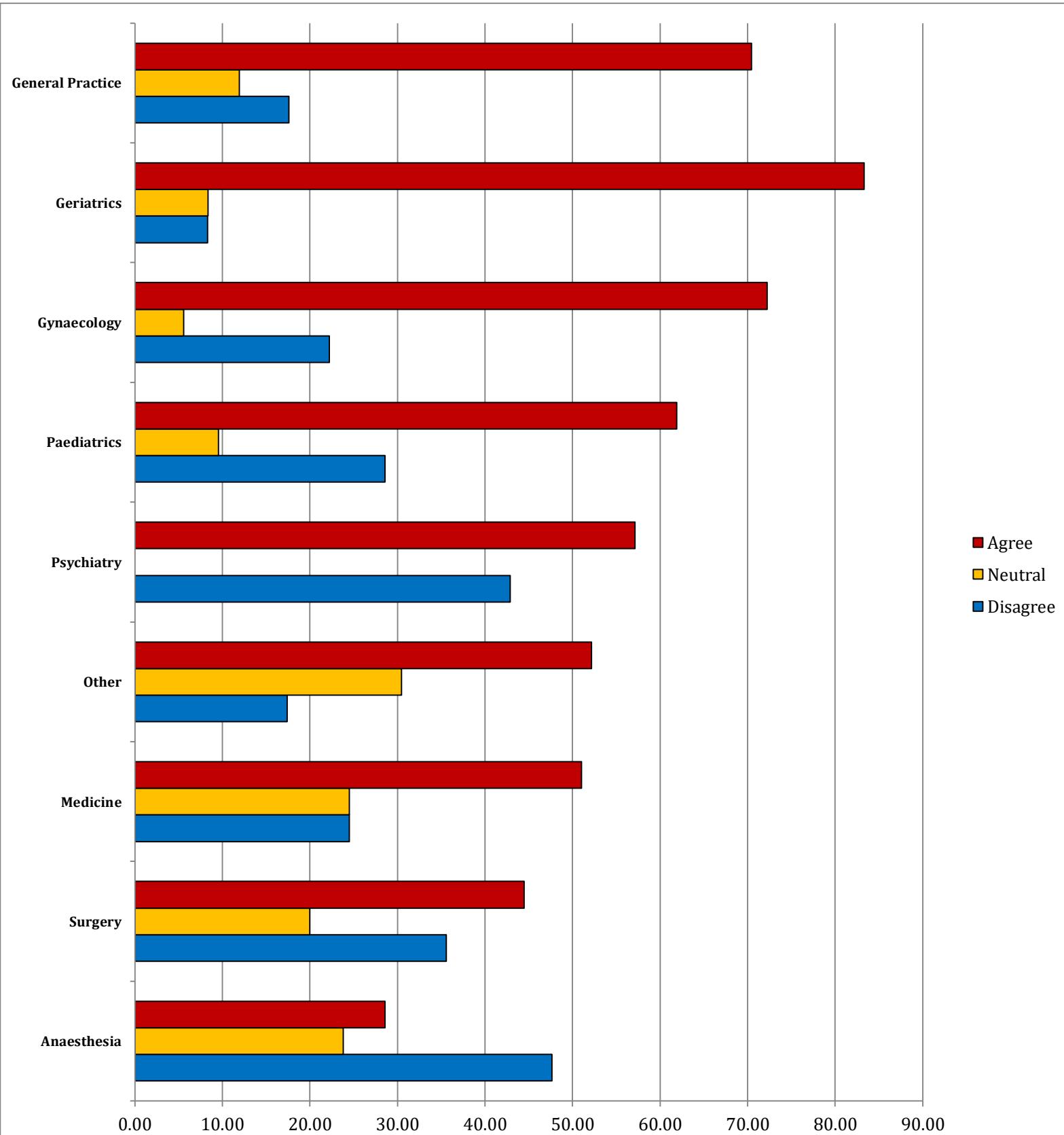


Table 3: Importance of religion vs withholding treatment and considering euthanasia)

Importance of religion	Withdrawing or withholding Rx ($p<0.001$)	
	YES	NO
Not or less important n=48	89.6% (43)	10.4% (5)
Important or Very Important (n=298)	65.2% (194)	34.8% (104)
Importance of religion		
Importance of religion	Consider Euthanasia ($p<0.001$)	
	YES	NO
Not or less important n=48	66.6% (36)	33.3% (12)
Important or Very Important (n=297)	6.7 (20)	93.3% (277)

VI. Qualitative analysis

At the end of the questionnaire, the respondents had the option to leave comments. 92 opted to comment and a representative summary of the various themes is listed here under, in order of decreasing frequency:

- *Importance of the subject*

‘This is one of the greatest dilemmas I could possibly face....it is also true that reassuring the patient of a dignified death reduced the request for euthanasia. I still do not feel comfortable in any way to help anyone hasten death’ (GP)

‘A much needed study!’ (Medicine)

‘This is a subject of extreme importance and which touches on one of the principal aims of medical practice’ (GP)

- *Ethical and religious issues*

‘I believe that a doctor’s own attitudes to life and death have a great bearing on the EoL situations. Also one’s own beliefs’ (Orthopaedics)

‘My religion has a reply to all this’ (GP)

- *Feeling uncomfortable*

‘There is a tendency to withhold proper palliative care with the fear that it hastens death’ (Paediatrics)

‘PC is an important topic. I really feel sad to see a patient, on post-take round in pain and ‘nothing’ is done since she is palliative’ (Gynae)

‘Complex and difficult in balancing out things’ (Surgery)

- *Symptom Control*

‘Whether or not the death of the patient is hastened, the comfort of the patient and relief provided by medication/surgery is paramount’ (Anaesthetist)

- *Legal Issues*

‘Law is totally lacking. If legal, I might consider it’ (GP)

‘With euthanasia likely to come up in Malta, legislation should protect doctors’ (GP)

‘Do no harm and abide by the law. The law must be sensitive...’ (Other – Radiology)

‘Law is totally lacking. If legal, I might consider it’ (Orthopaedics)

- *Service Provision*

‘MDH - lacuna where a lot of attention is given to treatment which is dubious. DNR orders without telling the patient’ (Medicine)

- *Need of Training*

‘Radiology is not considered a specialty where doctors have to BBN. But after

working for two years I realise that patients ask and therefore I feel that I need training' (Other - Radiology)

'A&E - need of training please' (Emergency Medicine)

- **Ripple Effect**

'And as we started with abortions....you start with the hard cases and end up with the frivolous cases'....slippery slope (Orthopaedics)

Discussion

End of life decisions are challenging. This comes through in the comments put forward by the respondents. On the other hand, moral guidelines on EoL are very clear and in fact similar in most religions. There is a general acceptance that there is a difference between killing and allowing to die, that one need not give treatment which is considered futile, that one is morally correct in avoiding extraordinary measures and that it is the patient who decides for himself what he or she considers ordinary or extraordinary.¹²⁻¹⁴ In this study, the majority of doctors are resonant with the idea of withdrawing/withholding treatment should such treatment be deemed to be futile, in line with what has been stated above.

In addition, they are in favour of intensification of analgesia (using opioids) even if this might theoretically impact on the length of survival of the patient. At the same time they strongly support the statement that physicians should always aim to preserve life. Indeed, these two responses embody the doctrine of double effect.¹⁵ In brief the doctrine of double effect concerns the idea that the bad effect is not the intended effect and that although a harm is foreseen, it is indirect and unintended – the intention and direct action being pain relief. Only a minority agree with sedating patients (in distress) at the end of life. This arises despite the fact that it has been shown that such practice actually lengthens (not shortens) life.¹⁶ Such issue might arise from the fact that sedation of patients at the end of life can be interpreted by fellow colleagues or family/carers as a 'modified form of euthanasia'.

Interestingly, the very strong majority of doctors *against* euthanasia (90.2%) seems to have increased from the time of the study by Inguanez and Savona Ventura where the percentage of doctors *in favour* of euthanasia was 24%.¹⁷ Abroad,

a recent survey by the Association of Palliative Medicine of Great Britain showed that 82.3% were against euthanasia. (Dr C. Gannon, Medical Director Princess Alice Hospice – personal communication).

It is interesting to note the (significant) relation identified between the doctor's own specialty and receiving requests for euthanasia. The specialties 'at risk' (general practice, medicine, geriatrics) might be so due to the possibly higher level of empowerment of the professionals involved in getting through/communicating with patients. Thus patients feel more at ease to open up, even with respect to such difficult requests. In addition, the specialty of the doctor also relates to the response given to the statement about preservation of life (figure 6). When one compares the latter with the (non-significant) association between specialties and views on euthanasia (table 4), there are some interesting differences. For example, whereas in anaesthesia, there is a large minority who do not agree with always preserving life, there is a huge majority against euthanasia. This can be interpreted as a practical approach to EoL where at times patients are 'clearly' approaching death and such aggressive drive ('*accanimento terapeutico*') to maintain life might be inappropriate.

The qualitative section of the results shows the amount of issues which EoL situations give rise to. In addition, it is quite evident that the absence of any guidance – which comes through in the plethora of comments in the qualitative section – is made up by the guidance provided by the religion of the individual doctors.

This study, which was done in a mostly Catholic country, raises concern that there might be lack of clear understanding of moral guidelines, which are accepted socially from a religious point of view. The main concerns seem a lack of a legal framework and possibly, fear of litigation by the relatives. It goes without saying that communication with relatives and patients can only occur if one knows moral guidelines well and indeed perhaps offers ethical/spiritual counselling both to patient and relatives. Further studies are needed to attenuate such concerns on behalf of professionals. In this regard, The ERASMUS+ EndCare project is currently being carried out.¹⁸ This project will try to address the critical issues of end of life treatment and, whilst repudiating euthanasia in all its forms, will examine the short

comings of health care professionals who might be ambivalent about such situations. EndCare will propose a curriculum framework and a complementary care protocol incorporating identified best practice from diverse jurisdictions throughout the European Union be developed and implemented in the fullest respect for ethical, moral, medical and socio-political considerations.

Table 4: Considering euthanasia and practising specialty ($p>0.05$)

Specialty	Not consider euthanasia (%)	Would consider euthanasia (%)
Anaesthesia	95.24	4.76
Surgery	80.00	20.00
Medicine	100	0
Other	80.95	19.05
Psychiatry	85.71	14.29
Paediatrics	95.24	4.76
Gynaecology	88.89	11.11
Geriatrics	100	0
General Practice	89.31	10.69

Strengths and Limitations

The response rate in this study was low, possibly related to the fact that no reminder was sent to respondents.¹⁹ Having said this, in the study by Inguanez and Savona Ventura, the response rate was the same.¹⁷ This study concerned a difficult subject area and as such should contribute to the local literature. It was a national cross sectional survey where *all* local doctors were included. The low response rate, though similar to a previous study, might have affected the results. The study employed a mixed methods approach thereby allowing a more holistic review of the topic.

Conclusion

Doctors commonly face EOL decisions. In general, they find this topic difficult and challenging and rely on the religion as the major source of guidance. There might be some confusion

as to the (accepted) moral values guiding such decisions. There is an absence of legal framework and official guidance on this topic, which further adds to the difficulty in such situations. Different specialties have slightly different views and approaches to EoL. The overall majority of doctors are against euthanasia. Finally, there needs to be broad guidance to doctors in such situations to support them better.

References

1. Charlton R, editor. Primary Palliative Care. 1st ed. Oxon: Radcliffe Medical Press; 2002.
2. Addington-Hall J, McCarthy M. Dying from cancer: results of a national population-based investigation. Palliat. Med. 1995; 9 (4):295-305.
3. Royal College of Physicians. [Internet] MRCP(UK) [updated 2015 Jun; cited 2016 Jan]. Available from: <https://www.mrcpuk.org>
4. European Society of Cardiology. Guidelines for the Management of acute and chronic Heart Failure. European Heart Journal (2012) 33, 1787-847.
5. Global Strategy for the management and prevention of COPD [Internet] Guidelines of the prevention and management of COPD. [updated 2015; cited 2016 Jan]. Available from: <http://www.goldcopd.org>
6. Treatment and care towards the end of life: good practice in decision making, General Medical Council UK, (2010).
7. Rushton CH, Aszniak AW, Halifax, JS. A Framework for Understanding Moral Distress among Palliative Care Clinicians. Journal of Palliative Medicine. 2013; 16 (9):1074-9.
8. Lofmark R, Milstum T, Cartwright C, EURELD Consortium. Physicians experiences with end-of-life decision-making: Survey in 6 European countries and Australia. BMC Palliat Care. 2008;6(4).
9. Kellerman SE, Herold J. Physician Response to Surveys - A review of the Literature. American Journal of Preventive Medicine, Am J Prev Med. 2001;20(1):61.
10. Seale C. End-of-life decisions in the UK: a response to van der Heide and colleagues. Palliat Med. 2009;23 (6):567-8.
11. Abela J. GPs and End of life decisions: views and experiences. Malta Med J. 2015; 27(2): 31-6.
12. Jecker N, Jonsen A, Pearlman R. Bioethics – An introduction to the History, Methods and Practice. Second Edition. Boston, Toronto, London Singapore. Jones and Barthlett Publishers. 2007: 484-5.
13. Magisterium of the Catholic Church. Catechism of the Catholic Church. Dublin, Vatican City. Veritas publishers, 1994.
14. Petrini M. Il Testamento biologico: status of art. Um. Nuova 2011; 6(198): 621-657
15. Jonsen AR, Siegler M, Winsdale WJ. Clinical Ethics. A practical approach to Ethical Decisions in Clinical Medicine. Second edition. New York, London Toronto: Macmillan Publishing Company. 1986, p 120.
16. Maltoni M, Scarpi E, Rosati M, Derni S, Fabbri L, Martini et al. Palliative sedation in end-of-life care and survival: a systematic review. J Clin Oncol. 2012; 30(27): 3429-33.
17. Inguanez J, Savona-Ventura C. Not a Euthanasia. DISCERN - Institute for Research on the Signs of the Times. 1st ed. Malta: Gutenberg Press Ltd.; 2008.

Original Article

18. Endcare. Erasmus + 2015: On harmonization and Dissemination of Good Practice at the End of Life. Project 2015-MT01-KA203-003728. 2015: Bioethics Research Programme, University of Malta.
19. Edwards P, Roberts I, Clarke M, DiGiuseppi C, Pratap S, Wentz R, et al. Increasing response rates to postal questionnaires: systematic review. *Br Med J*. 2002; 324: 1183-7.

Functional results following surgical repair of post-traumatic hand tendon injuries

Mark Bugeja, Max Mifsud, Jason Zammit

Abstract

Introduction: The study aims to determine whether early physical therapy following hand tendon repair gives better results and to look at any possible limiting factors locally.

Methods: Twenty adults were selected from those admitted to Mater Dei Hospital, with traumatic tendon injuries to the wrist and hand during the year 2014. Their medical records were reviewed and details on surgical repair and postoperative rehabilitation noted. Participants completed *QuickDASH* outcome measure questionnaires assessing their situation both on initial presentation to hand therapy and six months later. The range of motion in all joints of the injured digits, six months after commencement of therapy, was measured by manual hand goniometry and the Total Active Motion (TAM) score calculated.

Results: A negative correlation was found between delay in starting hand therapy and both TAM score ($r=-0.650$, $N=20$, $p<0.001$) and *QuickDASH* score ($r=-0.650$, $N=20$, $p<0.002$). Comparison of the two outcome measures resulted in a strong negative correlation ($r=-0.831$, $N=20$, $p<0.0005$).

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Conclusion: These findings support current literature confirming that a shorter delay in starting hand therapy following tendon repair is associated with a better outcome for the patient. Better documentation and interdisciplinary handover is required, and a new operation report template is being put forward.

Keywords

tendon, repair, laceration, *QuickDASH*, TAM, template

Introduction

The human hand is a sophisticated body part able of performing complex fine movements.¹ Injuries to the hand are common in young workers and lead to significant disability, hindering patients both at work and during social activities.² Despite the great advances in hand tendon surgery, successful tendon repair and rehabilitation still remains a difficult task, with poor functional outcomes after repair reported in up to 20% to 30% of cases.³

Aims

The primary aim of this retrospective study was to assess whether there is any correlation between a delay between surgical repair and instituting treatment, the range of movement at the joints of the finger at 6 months and the self-assessed perceived disability at 6 months.

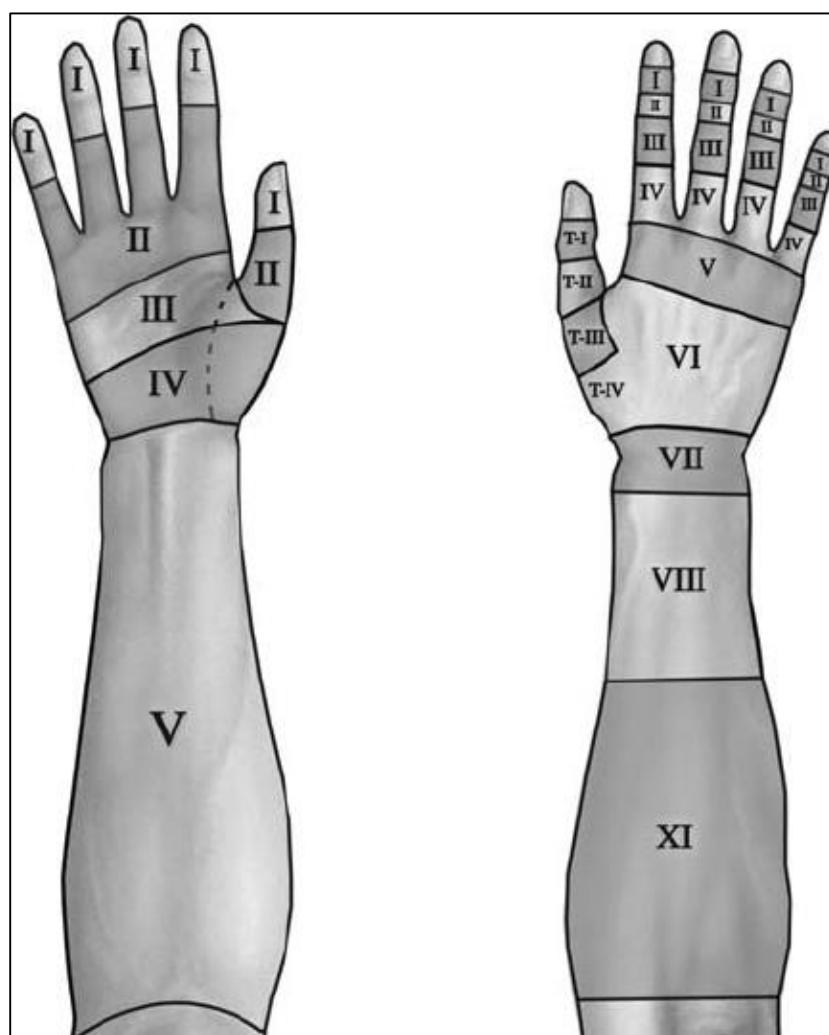
Methods

Approval was obtained from the University of Malta Research Ethics Committee, and the Data Protection Unit (Mater Dei Hospital, MDH). The list of patients with traumatic tendon injuries following lacerations to the wrist and hand in the year 2014 was obtained via the hospital's Clinical Performance Unit and the Occupational Therapy Department as the year progressed. Adult individuals were selected independently of their age, gender, injured tendon or zone injured.

Tendon injuries compounded by fractures (crush injuries) were excluded. Individuals with comorbidities such as osteoarthritis, rheumatoid arthritis, neuropathy (peripheral and focal), and diabetes were also excluded. Individuals who were eligible, accepted to participate, and signed a consent form, were recruited in this study.

The medical records of the recruits were reviewed and data collected on gender, age, date of admission, hand injured, previous trauma, operation performed, documentation on surgical repair and rehabilitation, and date of commencement of physical therapy. Injury sustained was further classified by location (Figure 1).⁴

Figure 1: Classification of injuries for flexor (left hand side) and extensor (right hand side) hand tendon injuries. Image taken from Burnham *et al.*⁴



The participants were asked to complete the QuickDASH outcome measure questionnaire,⁵ a standardised upper limb functional scoring tool, to assess their situation both on initial presentation to hand therapy department post-operatively and six months after surgery at outpatients follow-up. A paired student t-test was carried out on the QuickDASH scores to check whether there was a statistically significant difference between the pre-

and post-therapy results. Pearson correlation was used to assess the relationship between the delay in starting hand therapy and the QuickDASH score six months after surgery.

Active range of motion in all joints of the injured digits, approximately six months after commencement of therapy, was measured by manual hand goniometry using a standard finger goniometer (Baseline®). These measurements

were performed by the same investigator. The technique used was adopted from the University of Scranton website.⁶ The results were assessed using the Total Active Motion (TAM) clinical assessment score, as described by the American Society for Surgery of the Hand (ASSH).⁷ TAM is the sum of the degrees of active flexion minus the sum of incomplete active extension in the metacarpophalangeal, proximal phalangeal and distal phalangeal joints of the affected fingers. The normal TAM of the thumb was considered to be 130 degrees while that of the digits to be 260 degrees. Pearson correlation was used to assess the relationship between the delay in starting hand therapy and the TAM score six months after surgery.

The data collected were analysed using the IBM Statistical Package for the Social Sciences (SPSS) Statistics version 22.

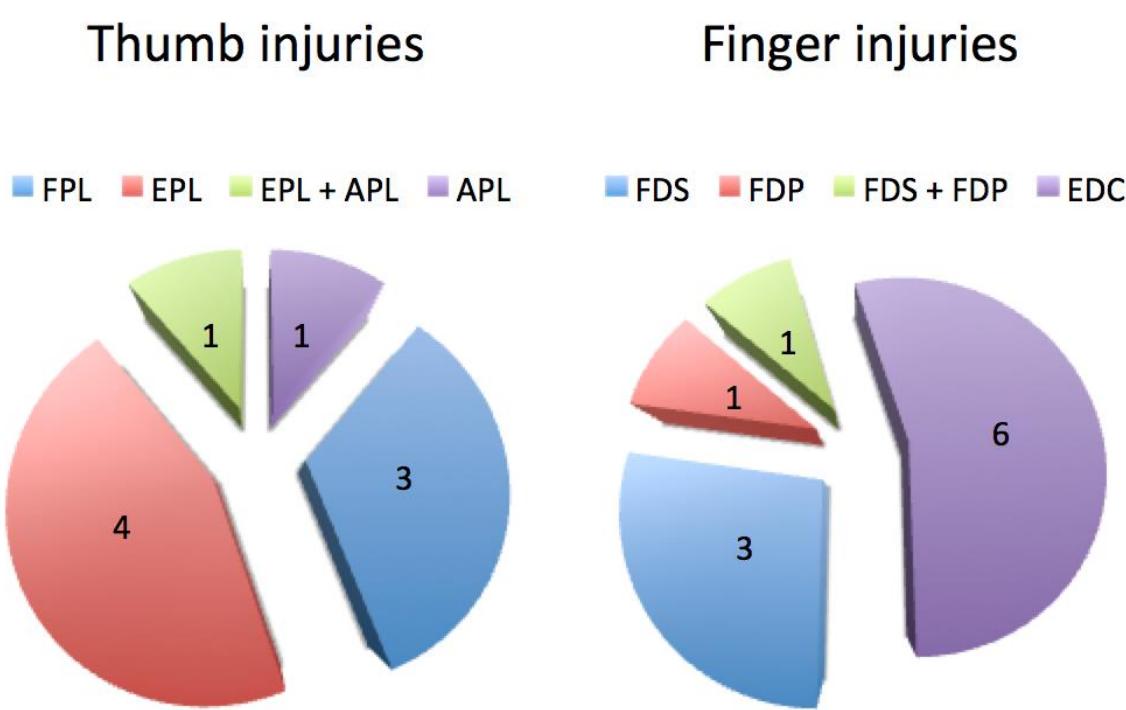
Results

The sample was made up of 20 people aged between 26 and 73 years with a mean age of 44.25

years (SD=12.63). The female to male ratio was 1:4. The dominant hand was injured in 40% ($n=8$) of cases, with right to left ratio of 9:11.

Figure 2 illustrates the distribution of tendon injuries. The thumb was injured in 45% ($n=9$) of cases. 15% ($n=3$) injured the flexor pollicis longus (FPL) in zone T2; the extensor pollicis longus (EPL) was injured in 20% ($n=4$), with half of them injuring zone T4, and the rest injuring zone T2 and T5; one case had injuries to both the EPL and the abductor pollicis longus (APL) in zone T5, and another case injured the APL in zone T3. With regards to the digits, the flexor tendons were affected in 25% ($n=5$) of cases, with 3 cases injuring the flexor digitorum superficialis (FDS), two injuring the tendon in zone 2 and one in zone 3; flexor digitorum profundus (FDP) was injured in zone 2 in one case; another case injured both FDS and FDP in zone 3. Extensor digitorum communis (EDC) tendons of the digits were affected in 30% ($n=6$) of cases, with 4 cases injuring the tendon in zone 2 and the other 2 cases injuring it in zone 5.

Figure 2: Pie charts showing distribution of tendon injuries. See text for abbreviations.



A Kessler suture technique was used in 35% ($n=7$) of cases, while the modified Kessler and interrupted sutures were used in 0.05% ($n=1$) of

cases. In 55% ($n=11$), the suture technique was not mentioned in the operation notes. In 95% ($n=19$) of cases, the protocol of postoperative rehabilitation to

be used was not mentioned in the operation note.

The mean QuickDASH score on initial assessment was 44.66 ($s=8.35$), which improved to 7.95 ($s=10.75$) after 6 months. The work module of the QuickDASH score was 89.47 on initial assessment, improving to 28.94 after 6 months. Paired T-test showed a statistical significant ($p=<0.001$) difference in means between QuickDASH on initial assessment and at 6 months (Table 1). In 4

cases (20%), after 6 months, the perceived disability was severe enough for the person to quit their job or to have severe difficulty at the workplace. Patient satisfaction with outcome of surgery was seen in 75% ($n=15$). With regards to TAM score, 75% ($n=15$) had a good to excellent score, while a fair score and a poor score was achieved in 20% ($n=4$) and 5% ($n=1$) respectively.

Table 1: Paired Student T-test between QuickDASH score when first seen by hand therapist and at 6 months ($N = 20$).

Paired Samples Test

	Paired Differences					t	df	Sig. (2-tailed)		
	Mean	Std. Deviation	Std. Error	95% Confidence Interval of the Difference						
				Mean	Lower	Upper				
Pair 1 QuickDASH score at first seen by hand therapist - QuickDASH score at 6 months	36.704	10.969	2.453	31.571	41.838	14.965	19	5.733 x 10 ⁻¹²		

Pearson's correlation was applied to the data. A negative correlation was seen between the delay (in days) to start physical therapy after surgery and the TAM score $r=-0.650$, $N=20$, $p<0.001$ (Figure 3). Another negative correlation between the delay before starting therapy and the self-assessed perceived disability 6 months after commencement of therapy was achieved $r=-0.650$, $N=20$, $p<0.002$

(Table 2). There was also a negative correlation between the percentage TAM and QuickDASH score 6 months after commencement of therapy $r=-0.831$, $N=20$, $p<0.000003$ (Figure 4).

In summary, the results show that the shorter the delay in starting hand therapy following surgical hand tendon repair was associated with a higher TAM score and a lower QuickDASH score.

Figure 3: Scatter Plot showing the correlation between %TAM score at 6 months and the delay (in days) in starting physical therapy after tendon repair ($N = 20$).

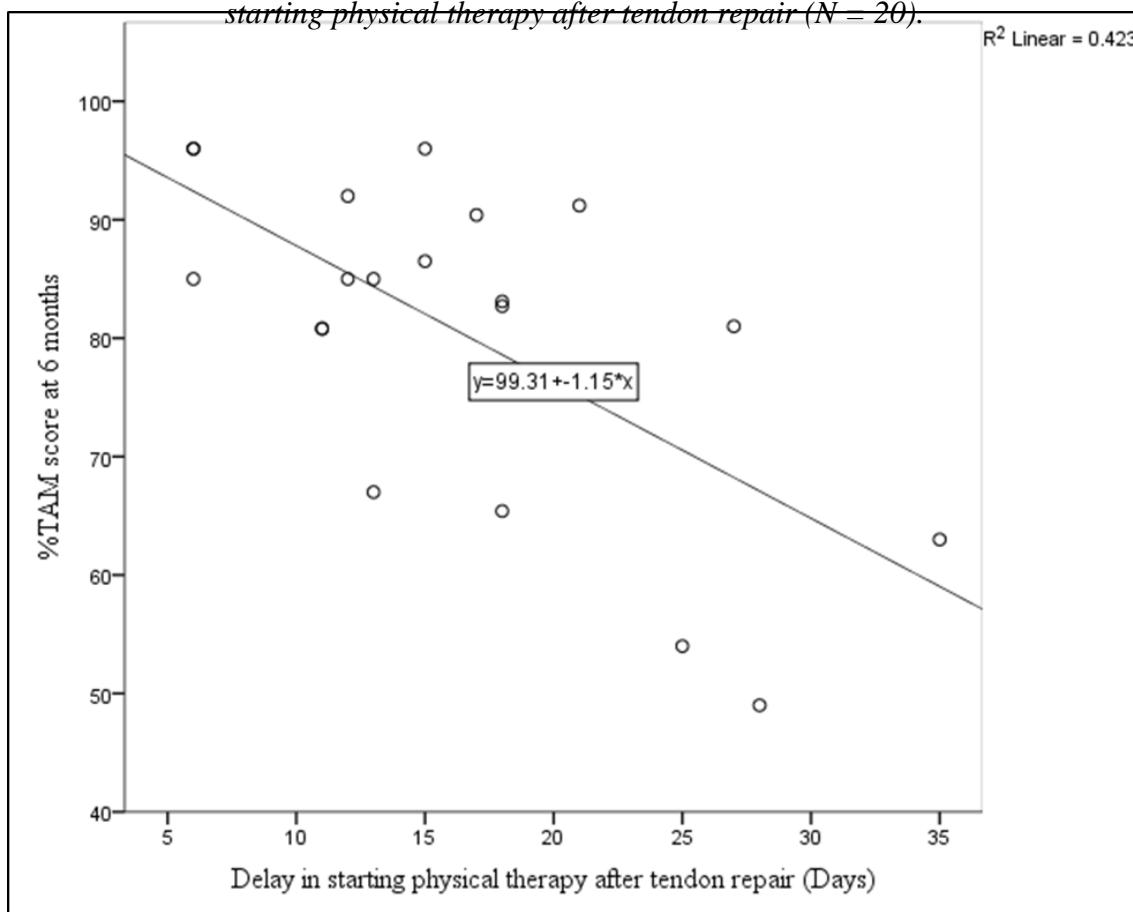
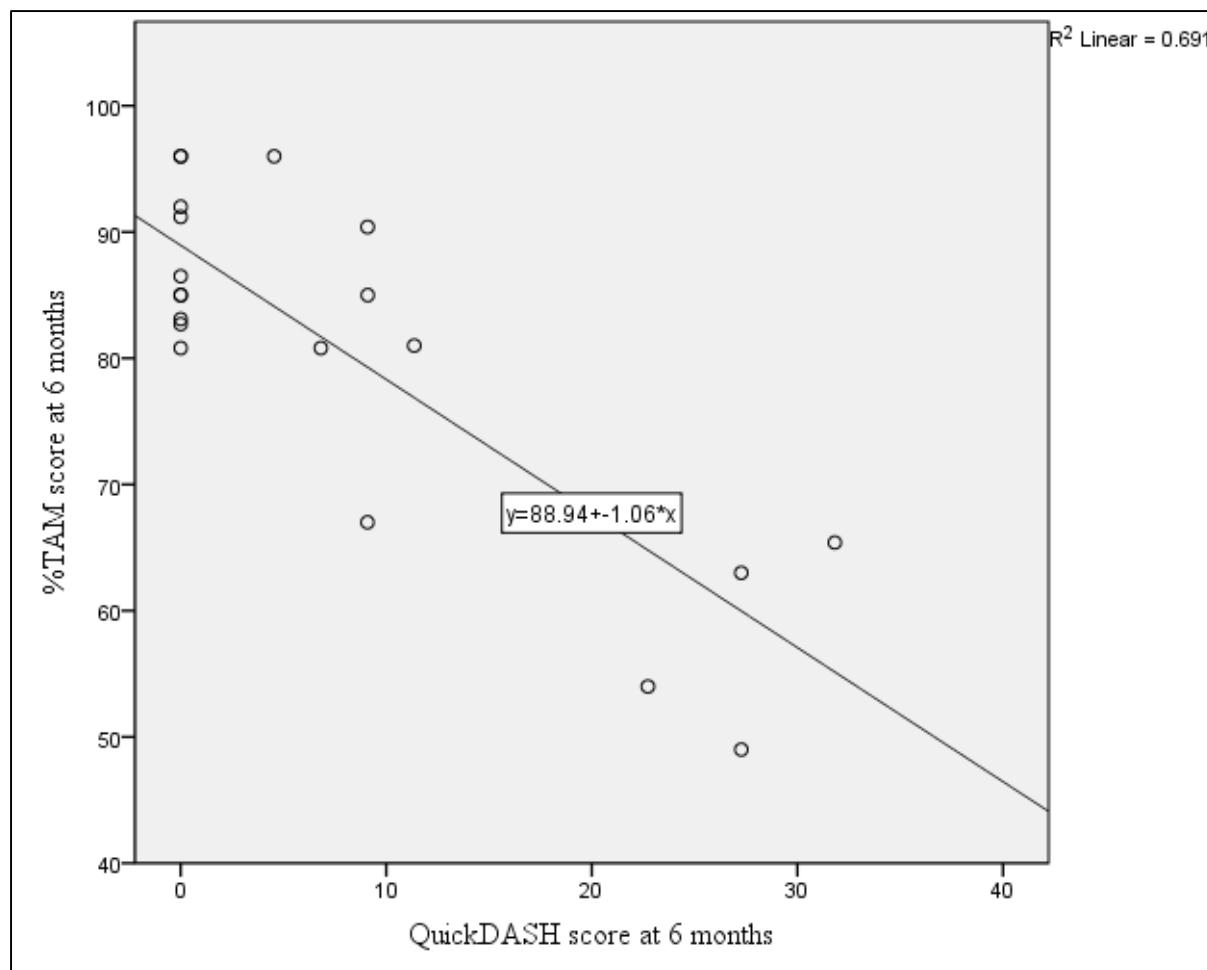


Table 2: Correlation between QuickDASH score at 6 months and the delay (in days) in starting physical therapy following tendon repair.

		QuickDASH Score at 6 months	Delay in starting physical therapy following tendon repair
QuickDASH score at 6 months	Pearson Correlation	1	.627**
	Sig. (1-tailed)		.002
	N	20	20
Delay in starting physical therapy following tendon repair (Days)	Pearson Correlation	.627**	1
	Sig. (1-tailed)	.002	
	N	20	20

**. Correlation is significant at the 0.01 level (1-tailed).

Figure 4: Scatter plot showing the relationship between percentage TAM score at 6 months and QuickDASH score at 6 months (N=20).



Discussion

Early mobilisation following tendon surgery dates back to World War I (1914-1918). Before this war, satisfactory hand tendon repair was rare.⁸ In 1917, Harmer published a paper revealing a new tendon suture.⁹ He wrote that a suture has to be strong enough to permit “very early use”,⁹ or else adhesions limit movement. He also recommended that “no splint is used”,⁹ with active movement commenced “as soon as the patient has recovered from the anaesthetic”.⁹ In 1918, Bunnell also agreed about early rehabilitation, but added that movement has to be applied “with care and judgement”.¹⁰ He discouraged very early movement in the first week, as it hindered healing of the incision and encouraged infection. As no antibiotics were available at that time, the practice was that tendons be repaired by delayed tendon grafting, and not by primary repair. Verdan, Young and Harman and Kleinert reversed this practice and improved postoperative rehabilitation, emphasising

on the immediate mobilisation post-surgical repair.¹¹

There is good evidence in the current literature that early tendon rehabilitation is associated with better results. Hsiao et al.¹² performed a retrospective study on 1,219 participants who underwent flexor or extensor tendon repair. They were divided into 3 groups: early rehabilitation (<1 week), intermediate rehabilitation (1 to 6 weeks), and late rehabilitation (>6 weeks) following surgical tendon repair.¹² Patients who underwent early rehabilitation had the lowest number of secondary surgical repairs and used less rehabilitation resources.¹²

With regards to flexor tendon injuries, the studies performed by Saini et al,¹³ Quadlbauer et al,¹⁴ and Nasab et al¹⁵ focused on early rehabilitation following flexor tendon repairs. Saini et al¹³ looked at flexor tendon repairs in zones 2 to 5 (25 patients), Quadlbauer et al¹⁴ looked at all flexor tendon repairs (115 flexor tendons), whilst Nasab et

al¹⁵ looked at flexor zone 5 tendon repairs (42 patients). They all showed overall good to excellent results with minimal complications.¹³⁻¹⁵

Hall et al¹⁶ published a study comparing immobilisation, early passive motion and early active motion protocols following extensor tendon injuries to zones 5 and 6 in 27 patients. Those with the early active motion achieved a greater active range of motion, less active extension lag and better self-report function score.¹⁶ Hirth et al.¹⁷ compared relative motion splinting with immobilisation in the rehabilitation of extensor tendon repairs in zones 5 and 6. The modified relative motion splinting which enables early mobilisation, gave better range of movement and early return to the workplace.¹⁷

Magnani et al,² performed a study to assess correlation between DASH (disabilities of the arm, shoulder and hand) questionnaire and Total Active Motion (TAM) after flexor tendon repair. A sample of 24 patients was administered the early passive motion protocol following surgical flexor tendon repair. In this study a negative correlation was noted between TAM and DASH score ($r=-0.3809$ to -0.5815 , $P<0.0001$).² Even though the tendons were mobilised early, after 12 weeks finger flexion did not equal the flexion of the contralateral finger.²

In this study traumatic tendon lacerations were most common in previously healthy young to middle aged people. The co-morbidities that were excluded were osteoarthritis, rheumatoid arthritis, neuropathy (peripheral or focal), and diabetes. The first three co-morbidities affect finger range of movement, while diabetes affects wound healing¹⁸ and delays the onset of aggressive hand therapy.

Men had a fourfold increased incidence of tendon injuries as compared to women and this is likely due to the increased prevalence on men in jobs of a construction nature locally. Delay in starting physical therapy post tendon repair resulted in worse TAM score and higher QuickDASH score, while a lower QuickDASH resulted in better TAM score. This confirms all the hypotheses set forth at the beginning of the research. The results are comparable to studies mentioned in the introduction, making the current practice in Malta comparable with other developed countries.

Good communication and handover between the surgeon, therapist and the patient is of paramount importance. However this study found that documentation was very poor both in the operation notes and other entries in the medical records. Important information such as the suturing technique used, and the postoperative rehabilitation required was omitted in most cases, most likely due to a lack of familiarity by the surgeons on the rehabilitation programmes available. This makes the work of the hand therapist difficult, especially in choosing the right rehabilitation protocol for the patient. The outcome of the multidisciplinary team could also be improved if the hand therapist reviews and scores the patient before surgical repair, and ensures an inpatient post-operative review or an early outpatient appointment with a view to starting the rehabilitation early.

This study has a number of limitations. One of the limitations is that the sample size was small ($N=20$), and this makes quantitative studies of specific tendon injuries difficult. Also, this study only recruited eligible individuals who signed a consent form, thus somewhat giving rise to selection bias. Another limitation is that this study included injuries in all hand tendons and was not specific to a particular rehabilitation protocol.

Conclusion

Early rehabilitation was associated with higher TAM score and lower QuickDASH score. This emphasizes the benefit of early rehabilitation following tendon repair. Good communication and handover between surgeon, hand therapist and patient needs to be improved.

To this end, we propose the introduction of a standardised operation report template (Figure 5) for all tendon injuries. A copy of this operation report can be attached to the referral note to the occupational therapy, providing the occupational therapist all the necessary information. The aim is to re-audit these introductions to assess their impact and outcomes. Furthermore, more local studies are needed to compare the types of rehabilitation protocols (especially early active motion with early passive motion), for different types of hand tendons and zones.

Figure 5: Proposed standardised operation report template for all tendon injuries to be used at Mater Dei Hospital



Operation note template Upper extremity tendon surgery

Bugeja M., Mifsud M., Zammit J

Patient name		Age	
ID number		Ward	
Date of surgery		Theatre number	
Procedure			
Lead surgeon			
Assistants			
Scrub nurse			

SURGICAL PROCEDURE

Routine P+D. on hand table. Antibiotics given at induction / in ward (delete as applicable).

Exploration of wound with extension to find distal and proximal ends of tendons, and repair of tendons in zones as follows:

Flexor zones 	Finger flexors <input type="checkbox"/> 1 <input type="checkbox"/> 2 <input type="checkbox"/> 3 <input type="checkbox"/> 4 <input type="checkbox"/> 5	Finger extensors <input type="checkbox"/> 1 <input type="checkbox"/> 2 <input type="checkbox"/> 3 <input type="checkbox"/> 4 <input type="checkbox"/> 5 <input type="checkbox"/> 6 <input type="checkbox"/> 7 <input type="checkbox"/> 8	Extensor zones
Thumb flexors <input type="checkbox"/> T1 <input type="checkbox"/> T2 <input type="checkbox"/> T3 <input type="checkbox"/> T4 <input type="checkbox"/> T5	Thumb extensors <input type="checkbox"/> T1 <input type="checkbox"/> T2 <input type="checkbox"/> T3 <input type="checkbox"/> T4 <input type="checkbox"/> T5		
Suture type and size used for tendon repair was <input type="checkbox"/> Ethibond _____ (write suture size) <input type="checkbox"/> Prolene _____ (write suture size) <input type="checkbox"/> Other _____ <small>(write suture name and size)</small>			
Number of suture strands used in repair <input type="checkbox"/> 4 <input type="checkbox"/> 6 <input type="checkbox"/> 2		<small>(2 strands should be used if justifiable. Write justification here)</small>	
Tendons repaired and percentage required 1. 2. 3. 4. 5.		Other structures damaged and repaired 1. 2. 3. 4.	
Skin suture and splint:			

POST-OP INSTRUCTIONS

Signature

References

1. Soucacos P. Anatomy and biomechanics of the finger joints. In: Bruiser P, Gilbert A, editors. *Finger Bone and Joint Injuries*. First Edit. Martin Dunitz Ltd; 1991. p. 151.
2. Magnani PE, Ferreira AM, da Silva Rodrigues EK, Barbosa RI, Mazzier N, Elui VMC, et al. Is there a correlation between patient-reported outcome assessed by the Disabilities of the Arm, Shoulder and Hand Questionnaire and total active motion after flexor tendon repair? *Hand Ther* [Internet]. 2012 May 18 [cited 2015 Jul 4];17(2):37–41. Available from: http://www.researchgate.net/publication/258139486_Is_there_a_correlation_between_patient-reported_outcome_assessed_by_the_Disabilities_of_the_Arm_Shoulder_and_Hand_Questionnaire_and_total_active_motion_after_flexor_tendon_repair.
3. Amadio PC. Tendon injuries and tendinopathies. In: Terri M. Skirven, Lee Osterman, Jane Fedorczyk PCA, editor. *Rehabilitation of the Hand and upper Extremity*. sixth edit. St Louis: Mosby; 2011. p. 439–44.
4. Burnham JM, Hollister AM, Rush DA, Avallone TJ, Shi R, Jordan JC. Technique for and an anatomic guide to forearm tendon repair. *Tech Hand Up Extrem Surg* [Internet]. 2011 Jun 1 [cited 2016 Mar 14];15(2):125–32. Available from: https://www.researchgate.net/publication/51160237_Technique_for_and_an_Anatomic_Guide_to_Forearm_Tendon_Repair.
5. Institute for Work and Health. The QuickDASH Outcome Measure - Disabilities of the Arm, Shoulder and Hand. [Internet]. 2006 [cited 2015 Jul 1]. Available from: http://dash.iwh.on.ca/system/files/quickdash_questionnaire_2010.pdf
6. Kosmahi E. Goniometry [Internet]. The University of Scranton. Available from: <http://www.scranton.edu/faculty/kosmahl/courses/gonio/index.shtml>.
7. ASSH. The Hand, Examination and Diagnosis. Third Edit. Churchill Livingstone; 1990.
8. Young RE, Harmon JM. Repair of tendon injuries of the hand. *Ann Surg* [Internet]. 1960 Apr [cited 2015 Dec 30];151:562–6. Available from: <http://www.ncbi.nlm.nih.gov/articlerender.fcgi?artid=1613583&tool=pmcentrez&rendertype=abstract>
9. Harmer TW. Tendon Suture. *Bost Med Surg J* [Internet]. 1917 Dec 6;177(23):808–10. Available from: <http://www.nejm.org/doi/abs/10.1056/NEJM191712061772303>.
10. Bunnell S. Repair of tendons in the fingers and description of two new instruments. *Surg Gynecol Obs*. 1918;(126):103–10.
11. Elliot D, Giesen T. Avoidance of unfavourable results following primary flexor tendon surgery. *Indian J Plast Surg* [Internet]. 2013 May [cited 2015 Dec 30];46(2):312–24. Available from: <http://www.ncbi.nlm.nih.gov/articlerender.fcgi?artid=3901913&tool=pmcentrez&rendertype=abstract>.
12. Hsiao P-C, Yang S-Y, Ho C-H, Chou W, Lu S-R. The benefit of early rehabilitation following tendon repair of the hand: A population-based claims database analysis. *J Hand Ther* [Internet]. 2015 Jan [cited 2015 Jun 25];28(1):20–5; quiz 26. Available from: <http://www.sciencedirect.com/science/article/pii/S0894113014001434>.
13. Saini N, Kundnani V, Patni P, Gupta S. Outcome of early active mobilization after flexor tendons repair in zones II–V in hand. *Indian J Orthop* [Internet]. 2010 Jul [cited 2015 Dec 30];44(3):314–21. Available from: <http://www.ncbi.nlm.nih.gov/articlerender.fcgi?artid=2911933&tool=pmcentrez&rendertype=abstract>.
14. Quadlbauer S, Pezzei C, Jurkowitsch J, Reb P, Beer T, Leixnering M. Early Passive Movement in flexor tendon injuries of the hand. *Arch Orthop Trauma Surg* [Internet]. 2015 Dec 11 [cited 2015 Dec 30]; Available from: <http://www.ncbi.nlm.nih.gov/pubmed/26659831>.
15. Mehdi Nasab SA, Sarrafan N, Saeidian SR, Emami H. Functional outcome of flexor tendon repair of the hand at Zone 5 and post operative early mobilization of the fingers. *Pakistan J Med Sci* [Internet]. 2013 Jan [cited 2015 Dec 30];29(1):43–6. Available from: <http://www.ncbi.nlm.nih.gov/articlerender.fcgi?artid=3809199&tool=pmcentrez&rendertype=abstract>.
16. Hall Barbara, Lee Hoe, Page Rohan, Rosenwax Lorna LHA. Comparing Three Postoperative Treatment Protocols for Extensor Tendon Repair in Zones V and VI of the Hand [Internet]. *The American Journal of Occupational Therapy*. 2010 [cited 2016 Jan 6]. Available from: <http://search.proquest.com.ejournals.um.edu.mt/docview/758663831/fulltextPDF?accountid=27934>.
17. Hirth MJ, Bennett K, Mah E, Farrow HC, Cavallo A V., Ritz M, et al. Early return to work and improved range of motion with modified relative motion splinting: a retrospective comparison with immobilization splinting for zones V and VI extensor tendon repairs. *Hand Ther* [Internet]. 2011 Oct 21 [cited 2016 Jan 6];16(4):86–94. Available from: https://www.researchgate.net/publication/258139480_Early_return_to_work_and_improved_range_of_motion_with_modified_relative_motion_splinting_a_retrospective_comparison_with_immobilization_splinting_for_zones_V_and_VI_extensor_tendon_repairs.
18. Ahmed AS, Schizas N, Li J, Ahmed M, Östenson C-G, Salo P, et al. Type 2 diabetes impairs tendon repair after injury in a rat model. *J Appl Physiol* [Internet]. 2012 Dec 1 [cited 2016 Mar 11];113(11):1784–91. Available from: <http://jap.physiology.org/content/113/11/1784.long>.

A review of diabetic patients' knowledge in a high prevalent European country – Malta

Sarah Cuschieri, Daniel Borg, Sean Pace, Francesca Camilleri

Abstract

Education is the first milestone in the care pathway of all diabetic patients. The aim of this study was to assess the educational knowledge and awareness among a diabetic patient cohort and compare this knowledge to a previously conducted study. Acquiring information on diabetes knowledge is essential for both clinicians and policy makers. Interviews using validated questionnaires covering various aspects of diabetes knowledge were conducted among a diabetic cohort between August and September of 2014 at the state hospital in Malta. The majority exhibited correct knowledge on diabetes and related complications. Knowledge levels appeared to have improved and were influenced by gender, type of diabetes and length of diabetes awareness. We conclude that educational approaches should be targeted towards every diabetic individual and should start immediately after diagnosis. This would lead to improved self-care, with a reduction in diabetic complications and a decrease in health-care expenditure.

Keywords

Education, Medical; Diabetes Mellitus; Knowledge; Self Care; Health Expenditures

Introduction

Diabetes mellitus is a growing epidemic that is afflicting every country all over the globe. In 2015, Europe was estimated to have 59.8 million adults diagnosed with diabetes with 193 million having undiagnosed diabetes.¹ Unfortunately diabetes is responsible for a number of general health complications and increases the mortality among those affected. It has been estimated that in Europe, diabetes directly resulted in 627, 000 deaths in 2015.¹

Responsibility for prevention of this disease should be assumed upon by society in general, including the policy makers. Diabetes leads to a decrease in quality of life, with an impact on the social wellbeing and drastically increases health services expenditure. In fact diabetes type 2 alone, contributed to 9% of the total health expenditure in the European region in 2015. The diabetic health expenditure included the provision of health services for preventative and curative means, for family planning activities, nutritional activities and for emergency services.¹

Evidence has shown that education alone, apart from the pharmaceutical and surgical interventions, has a positive impact on the quality of life of these patients.² Therefore adequate knowledge about diabetes is the key for better diabetes care.³ Knowledge is a dynamic subject and challenging to assess. Taking a representative sample of diabetic patients and assessing their knowledge using a number of set questions, is a feasible procedure although to our knowledge this has never been undertaken in a European country (please see details of literature search in Section 4.1.2 below).

Malta is a small island in the Mediterranean sea located between the European and African continents which have both registered a high

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diabetes prevalence for a long period of time.⁴ The last prevalence study performed in 1981 stated that 7.7% of the total population suffered from diabetes type 2.⁵ According to the last International Diabetes Federation Atlas, in 2015 Malta had an estimated diabetes prevalence of 13.9%.¹ The reason behind this drastic prevalence increase could be multifactorial ranging from genetics to different lifestyle exposures.⁶

The primary aim of this study was to evaluate the general educational awareness and knowledge of diabetes in Maltese diabetic patients. The secondary aims were to: assess the impact of knowledge about the disease on the prevalence of diabetes and/to compare current diabetes awareness with that measured in a study performed in 2007.

Method

A clinical study was performed to assess the educational knowledge of diabetic patients on their condition by using a validated questionnaire. The study cohort included all diabetic patients attending the Diabetes Clinic at Mater Dei Hospital, Malta during the summer months (August – September) of 2014. Mater Dei Hospital is the only state hospital in Malta and the vast majority of diabetic patients in the country attend this clinic. Data collection was performed everyday during different consultant-led clinics, until a convenience sample size was obtained. The sample was of similar size and gender distribution to the study performed in 2007.

The questionnaire contained questions covering demographic data and different aspect of diabetes knowledge including: general diabetes knowledge, knowledge on hypoglycemia and its management, physical activity, diet, complications of diabetes and the appropriate plasma glucose level when fasted and postprandial. The questions were picked from open access validated questionnaires.⁷⁻⁹

The questionnaires were distributed to the diabetic patients while they were waiting for their outpatient appointment. The study was explained to every patient by one of the three medical students researchers who were trained on how to conduct interviews without biases by the main author. Those that agreed to participate were requested to sign a

consent form and then given the questionnaire to fill in with the help of the researcher. The same three researchers were responsible for the data collection in order to standardize the data collected.

The inclusion criteria were all patients attending the diabetes clinic at Mater Dei Hospital during the study period. All patients who did not attend the outpatient clinic appointment at Mater Dei Hospital or attended a primary health or private clinic were excluded from this exercise.

All the data was transferred onto a spreadsheet and double-checked by all the researchers in order to minimize human errors. Statistical analyses were performed by BMI SPSS v. 21 for Mac and Excel 2011 for Mac. A diabetic score was elaborated for the questions regarding general diabetes knowledge, symptoms of hypoglycemia, management of hypoglycemia and physical activity. For every correct response, a nominal value of 1 was assigned, the sum of which was calculated. The scores of the different questions were analyzed as follows; a student t-test for gender, ANOVA for education and the different types of diabetes, Kruskal-Wallis for location they live in and Pearson's correlation for the length of diabetes awareness in relation to the diabetic scores obtained for each question. All tests were conducted with a confidence interval of 95%. p-values of less than 0.05 were considered as statistically significant associations.

The questions on physical activity and complications of diabetes were compared to a study by Cutajar⁷ which had assessed these factors among the Maltese diabetic population in 2007.

Ethical permission was obtained from the University of Malta Ethics Research Committee. Authorization to distribute the questionnaires was obtained from the diabetes clinic consultants and nursing officer along with the Mater Dei Hospital administration and data protection office.

Results

The study was based on a cohort of 130 patients (62 male, 68 female) with a mean age of 60.42 (SD: 12.7) years. Table 1 illustrates the demographic data of the population under study.

Table 1: Demographic data of the sample population

Variable	No. of patients (n=130)	%		
Sex				
Male	62	48%		
Female	68	52%		
			Gender	
			Male	Female
Age (years)				
≤30	3	2.3%	1	2
31 – 40	6	4.6%	2	4
41 – 50	15	11.5%	8	7
51 – 60	30	23.1%	16	14
61 – 70	55	42.3%	25	30
≥71	21	16.2%	10	11
Educational Level				
Illiterate	1	1%	0	1
Primary	28	22%	11	16
Did not finish Secondary	16	12%	6	10
Finished Secondary	51	39%	25	26
Sixth form	17	13%	11	6
Undergraduate Courses (University, MCAST)	5	4%	4	1
Postgraduate	12	9%	4	8

The majority of the patients suffered from type 2 diabetes, although 41% of the study population did not know what type of diabetes they suffered from. Table 2 illustrates the different diabetes types as perceived by the patients and interviewed during the study period. The patients had been aware of their condition for a mean of 9.94 years (SD: 8.9) and the majority of them had good knowledge on diabetes. Table 3 shows the general diabetes knowledge among the study population. Diabetes knowledge was rated as into a score and was found to be statistically significantly related to gender ($p=0.002$), duration of diabetes awareness ($p=0.02$) and to the type of diabetes the patients suffered from ($p=0.02$) but not statistically significant related to the location the patient lived in, nor to their educational level ($p=0.723$; $p=0.427$ respectively). Table 4 illustrates the different patients' habitual localities. There was an excellent level of knowledge when it came to the desired fasting plasma glucose level and 2-hour postprandial glucose level a patient should aim for, with 73% and 48% demonstrating a correct response respectively.

When questioned about hypoglycaemia symptoms, 67% responded that feeling thirsty is a relevant symptom and 44% thought that polyuria is also a relevant symptom. It was clear that respondents often confused the significance of hyperglycaemic and hypoglycaemic symptoms. Whether this was due to lack of educational knowledge or to misunderstanding of the question is not clear. There was also a misconception by 83% of the population that the immediate treatment of hypoglycemia is to eat a bar of chocolate or biscuits, when in actual fact this is not correct (Table 5).

A list of different common conditions was provided to assess whether the diabetic patients

knew which of the complications might arise if diabetes is uncontrolled. Interestingly, for every condition the majority of the patients answered correctly especially for the diabetic microvascular and macrovascular complications. Table 6 shows the different complications and the answers provided by the study population.

The majority of the diabetic patients knew about the importance of physical exercise and 58% were aware that at least 30 minutes of daily physical activity is required. A statistically significant relation was observed between physical activity knowledge and the type of diabetes the patients suffered from ($p=0.021$).

By providing a list of different dietary foods we evaluated the educational knowledge of how healthy each item was deemed by the patients. Table 7 lists the different food items and whether the patients knew correctly the health benefits of each item. It was noted that 65% thought incorrectly that cereals were healthier than other type of food; same with chicken (95%) and light yogurt (70%), where in actual fact these items fall under moderate food items category, meaning they should be consumed in moderation.

Table 2: The different types of diabetes as perceived by the patient

Type of Diabetes	No. of patients (n=130)	%	Gender	
			Male	Female
Diabetes type 1	11	8%	5	6
Diabetes type 2	62	48%	29	33
Do not know	53	41%	28	25
Others	4	3%	0	4

Table 3: Questions on diabetes knowledge distributed among the study population (n=130) and their corresponding answers

Item	Correct (%)	Incorrect (%)	Do not know (%)
Diabetes can be controlled with treatment	127 (98)	3 (2)	0 (0)
A little glucose in the urine is a good thing	77 (59)	19 (15)	34 (26)
Diabetes is likely to go away after a while	109 (84)	20 (15)	1 (1)
Stressful experiences can affect blood glucose levels	122 (94)	3 (2)	5 (4)
Blood glucose levels do not affect your chances of developing complications	111 (85)	13 (10)	6 (5)

Table 4: Illustrates the locality distribution of the participating diabetic patients

Locality	Number	%
Attard	3	2.31
Balzan	2	1.54
B'Kara	6	4.62
Bormla	1	0.77
Bugibba	2	1.54
Dingli	2	1.54
Fgura	2	1.54
Fleur De Lyns	1	0.77
Floriana	2	1.54
Ghaxaq	1	0.77
G'mangia	1	0.77
Gzira	4	3.08
Dingli	2	1.54
Hal Safi	2	1.54
Hamrun	7	5.38
Ibragg	2	1.54
Kappara	2	1.54
Luqa	1	0.77
Marsa	1	0.77
Marsascala	2	1.54
Marsaxlokk	1	0.77
Mellieha	3	2.31
Mosta	3	2.31
Msida	3	2.31
Mtarfa	1	0.77

Cont. Table 4: Illustrates the locality distribution of the participating diabetic patients

Locality	Number	%
Nazzar	2	1.54
Poala	1	0.77
Pembroke	2	1.54
Pieta'	1	0.77
Qawra	1	0.77
Qormi	5	3.85
Qrendi	1	0.77
Rabat	3	2.31
Rahal gdid	4	3.08
Salina	2	1.54
San Giljan	4	3.08
San Gwann	4	3.08
San Pawl	1	0.77
St Lucia	1	0.77
Santa Venera	3	2.31
Senglea	2	1.54
Siggiewi	4	3.08
Sliema	4	3.08
St Andrew's	1	0.77
Ta Xbiex	2	1.54
Tarxien	3	2.31
Xghajra	1	0.77
Zabbar	8	6.15
Zebbug	3	2.31
Zejtun	6	4.62
Zurrieq	4	3.08
Total	130	100

Table 5: Questions on knowledge about hypoglycaemia which were distributed among the study population (n=130) and their corresponding replies

Symptoms of Hypoglycemia	Correct (%)	Incorrect (%)	Do not know (%)
Slurred speech	75 (85)	17 (13)	38 (29)
Feeling very thirsty	27 (21)	87 (67)	16 (12)
Sweating	97 (75)	11 (8)	22 (17)
Dizziness	107 (82)	14 (11)	9 (7)
Confused thinking	87 (67)	19 (15)	24 (18)
Passing more urine than usual (Polyuria)	39 (30)	57 (44)	34 (26)
<hr/>			
Immediate management of Hypoglycemia	Correct (%)	Incorrect (%)	Do not know (%)
Have a sugary drink immediately	127 (98)	2 (2)	1 (1)
Eat a bar of chocolate or some biscuits immediately	20 (15)	108 (83)	2 (2)
Treat hypo and rest for 15 minutes	109 (84)	7 (5)	14 (11)

Table 6: Questions about diabetes complications knowledge which were distributed among the study population (n=130) and their corresponding answers

Diabetes Complications	Correct (%)	Incorrect (%)	Do not know (%)
Asthma	72 (55)	16 (12)	42 (32)
Poor circulation of the feet and hands	124 (95)	1 (1)	5 (4)
Heart attack	124 (95)	3 (2)	3 (2)
Back pain	55 (42)	27 (21)	48 (37)
Eye problems	126 (97)	1 (1)	3 (2)
Bronchitis	72 (55)	13 (10)	45 (35)
Kidney problems	111 (85)	9 (7)	10 (8)
Arthritis	69 (53)	35 (27)	26 (20)

Table 7: Correct answers on dietary products health value

Food Item	% Correct
Rice	28
Chocolate	96
Cheesecake	99
Fish	93
Cereal	35
Fresh grapes / figs	18
Oranges and apples	43
Pasta	56
Fruit Juice	19
Light yogurt	30
Bread	67
Soft cheese	65
Chicken	5
Potatoes	35
Vegetables	97

Discussions and Conclusion

Discussion

Education is key to the successful management and prevention of complications that may arise from diabetes mellitus. Knowledge is also important for sufficient self-care by patients.^{9,10} The objectives of the study were to evaluate different aspects of educational diabetes knowledge among Maltese diabetic patients and to assess whether there have been any improvements over the years.

Comparison between our study and Cutajar study⁷

In 2007, a study ($n=110$) was performed to assess a number of factors, one of which was the knowledge about the disease among diabetics attending the Diabetes Clinic in two different health centers in Malta. There are significant methodological differences between the two studies. Ours was carried out in a centralized hospital setting whereas the previous study had been carried out in the primary health care setting. A different population group was studied and percentage comparisons were made between both studies. Unfortunately the samples could not be matched in terms of age and gender due to lack of such information present in the 2007 study.

Our findings show that the general awareness of the majority of participants in the current study population was good, with 73% aware of the correct fasting plasma glucose value unlike in the 2007 study group where 55% were unable to give an approximate value. In our study population it was found that there was better awareness of diabetes-related complications than the other study. 95% of our participants knew that cardiac circulatory pathology could be directly attributable to diabetes whereas in the other study only 74.5% responded correctly. In the 2007 study, arthritis and asthma were incorrectly linked with diabetes (83.6% and 66% respectively), while in our study only 12% and 27% respectively answered incorrectly. Regarding the recommended level of physical activity there was a striking difference. In 2007, 54% of patients were unaware of the basic requirements, whereas only 2% in our population sample were not updated with the current exercise regimes advised.

It is encouraging to note that on the whole, Maltese diabetic patients are well educated on the general aspects of this common disease. There is still some confusion regarding the different

symptoms attributable to hypoglycaemic versus hyperglycaemic episodes. These should be common knowledge to all diabetics, as they should be trained how to spot and manage these symptoms in an acute scenario.

Diabetes knowledge and the way forward

The type of diabetes a patient suffers from, the gender and the length of time the patients were aware of their condition appear to be predictors of diabetes knowledge in Malta. This suggests that education should be readily available to each diabetic patient irrelevant of the type of diabetes they suffer from. All efforts should be taken to educate these patients about their disease and on how to look out for any possible complications related to the disease. Also, improving knowledge among diabetic patients will improve self-care. Achieving a good self-care level implies that, patients need to gain knowledge on all aspects of their condition ranging from risk factors to complications and management.¹¹ Complications development would decrease if patients were capable of taking care of their condition sufficiently. This is not only beneficial for the patient's quality of life but it would also have a positive economic impact on the health care system and a decrease in the productivity loss to society, brought about by associated complications and ill health.¹² Therefore it is encouraged that investing in educational sessions for diabetic patients would lead to long-term benefits from a psychosocial and likely to lead to reductions in health care expenditure. It is important to keep an open eye for knowledge barriers that sometimes arise from health care professions¹³⁻¹⁴, for organizational interventions¹⁵ as well as from patients themselves.¹⁶ It is the duty of all health professions (doctors, nurses, pharmacists, podiatrists, dietitians) that at every encounter with diabetic patients, they should counsel and educate individual patients. Also regular educational updates should be organized at different localities, making educational sessions more accessible to all patients as well as reducing the stigma associated with hospital-based care.¹⁷

This study, to the best of our knowledge, is the first to discuss diabetes knowledge and awareness in a European country after a Google Scholar search was performed in the end of

December 2014. It has shown that diabetes knowledge may have actually improved even though the prevalence of diabetes along with complications within the country has increased. The reason behind the improved diabetes knowledge could be from the frequent occurrence of this disease within families, which may influence diabetes knowledge. This is consistent with Foma et al.¹⁸ who found a correlation between diabetes knowledge and having a family member with diabetes. Another reason could be the increased coverage of aspects of diabetes care and prevention by the social media and in televised diabetic educational programs and in the national newspapers are likely to have increased public awareness. Such initiatives should be developed further. In Malta, the information and aids give to our diabetic patients by the local diabetes association helped in the level of knowledge achieved by participants. It is also suggested that from a small age, children should be made aware of this chronic disease, its symptoms, its complications and most importantly the measures that prevent developing this disease.

Study Limitation

Only patients attending during the months of August and September of 2014 at Mater Dei Hospital were studied. Patients attending health centers or private diabetic clinics were excluded. The study was performed during the summer; during which period the patient's attendance rate decreases due to the hot weather. Also many of the consultants take their annual leave during this period. This may have affected the number of daily patient encounters as well as the demographic and diabetes status of the patients attending. The population under study was different from the population under study by Cutajar's study in 2007, so results and comparisons may not be totally representative. Since this is a study on knowledge, one needs to keep in mind that patients may have answered randomly without really understanding the question or because of lack of knowledge. Although the researchers were constantly present during the interview and enquired whether any clarifications were required, patients may still have not understood the question.

Conclusion

The level of knowledge and awareness about diabetes mellitus in Malta is fairly good considering that the majority of the participants answered correctly. Comparison with a similar study performed in the same country shows knowledge may have improved over time. This is an encouraging finding especially when one considers that the prevalence of diabetes has increased over the years, further research is therefore required to find the etiology behind this epidemic within the Maltese islands⁴.

Knowledge levels appear to be influenced by gender, the type of diabetes that participants suffer from and the length of diabetes awareness. This implies that it is essential that educational approach is targeted to every diabetic and that they should start immediately following diagnoses. This would lead to a better self-care, with a reduction in diabetic complications and to a decrease in health care expenditure.

Reference

1. International Diabetes Federation. IDF Diabetes Atlas 7th edn. Brussels, Belgium : International Diabetes Federation. 2015.
2. Tamayo T, Rosenbauer J, Wild SH, Spijkerman Am, Baan C, Forouhi NG et al Diabetes in Europe: an Update. *Diabetes Res Clin Pract.*, 2014; 103(2), 206 – 217.
3. Baser RS, Richardson DL, Hollerworth HJ. Education in the treatment of diabetes. In: Joslin P, Kahn CR, Weir GC editors. *Joslin's diabetes mellitus* 13th ed. Philadelphia: Lea and Febiger. 1994; 404 - 414.
4. Cuschieri S, Mamo J. Malta: Mediterranean Diabetes hub - a journey through the years. *Malta Medical Journal*, 2014; 26 (03): 27 - 31.
5. Katona G, Aganovic I, Vuskan V, Skrabalo Z. National Diabetes Programme in Malta: Phase 1 and II Final Report. World Health Organization 1983.
6. Tuomilehto J, Lindstrom J, Eriksson JG, Valle TT, Hamalainen H, Ilanne-Parikka P et al. Prevention of type 2 diabetes mellitus by changes in lifestyle among subjects with impaired glucose tolerance. *The New England Journal of Medicine* 2001; 344(18): 1343 - 1350.
7. Cutajar, J. An evaluation of type 2 diabetes care in the primary care setting *Malta Medical Journal*, 2008; 20(03): 21 - 31.
8. HIS: Health Interview Survey. Department of Health Information and Research Strategy and Sustainability Division Ministry for Health Elderly and Community Care. Malta 2008
9. Speight J, Bradley C. The ADKnowl: identifying knowledge deficits in diabetes care. *Diabetic Medicine* 2001; 18: 626 - 633.
10. Caliskan D, Ozdemir O, Ocaktan E, Idil A. Evaluation of awareness of Diabetes Mellitus and associated factors in four health center areas. *Patient Education and Counseling*. 2006; 62: 142 - 147.

Original Article

11. Piette, J. The Effectiveness of Diabetes Self-Management Education; An overview of published studies. . Retrieved from Centre for Practice Management and Outcomes Research, VA Ann Arbor Health Care System and the Department of Internal Medicine, University of Michigan, 2006
12. World Health Organisation. Prevention of diabetes mellitus. WHO Technical Report Series, 844, Geneva. 1994
13. Pill R, Scott NCH, Rollnick SR, Rees M. A randomised controlled trial of an intervention designed to improve the care given in general practice to type 2 diabetes patients: patient outcomes and professional ability to change behaviour. . Family Practice 1998; 15: 229 - 235
14. Wylie G, Hungin APS, Neely J. Impaired glucose tolerance: qualitative and quantitative study of general practitioners' knowledge and perceptions. . British Medical Journal, 2002; 324: 11909.
15. Renders CM, Griffin S, Valk GD, Wagner EH, Eijk JTHM, van Assendelft WJJ. Interventions to improve the management of diabetes mellitus in primary care, outpatient and community settings. The Cochrane Database of Systemic Reviews, Issue 4. art. No. : CD001481. 2000
16. Marrero DG, Kakos Kraft S, Mayfield J, Wheeler ML, Fineberg N. Nutrition management of type 2 diabetes by primary care physicians. J Gen Intern Med, 2000; 15: 818 - 821.
17. Ministry for Health the Elderly and Community Care. Diabetes: A National Public Health Priority 2015 - 2020. Proposal for a National Strategy for Diabetes. 2015
18. Foma MA, Saidu Y, Omoleke SA, Jafali J. Awareness of diabetes mellitus among diabetic patients in the Gambia: a strong case for health education and promotion. BMC Public Health 2013; 13, 1124.

Video-EEG Long Term Monitoring as a new service at Mater Dei Hospital

Gilbert Gravino, Bernard Galea, Doriette Soler, Norbert Vella, Josanne Aquilina

Abstract

Introduction: Video-EEG long-term monitoring (LTM) was introduced into Mater Dei Hospital (MDH) in May 2012. The audit aims to evaluate LTM in terms of diagnostic outcomes and impact on patient management.

Methods: Analysis was carried out after retrospective review of 30 inpatients who underwent LTM at MDH between May 2012 and May 2014. 31 LTM sessions were performed. Referrals were made by 3 consultant neurologists. LTM and medical records were compared to evaluate whether LTM determined a change in diagnosis and how this affected management outcomes.

Results: Patient ages ranged from 3 months to 73 years (35.5% paediatric cases) (16 male, 15 female studies). The most common indication was for uncontrolled seizures (54.8%), followed by suspected non-epileptic seizures (NES) (29%). The average hospital stay was 2 days for paediatric patients and 5 for adult cases. Major monitoring interruptions were recorded in 5 paediatric and 1 adult case. Comparing pre- with post-LTM diagnosis showed that the investigation changed or identified a new diagnosis in 38.7%, confirmed the diagnosis in 29%, and was inconclusive in 32.3% (inconclusive in 45.5% of paediatric cohort and 25% of adult cohort). It led to medication optimisation in 38.7% and neuropsychiatry referrals in 22.6%. The remaining were unchanged, not followed up or referred for other tests. None were referred for surgery.

Conclusion: LTM is an important tool which influenced patient management through changes in medication or referrals in 64.5% of cases. Continuous evaluation of the techniques used and resources available is recommended to increase the yield of conclusive LTM studies.

Keywords

epileptic seizures, non-epileptic seizures, video-EEG monitoring.

Introduction

Long term Video-Electroencephalography (EEG) Telemetry Monitoring (LTM) combines two investigative approaches, video imaging and EEG recording, which are viewed simultaneously and in synchrony (Figure 1). This technique was initially used exclusively in specialised units and only reserved for specific circumstances. However, advancements lead to more readily available equipment allowing its introduction into different clinical settings which now include tertiary hospitals, general hospitals, and outpatient clinics.¹ The practice has also been introduced into Mater

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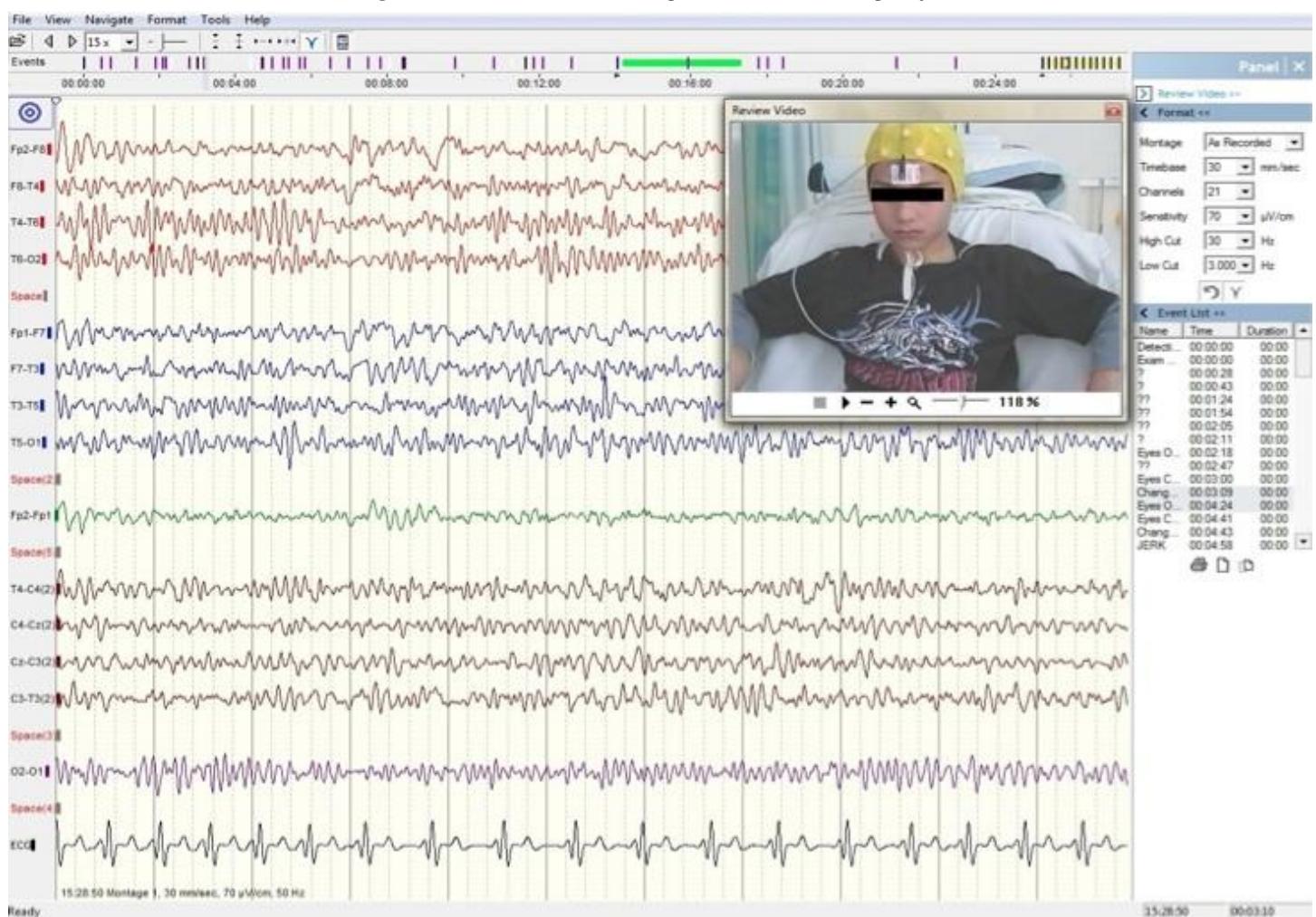
Dei Hospital, Malta since May 2012, where inpatient LTM is being used by the neurologists for diagnostic purposes.

The consensus definition by the International League Against Epilepsy (ILAE) and the International Bureau for Epilepsy (IBE) explains that an epileptic seizure (ES) is the “transient occurrence of signs and/or symptoms due to abnormal excessive or synchronous neuronal activity in the brain”.² NES refer to paroxysmal changes in behaviour mimicking true epileptic seizures, but have no electrophysiological correlate (not associated with abnormal electrical discharges in the brain) or clinical evidence for epilepsy.³⁻⁶ These can either be due to organic causes or due to

psychogenic causes. Organic causes of NES include syncope, motor tics, transient ischaemic attacks, narcolepsy, hemiplegic migraine, paroxysmal vertigo, cardiac arrhythmias and hypoglycaemia.⁷ Psychogenic NES (PNES) are known as such due to their emotional and psychological nature.⁶

Video-EEG LTM can potentially help in the prevention of misdiagnoses and therefore also prevent inappropriate treatment regimens. This study aims to evaluate the usefulness of LTM in terms of its indications, its diagnostic outcomes and its role in influencing patient management. It is also intended to help establish the extent to which LTM is achieving its expected outcomes.

Figure 1: Video -EEG Long Term Monitoring Software



Methods**Video-EEG LTM Protocol**

After an LTM referral to MDH, both adult and paediatric patients are admitted to the neuromedical ward (NMW) which has the necessary facilities. During their stay they are attended continuously by family members and nursing staff. Upon admission each patient undergoes a detailed neurological examination. The patient is placed in a single room where the LTM equipment is set up. Viasys Healthcare system is used for neurophysiological monitoring and NicVue is the software that enables processing of data. Equipment includes the wall mounted cameras which are connected to a central server and EEG monitoring using the 10-20 international system for electrode placement. The video and EEG signals are displayed simultaneously for online observation. All data is recorded in a digitally referential format and then the montage is reformatted for later review. Automated computer detection software allows identification of interictal epileptiform discharges, which greatly reduces the amount of raw data that need to be reviewed for reporting purposes. The patient is also given an event button to activate when an event is experienced. This helps notify medical staff so that they can witness the live event and ensures video-EEG review of that episode.

During recording some patients are subjected to potential epileptic triggers which are also used in conventional EEG monitoring. These include hyperventilation, photic stimulation and sleep deprivation. Tapering of anticonvulsant medication is used in very few cases and placebo drug administration has never been used locally.

The referential video-EEG montage is reviewed and reported by the referring consultant neurologists.

Data Collection

The study was approved by the ethics committee at MDH. A retrospective review of 30 inpatients who underwent LTM at MDH between May 2012 and May 2014 was carried out. Over this 2 year period, 31 VEM sessions were performed, with one patient having done the LTM twice. All patients were referred for monitoring by 3 consultant neurologists at MDH; 2 consultant adult neurologists and 1 consultant paediatric neurologist. The Video-EEG results and medical records were used to collect data on a structured proforma for

comprehensive data collection. The data was evaluated using descriptive statistical analysis and the results are expressed as absolute numbers and percentages.

The outcomes were classified as 'conclusive' (successfully diagnosing ES or NES) or 'inconclusive' (uneventful sessions or those with inability to clarify the nature of events).

Results and discussion

Adding videography to EEG is advantageous since it allows correlation between clinical events and EEG activity. The simultaneous recordings and playback of the EEG and clinical events facilitates review and specialist discussions, thereby yielding better diagnostic outcomes.⁸ LTM has also been regarded as 'an important auxiliary diagnostic instrument in epilepsy'.⁹ However, this method of evaluating patients is resource intensive and also has its disadvantages which must be recognised in order to avoid its unnecessary use. These include the high costs associated with hospital admission, patient discomfort, the fact that it is highly time consuming and the need of highly trained staff to manage the equipment during the procedure.¹⁰⁻¹¹

This audit included a total of 30 patients. One patient had the LTM study performed twice for different indications. 64.5% ($n=20$) of LTMs were performed on adults and the other 35.5% ($n=11$) were paediatric patients (< 18 years). The age ranged from a 3 month infant to 73 years. In total, 16 male studies and 15 female studies were performed. In many of the previous study reports, women constituted the majority of the patient population undergoing LTM.¹²⁻¹⁷ Lobello et al. (2006) suggested that this may represent a selection bias on the part of clinicians, such that more women are suspected of having PNES and are therefore monitored for this purpose.¹² However, data collection from this audit is not in keeping with this observation since there was one more male LTM study than female study. In fact, the patient having the LTM done twice was male, which makes the actual male to female patient ratio 1:1.

Reduction of anticonvulsant therapy

The reduction of anticonvulsant therapy was only implemented in two LTM studies (6.5%). One was a 27 year old patient known to suffer from complex partial seizures which had increased in frequency and was on Sodium Valproate,

Topiramate, Levetiracetam, and Pregabalin. The latter was stopped on days 3 to 5. This patient had a habitual clinical event after withdrawal but was diagnosed with NES. The other was a 21 year old patient with uncontrolled seizures who was on Sodium Valproate and Methylphenidate. The former was stopped on days 4 to 5. This patient also had a clinical event after drug withdrawal but no significant EEG changes were recorded and the LTM outcome was inconclusive.

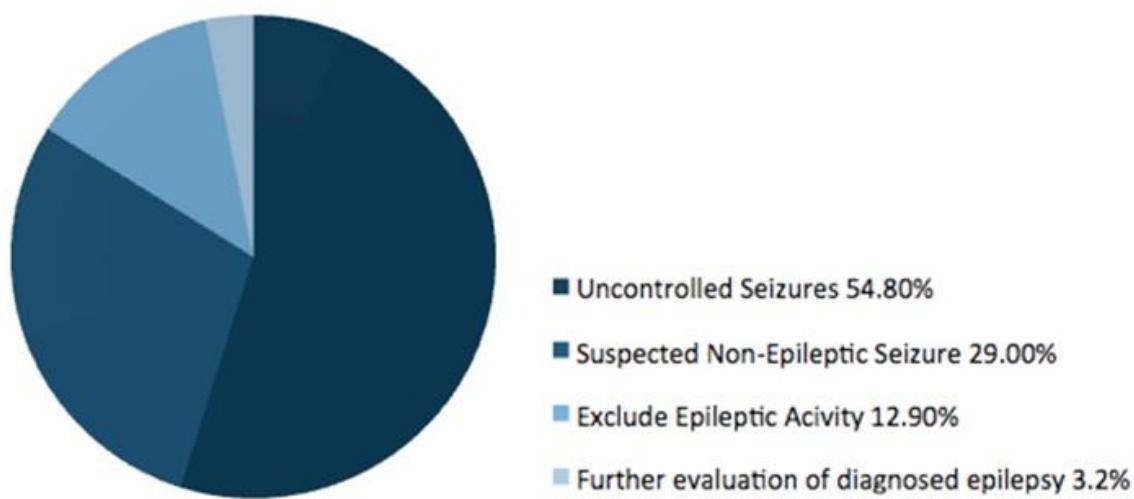
A study by Risvi et al. (2014) reported that combined sleep deprivation and protocol driven withdrawal of antiepileptic medication is a safe and effective investigative technique with no adverse long-term sequelae. However, some other LTM

studies reported no improvement in recoded events when withdrawing drugs.¹⁸ Chen et. Al (1995) reported that there was no statistical difference in the rate of capturing habitual events between children with and without antiepileptic drugs withdrawn.¹⁹

Indications for LTM studies (Figure 2)

The most common indication for LTM in this audit was uncontrolled seizures (54.8%, $n=17$), followed by suspected NES (29%, $n=9$). The remaining 16.1% ($n=5$) of LTMs were indicated for other purposes; 'exclude epileptic activity' (12.9%, $n=4$) and to acquire a baseline for frequency and duration of seizures before starting a new treatment (3.2%, $n=1$).

Figure 2: Indications for Video -EEG Long Term Monitoring



As the availability of this diagnostic tool became more widespread, indications for its use have also increased. Generally, studies report that the most common indications are the diagnoses of epilepsy syndrome, identifying the nature of other paroxysmal events and diagnose non-epileptic causes, quantifying the frequency and duration of seizures, and identifying candidates for surgery.^{1,20} The majority of indications in many centres are in fact intended to differentiate between true epileptic seizures due to epilepsy syndrome ES and NES.¹³

No patients at MDH were referred for LTM as potential surgical candidates since this service is not available locally. However, this is a major indication in other institutions for highly selected patients with intractable epilepsy where they may also be investigated with intracranial telemetry.²¹ Intracranial telemetry is performed for localization

of the ictal onset zone or functional mapping.²² The rationale for surgical treatment is excision of the epileptic zone (EZ).

Duration of LTM studies

The length of stay (LOS) in hospital for the LTM studies ranged from a minimum of 1 day to a maximum of 5 days. All adult cases were at least 3 days long. 5 day studies were performed in a total of 19 (61.3%) LTMs, including both adults and paediatric cases. The estimated average LOS for all the cohort was 4 days. It was 2 days for paediatric patients alone and 5 days for adult cases. Major monitoring interruptions (defined by the patient having to leave the hospital and then return to continue the monitoring) were recorded in 6 cases, 5 of which were paediatric cases.

These results are in keeping with the LOS

reported by other studies. In many centres the average LOS for children (adolescents aside) is 1.2–1.5 days, whereas 3–4 days are more typical LOS for adults (including the elderly).¹ Given the shorter hospital stay for paediatric cases, several centres have reported on the utility of using Video-EEG in the outpatient setting.^{11,23} Nordli (2006) suggests that adding a brief video to a routine EEG can increase the diagnostic yield, particularly when there are frequent paroxysmal events.¹

Capturing events

Overall, 80.6% ($n=25/31$) of LTMs recorded some sort of event (clinical event or significant EEG changes). In turn, only 32% ($n=8/25$) of these showed both clinical changes and abnormal EEG findings. Some clinical phenomena occurred without any EEG changes and *vice versa*. In fact, 71% ($n=22/31$) of cases reported a clinical event during the LTM and only 35.5% ($n=11/31$) recorded an actual EEG event. The rate of capturing seizures or clinical habitual events varies between studies. An adult study by Lobello et al. (2006) reported an overall capturing rate of 83.9%, whereas capturing rates in paediatric studies range from 53% to over 80%.^{1,11,19,24-26} The difference in reported rates may be attributed to multiple factors such as frequency of the habitual events and adjustment of anti-epileptic medications.²⁴ In paediatric studies it has been suggested that selection of children with daily seizures is an important factor associated with a high chance of

capturing habitual events.^{11,19}

Overall, 64% ($n=16/25$) of patients who had an event did so during the first 2 days of admission. 48% ($n=12/25$) had their first event on day 1 and 16% ($n=4/25$) had their first event on day 2. This is comparatively lower to the results in a study by Lobello et al. (2006) which reported 87.7% of LTMs having their first event in the first 2 days of admission.¹

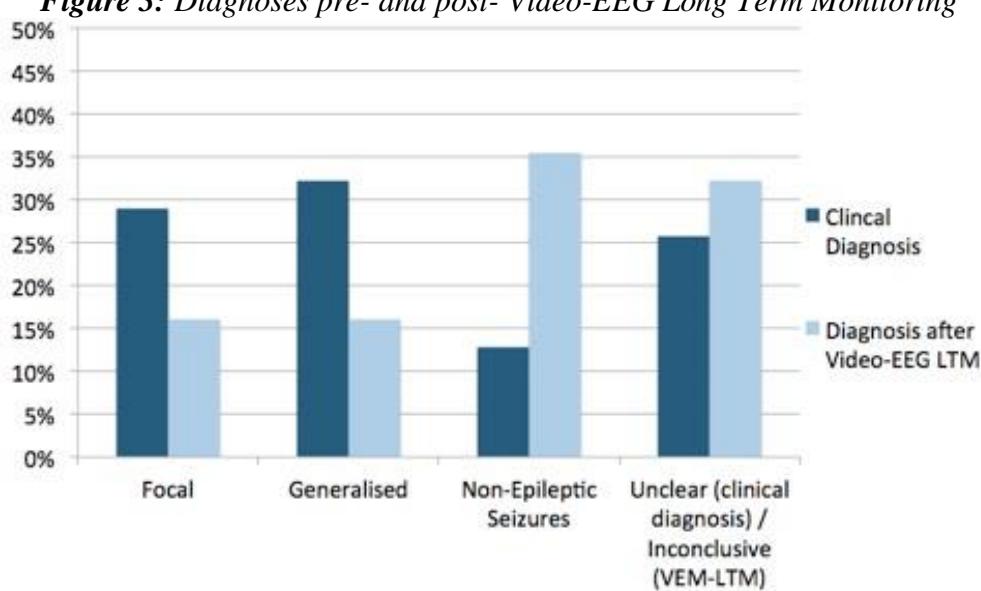
Imaging and routine EEG findings

The routine EEGs against which LTMs were compared showed that 64.5% ($n=20$) were normal and 32.3% ($n=10$) were abnormal. In one case the routine EEG was not found in the patient's records. Imaging studies in the form of either a CT scan or MRI scan was found to be normal in 80.6% ($n=25$), abnormal in 9.7% ($n=3$), and 9.7% ($n=3$) did not have any imaging done.

Diagnosis

The clinical diagnosis for the audited cases (i.e. before LTM investigation) were 29% focal onset epilepsy, 32.3% generalised epilepsy, 12.9% NES and 25.8% were unclear. The LTM studies rendered changes, with the diagnoses becoming 16.1% focal, 16.1% generalised, 35.5% NES and 32.3% remained inconclusive (Figure 3). In the paediatric cohort 45.5% of LTMs were inconclusive, whereas a 25% inconclusive rate was recorded in the adult cohort.

Figure 3: Diagnoses pre- and post- Video-EEG Long Term Monitoring



Overall, this translates into the LTM studies changing or identifying a new diagnosis in 38.7% ($n=12$), confirming the diagnosis in 29% ($n=9$), and inconclusive in 32.3% ($n=10$) (Figure 4).

These LTM results led to medication optimisation in 38.7% and neuropsychiatry referrals in 22.6%. In 19.4% there was no management change and 16.1% had no follow up recorded (Figure 5). One case (3.2%) was simply referred for further cardiovascular investigation with 24 hour blood pressure and Holter ECG monitoring. None were referred for surgery. The results are comparatively better than the results in a study (including all age groups) by Alsaadi et al. (2004) which reported a change in diagnosis in 24% after LTM.²⁷ Elderly LTM studies by Keranen, Rainesalo

& Peltola (2002) and Lancman et al. (1996) reported the change in either diagnosis or treatment as 38.9% and 55% respectively.¹⁴⁻¹⁵

Further analysis of the 21 patients with conclusive outcomes revealed that the most prevalent diagnosis was NES in 52.4% and ES followed with 47.6%. The higher prevalence of NES has also been reported in other previous studies.¹³⁻¹⁴ The cohort diagnosed with true epileptic seizure after LTM was made up of 60% ($n=6/10$) male and 40% ($n=4/10$) female, whereas those diagnosed with NES were 27.3% ($n=3/11$) male and 72.7% ($n=8/11$) female. This higher prevalence of NES in females is in keeping with other studies.¹

Figure 4: Outcomes of Video-EEG Long Term Monitoring

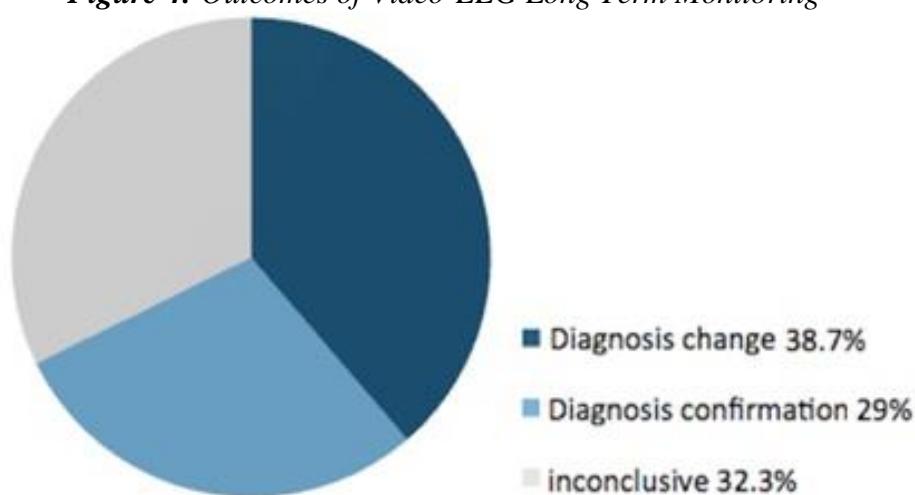
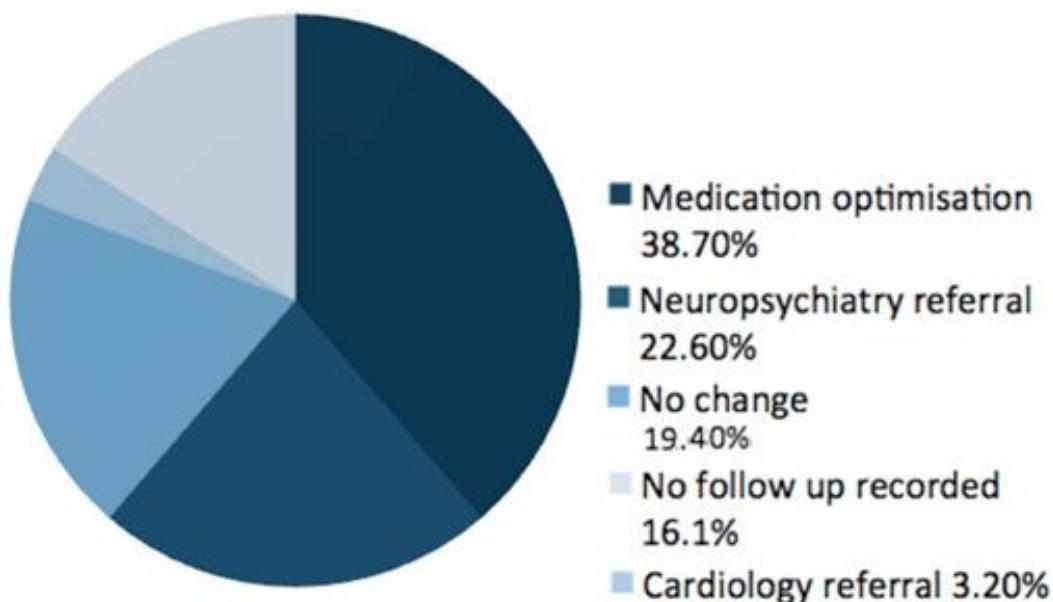


Figure 5: Management Outcome after Video-EEG Long Term Monitoring



Differentiating Epilepsy Syndrome from Non-Epileptic Seizures

Differentiation between ES and NES, particularly PNES, is a major problem. In fact, discriminating between ES and PNES can be difficult even for experienced physicians.²⁷ Without LTM clinicians cannot witness the seizures and therefore are forced to make the diagnosis based on the history and the witness' descriptions and routine EEG. Descriptions can often be misleading due to inaccuracy, and EEG has been reported to show normal activity on initial testing in 40% of true epileptic patients.²⁸ Moreover, If no EEG paroxysms become evident during a seizure it does not completely exclude the possibility of a true epileptic seizure since deep cerebral discharges may not be detected by surface electrodes.²⁹⁻³⁰

There is also difficulty in interpreting EEG findings. True epileptic seizures may sometimes show ictal EEG changes which are not 'epileptiform' and patients diagnosed with PNES have also been reported to have 'epileptiform' EEGs.^{1,31} However, a study by Benbadis and Tatum (2003) evaluated patients diagnosed with PNES and having epileptiform abnormalities reported by neurologists (not epileptologists or electroencephalographers), and identified that none of them had true epileptiform abnormalities.³² Instead findings included multiple normal variants (wicket spikes, hypnagogic hypersynchrony, and hyperventilation-induced slowing), as well as overreading of simple fluctuations of sharply contoured background rhythms. This explains why epileptologists regard EEG "over-reading" as being more harmful than "under-reading".

Diagnosis may therefore be erratic in three main ways:

1. Diagnosis of PNES despite actual ES
2. Diagnosis of ES despite a psychogenic aetiology
3. Unrecognised coexistent PNES and ES

The latter has been reinforced by studies reporting that PNES and epilepsy coexist in 10-13% of cases.^{3,17,33-34} This presents a further diagnostic challenge. All these errors have huge implications on patient management. The correct management plan requires antiepileptic drugs (AED) tailored to each patient's epileptic syndrome and psychological therapy to target any psychosocial factors.³⁵⁻³⁶

Differentiating between ES and PNES is extremely important since unnecessary AED

treatment is costly and has potential side effects, and undiagnosed/untreated ES is associated with morbidity and mortality (including sudden unexpected death).¹² In addition, early recognition of PNES is associated with better outcomes.¹⁶ These consequences emphasise the need for a diagnostic tool such as video-EEG LTM which helps to prevent such errors. The tool helps minimise these mistakes but still carries the risk that some patients having both ES and NES can get an incomplete diagnosis if only one of these is captured during LTM.

Paediatric video-EEG LTM

Video-EEG LTM in children, although similar to adult LTM, has been noted to present additional challenges. Reported literature identifies the following difficulties encountered in paediatric LTM^{24,37-39}:

- a parent or guardian is almost always required to stay with the patient
- children may not tolerate lengthy admissions
- accurate estimation of seizure frequency (which in turn has been associated with higher chance of capturing habitual event) is difficult when based on the information from the parents alone, since seizures are often very subtle.

Additionally, MDH lacks dedicated facilities for paediatric LTMs (instead, these are performed in the adult NMW which does not provide the desired environment) and is short in nursing staff who can provide dedicated monitoring of children overnight. Therefore, the higher rates of interrupted studies and inconclusive outcomes observed in paediatric cases may be attributed to these limitations. It is very important to consider these shortcomings when evaluating the usefulness of paediatric LTM.

Conclusion and suggestions

Video-EEG LTM at MDH has proved to be an important tool for proper understanding of the problem, and consequently proper handling and management. It helped change or identify a new diagnosis in 38.7% and confirmed the diagnosis in 29%. It also influenced patient management by leading to changes in medication and appropriate referrals in 64.5% of the cases. Knowing the exact diagnosis reassures the patient and the physician, and enables clinicians to choose the most suitable treatment avoiding unnecessary empirical trials with

anticonvulsants. The information from this audit is useful both for the clinical neurologist and the patients in that it provides what can be expected from subsequent video-EEG LTM sessions.

The audit also highlights areas for improvement. There must be continuous evaluation of the techniques used and the resources available in order to increase the yield of conclusive information that LTM studies can provide. The audit led to a number of suggestions:

1. Acquire a base-line EEG on admission to be used for comparison with LTM results, rather than using an older routine EEG.
2. Review the character of each LTM event on video with patient and family so as to ensure that the episode recorded was representative of typical events that had led to the monitoring evaluation.
3. Consider developing dedicated facilities for paediatric LTM and increasing dedicated nursing staff, both of which may help improve the rate of conclusive paediatric LTM studies.
4. Repeat the audit with more exhaustive data collection and include patient follow-up after LTM diagnosis and management change confirm that this led to an improvement in patients' well being.
5. Retrospective collection of data for this audit meant that some relevant information was not easily available or not available at all. This includes frequency of seizures, typical duration of each habitual event, accurate dates for symptom onset and routine EEG results. A dedicated proforma for patients undergoing Video-EEG LTM may help with a more comprehensive gathering of data. It would facilitate clinical practice as well as future auditing and research in epilepsy.

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References

1. Nordli DR Jr. Usefulness of video-EEG monitoring. *Epilepsia*. 2006;47:26-30.
2. Fisher RS, van Emde Boas W, Blume W, Elger C, Genton P, Lee P, et al. Epileptic seizures and epilepsy: definitions proposed by the International League Against Epilepsy (ILAE) and the International Bureau for Epilepsy (IBE). *Epilepsia*. 2005;46:470-2.
3. Krumholz A, Niedermeyer E. Psychogenic seizures: a clinical study with followup data. *Neurology*. 1983;33:498-502.
4. Leis AA, Ross MA, Summers AK. Psychogenic seizures: ictal characteristics and diagnostic pitfalls. *Neurology*. 1992;42:95-9.
5. Marquez AV, Farias ST, Apperson M, Koopmans S, Jorgensen J, Shatzel A, et al. Psychogenic nonepileptic seizures are associated with an increased risk of obesity. *Epilepsy Behav*. 2004;5:88-93.
6. Reuber M, Elger CE. Psychogenic nonepileptic seizures: review and update. *Epilepsy Behav*. 2003;4:205-16.
7. Gibbs J, Appleton RE. False diagnosis of epilepsy in children. *Seizure*. 1992;1:15-8.
8. Raymond AA, Gilmore WV, Scott CA, Fish DR, Smith SJ. Video-EEG telemetry: apparent manifestation of both epileptic and non-epileptic attacks causing potential diagnostic pitfalls. *Epileptic Disord*. 1999;1:101-6.
9. Cosenza-Andraus ME, Nunes-Cosenza CA, Gomes-Nunes R, Fantezia-Andraus C, Alves-Leon SV. Video-electroencephalography prolonged monitoring in patients with ambulatory diagnosis of medically refractory temporal lobe epilepsy: application of fuzzy logic's model. [Article in Spanish]. *Rev Neurol*. 2006;43:7-14.
10. Valente KD, Freitas A, Fiore LA, Groncik G, Negrão N. The diagnostic role of short duration outpatient V-EEG monitoring in children. *Pediatr Neurol*. 2003;28:285-91.
11. Connolly MB, Wong PKH, Karim Y, Smith S, Farrell K. Outpatient video-EEG monitoring in children. *Epilepsia*. 1994; 35, 477-81.
12. Lobello K, Morgenlander JC, Radtke RA, Bushnell CD. Video/EEG monitoring in the evaluation of paroxysmal behavioral events: duration, effectiveness, and limitations. *Epilepsy Behav*. 2006;8:261-6.
13. Aljandeel GhB, Alarcon G. The Role of telemetry (Simultaneous video and EEG monitoring) in the proper management of epilepsy. *Iraqi Postgrad Med J*. 2011;10:408-13.
14. Keränen T, Rainesalo S, Peltola J. The usefulness of video-EEG monitoring in elderly patients with seizure disorders. *Seizure*. 2002;11:269-72.
15. Lancman ME, O'Donovan C, Dinner D, Coelho M, Lüders HO. Usefulness of prolonged video-EEG monitoring in elderly. *J Neurol Sci*. 1996;142:54-8.
16. Walczak T, Savvas P, Williams D, Scheuer M, Lebowitz N, Notarfrancesco A. Outcome after diagnosis of psychogenic nonepileptic seizures. *Epilepsia*. 1995;36:1131-7.
17. Meierkord H, Will B, Fish D, Shorvon S. The clinical features and prognosis of pseudoseizures diagnosed using video-EEG telemetry. *Neurology*. 1991;41:1643-6.
18. Risvi SA, Hernandez-Ronquillo L, Wu A, Téllez Zenteno JF. Is rapid withdrawal of anti-epileptic drug therapy during video EEG monitoring safe and efficacious? *Epilepsy Res*. 2014;108:755-64.
19. Chen LS, Mitchell WG, Horton EJ, Snead III OC. Clinical utility of video-EEG monitoring. *Pediatr. Neurology*. 1995;12:220-4.
20. Holmes GL, Moshe S, Ryden Jones H Jr. Clinical Neurophysiology of Infancy, Childhood, and Adolescence. Butterworth-Heinemann, 2006.
21. Daly DD. Epilepsy and syncope. In Daly DD, Pedley TA (ed): Current Practice of Clinical EEG. New York Raven Press. 1990.
22. Risinger MW, Engel Jr J, Van Ness PC, et al. Ictal localization of temporal lobe seizures with scalp/sphenoidal recordings. *Neurology*. 1989;39:1288-93.

23. Watemberg N, Tziperman B, Dabby R, Hasan M, Zehavi L, Lerman-Sagie T. Adding video recording increases the diagnostic yield of routine electroencephalograms in children with frequent paroxysmal events. *Epilepsia*. 2005;46:716-9.
24. Asano E, Pawlak C, Shah A, Shah J, Luat AF, Ahn-Ewing *et al.* The diagnostic value of initial video-EEG monitoring in children - Review of 1000 cases. *Epilepsy Res.* 2005;66:129-35.
25. Foley CM, Legido A, Miles DK, Griver WD. Diagnostic value of pediatric outpatient video-EEG. *Pediatr Neurol.* 1995;12:120-4.
26. Valente KD, Freitas A, Fiore LA, Groncik G, Negrão N. The diagnostic role of short duration outpatient V-EEG monitoring in children. *Pediatr Neurol.* 2003;28:285-91.
27. Alsaadi TM, Thieman C, Shatzel A, Farias S. Video-EEG telemetry can be a crucial tool for neurologists experienced in epilepsy when diagnosing seizure disorders. *Seizure*. 2004;13:32-4.
28. Rugg-Gunn FJ, Harrison NA, Duncan JS. Evaluation of the accuracy of seizure descriptions by the relatives of patients with epilepsy. *Epilepsy Res.* 2001;43:193-9.
29. Holmes GL, Sackellares JC, McKiernan J, Ragland M, Dreifuss FE. Evaluation of childhood pseudoseizures using EEG telemetry and video tape monitoring. *J Pediatr.* 1980;97:554-8.
30. Liske E, Foster FM. Pseudoseizures: a problem in diagnosis and management of epileptic patients. *Neurology*. 1963;14:41-9.
31. Binnie CD, Cooper R, Mauguiere F, Osselton J, Prior PF, Tedman BM. *Clinical Neurophysiology* (Vol. 2). Elsevier Science BV, 2003.
32. Benbadis S, Tatum W. Overinterpretation of EEGs and misdiagnosis of epilepsy. *J Clin Neurophys.* 2003;20:42-4.
33. Lesser RP, Luders H, Dinner DS. Evidence for epilepsy is rare in patients with psychogenic seizures. *Neurology*. 1983;33:502-4.
34. Benbadis SR, Agrawal V, Tatum WO. How many patients with psychogenic nonepileptic seizures also have epilepsy? *Neurology*. 2001;57:915-7.
35. Ramani SV, Quesney LF, Olson D, Gumnit RJ. Diagnosis of hysterical seizures in epileptic patients. *Am J Psychiatry*. 1980;137:705-9.
36. Ramani V, Gumnit RJ. Management of hysterical seizures in epileptic patients. *Arch Neurol*. 1982;39:78-81.
37. Grunewald RA, Chroni E, Panayiotopoulos CP. Delayed diagnosis of juvenile myoclonic epilepsy. *J Neurol Neurosurg Psychiatry*. 1992;55:497-9.
38. Atakli D, Sozuer D, Atay T, Baybas S, Arpacı B. Mis-diagnosis and treatment in juvenile myoclonic epilepsy. *Seizure*. 1998;7:63-6.
39. Gaily E, Liukkonen E, Paetav R, Rekola R, Granstrom ML. Infantile spasm: diagnosis and assessment of treatment response by video-EEG. *Dev Med Child Neurol*. 2001;43:658-67.

Challenges in the management of Phenylketonuria in Malta

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Abstract

Phenylketonuria (PKU) is a rare metabolic disorder comprising a number of different enzyme deficiencies. In Malta, dihydropteridine reductase (DHPR) deficiency appears to be more common than phenylalanine hydroxylase deficiency (classical PKU), and is associated with greater and long term neurodisability. The absence of newborn screening for PKU in Malta results in a later diagnosis and, to-date, all affected patients require medical support for one or several problems including developmental delay, behavioural issues, cognitive impairment, epilepsy and neurodisability. These are compounded by problems in providing and adhering to strict low-phenylalanine diets and, in those with DHPR, the regular provision of neurotransmitter and cofactor supplementation. As a result, although a small cohort, these patients create a disproportionate demand on health services and, in most cases, will continue to require long term support at all levels since most will be unable to lead an independent existence. A radical and comprehensive overhaul of the local care provided to children with rare metabolic diseases is required at all levels, starting with the introduction of newborn screening, followed by effective dietary and pharmaceutical provision throughout childhood and through to later life.

Keywords

phenylketonuria, Malta

Introduction

In Malta, during the period 1996-2015, five paediatric cases from three families with the same form of tetrahydrobiopterin (BH₄) disorder, namely dihydropteridine reductase (DHPR) deficiency and just one child with classical PKU due to phenylalanine hydroxylase (PAH) deficiency have been diagnosed. Out of a childhood population of about 90,000¹, the prevalence of PKU is therefore approximately 5.5 x 10⁵. The carrier rate of DHPR deficiency in the Maltese population reported by Farrugia *et al* (2002) is high at 3.3%.² In comparison, the carrier rate of PAH deficiency is 2% in northern Europe, 3.8% in Turkey and 3% in Ireland, but is unknown in Malta.²

Case Summaries

Case 1: PAH deficiency (Classical PKU)

A 3 year 8 month old girl was born prematurely at 34 weeks gestation with respiratory distress and birth weight on the 50th centile. She was lost to neonatal follow-up and presented at 23 months of age with feeding difficulties, developmental delay and failure to thrive in the context of gross neglect and social problems. She was taken into care and fostered. As well as failure to thrive, she was noted to have microcephaly, fair hair and blue eyes. A phenylalanine (Phe) level was documented at 120umol/L with a tyrosine level (Tyr) of 38umol/L (normal Phe values: 6 – 50umol/L <1 year and 10 – 30umol/L >1 year. Table 1).

The DHPR gene was normal and sepiapterin reductase was negative. She was started on a low phenylalanine diet with Anamix Child at 23 months of age with a marked improvement in terms of developmental progress and brisk darkening of her

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hair. Nevertheless, mild hypotonia persisted and an MR of the brain showed leukomalacia. CSF neurotransmitters were not tested. To-date, she has no signs of epilepsy but remains developmentally

delayed and attends school with the help of a learning school assistant (LSA) on a 1:1 basis (Table 2).

Table 1: Normal Phenylalanine and Tyrosine levels at 0 – 31 days of life on protein containing feeds

Phenylalanine	40 – 120 umol/L normal 120 – 600 umol/L hyperphenylalaninaemia 600 – 1200 umol/L mild PKU >1200 umol/L classical PKU
Tyrosine	55 – 147 umol/L normal
Phe : Tyr ratio	>3 is abnormal

Table 2: Summary of patient details

Case	Age at diagnosis	Disorder	Phe level diagnosis	PKU phenotype	Microcephaly	Motor disorder	Develop delay	Behavioural problems	Seizures
1	23mo	PAH	1693	yes	yes	+	+	+	-
4	8mo	DHPR	906	yes	yes	++	+++	++	+++
2	5mo	DHPR	700	no	yes	++	++	++	+
3	5mo	DHPR	550	yes	no	+	++	++	-
5*	newborn	DHPR	-	no	no	+	+	+	-
6*	newborn	DHPR	-	no	no	-	+	-	-

*Siblings of case 4 diagnosed on newborn testing

Case 2: DHPR deficiency (atypical PKU)

A 17 year old young man was born at 40 weeks gestation after a normal pregnancy. His birth weight was 2.7 kg (3rd percentile) and head circumference 33cms (5th percentile). Apgar scores were 8 and 9 at 1 and 5 minutes, respectively. Apart from some light meconium staining of the liquor, there were no other concerns until two months of age when he presented with seizures. These were initially not controlled with sodium valproate, and he required additional anticonvulsants with good effect. He did not have the typical 'fair hair, blue eyes' PKU phenotype, but developed hypotonia, global developmental delay and microcephaly. Amino acid analysis was carried at 5 months of age as part of the investigation for developmental delay, and confirmed a Phe level in excess of 700umol/L.

The DHPR level was low and genetics subsequently confirmed the mutation consistent with DHPR deficiency. He was started on a low phenylalanine PKU diet at 5 months of age with 8 daily exchanges, low protein diet and 4 daily PKU coolers. There was a slow response in terms of seizure control, and his developmental delay persisted with significant behavioural difficulties. CSF neurotransmitter levels were checked regularly: homovanillic acid (HVA) and 5-hydroxyindole-acetic acid (5HIAA) levels were low, initially with reversed ratios. He required high doses of neurotransmitter precursors including L-3,4-dihydroxyphenylalanine (L-DOPA), 5-hydroxytryptophan (5HT) and folinic acid. Periodic episodes when his medication was not available or out of stock, rapidly resulted in increased symptomatology particularly with increased dystonic movements, behavioural changes and aggression generally over the subsequent 24-36 hours from not receiving medication.

This patient walked at 21 months, continued to progress and ran clumsily with feet apart. He uttered a few short sentences at 5 – 6 years of age and was able to fasten a few buttons at 8 years of age. Oculogyric crises were seen early on, with hand tremors lasting a few seconds and transient dystonia. The latter responded to clonazepam, whilst seizures responded partially to sodium valproate. No clear pyramidal or extrapyramidal motor signs were found. At 5 years of age, he was functioning at around the 3½ year level, with additional hyperactive

and aggressive tendencies (Table 2). Brain imaging showed no specific abnormality.

He has been very sensitive to treatment changes. Phe levels have remained moderately high, averaging 210 – 390umol/L, with peaks up to 472 (2005) and between 500 – 600umol/L (2007) during periods of poor health and/or poor compliance. He has required a 1:1 LSA support at all times at school. He is currently employed under a 'protected' work placement attaching labels to products on a part-time basis. He is able to prepare simple meals and catch the bus home, but requires help with more complex tasks and will have difficulty leading a fully independent existence.

Case 3: DHPR deficiency (atypical PKU)

A 15 year old was born after a normal pregnancy and vaginal delivery at 40 weeks gestation. Apgar scores were 8 and 9 at 1 and 5 minutes, respectively. Birth weight was 3.55 kg (50th percentile) and head circumference 35cms (45th percentile). He was well until 5 months of age when he presented with motor delay, hypertonia and typical PKU phenotype with fair hair and blue eyes. The first Phe level at 5 months of age confirmed a Phe level of 550umol/L with a tyrosine level of 75umol/L.

The DHPR level was low and genetics subsequently confirmed DHPR deficiency. Initial CSF neurotransmitters including homovanillic acid (HVA), 5-hydroxyindole-acetic acid (5HIAA) and methyltetrahydrofolate (MTHF) were normal. He was started on a PKU diet with significantly reduced phenylalanine content at 5 months of age, initially via highly modified milk (Lofenalac), plus Aminogram, Aminex rusks, Duocal, PKU gel, permitted but controlled Phe-containing protein exchanges and PKU coolers. There was an improvement in terms of hypertonia, and moderate developmental progress was seen. He developed a transient dermatitis as a result of being on Lofenalac without any natural protein, and subsequently low Phe levels. This responded well to alterations in the Phe exchanges and his skin pigmentation improved.

Despite normal CSF neurotransmitter levels, this child also required regular L-Dopa with 5-hydroxytryptophan (5-HT) and folinic acid supplementation on a 4-times and daily basis, respectively. During periods when his medication was not available, he rapidly developed increased dystonic movements and behavioural changes over

the subsequent 24hrs from not receiving medication. Unfortunately, these episodes have been a relatively frequent event, especially since his medication is highly specialised, only procured for a very small number of patients locally and not readily available from many sources. Numerous attempts to guarantee continuous supply and availability of all medications and specialized dietary products for PKU with the local pharmacy service have met with varying degrees of success and, despite strenuous and repeated efforts, intermittent non-availability remains an ongoing problem for all patients with PKU.

Developmentally, he walked at 21 months of age, and ran soon afterwards. There have been significant behavioural difficulties, mainly in the form of aggression, attention deficit hyperactivity disorder and mood disturbance. He had several oculogyric crises. His head circumference remained normal, but he developed a mild motor disorder with mild hypertonia and brisk tendon reflexes. More recently, he has also developed dystonic movements and equinus gait disturbance. Neuro-imaging showed no specific abnormality. He has required a 1:1 LSA support at all times at school and now attends a special school for children/adolescents with significant neurodevelopmental problems (Table 2). He will require a sheltered and protected work placement and will be unable to lead an independent existence without significant, long term support.

Cases 4, 5 and 6: Siblings with DHPR deficiency (atypical PKU)

Case 4: An 18 year old young man was born at 38 weeks gestation by precipitate vaginal delivery. His birth weight was 2.9 kg (5th percentile) and head circumference 34cm (15th centile). His Apgar scores were 6 and 7 at 1 and 5 minutes, respectively and, apart from mild respiratory distress and hyperbilirubinaemia, was well till around 6 months of age when concerns arose relating to motor delay, reduced head growth from 50th centile to the 10th percentile and central hypotonia. He had a classical PKU phenotype and was subsequently diagnosed with DHPR deficiency at 9 months of age. An initial Phe level was 906umol/L, Tyr was 51umol/L, DHPR activity was low and bipterin level was high. The first CSF neurotransmitter levels showed an HVA of 85 (154 – 867umol/L); HIAA 43 (89 – 367umol/L),

and folate 16.4nmol/L (normative values at ages 0-5 years: 13 nmol/L and >6 years: 10 nmol/L).

He was started on a low Phe diet at 7 months of age with Lofenalac with added aminogram, protein exchanges, aminoacid supplements, Serevit vitamins and mineral supplements. His response to diet in terms of decreasing Phe levels was very slow, and Phe levels persisted around 200umol/L. This was thought to be related to a lack of compliance with his diet. He was started on L-Dopa, 5- tryptophan and folinic acid.

At 4years 8months he was functioning at the 2.5 - 3 year level, and at 6 years he could count up to 50 and carry out simple addition and subtractions. He developed a significant dystonic four limb motor disorder with spasticity and facial tics, and frequent adjustments of medication were carried out. Neuro-imaging showed white matter changes in both occipital and temporal lobes extending to the periventricular, parietal and posterior frontal white matter. At 5 years of age, he developed absence seizures with bilateral continuous occipital discharges that were resistant to treatment. This evolved and included drop attacks that occurred several times a day, and required various combinations of anti-epileptic medications including lamotrigine, topiramate, clobazam and levetiracetam. Due to the dietary restrictions imposed by the PKU diet itself, a ketogenic diet was not possible at the time. A trial of steroids was also very difficult and not tolerated. He was referred for further assessment of his refractory epilepsy to Guy's Hospital in London where a vagal nerve stimulator (VNS) was implanted. This reduced his seizure frequency by approximately 50% but required frequent adjustments and, in one year alone, he travelled to London 11 times for treatment. The family struggled with this child's medical condition and other practical medical problems, and emigrated to the UK.

This patient has remained with significant learning difficulties and neurodevelopmental delay (Table 2). He will require a sheltered and protected work placement and will be unable to lead an independent existence without significant, long term support.

Case 5: A younger brother of case 4, now aged 13 years, was diagnosed with DHPR deficiency by genetic testing shortly after birth. Unlike his brother, he did not have a classical PKU phenotype.

Nevertheless, his first Phe level was also elevated and CSF neurotransmitters showed: HVA 222 nmol/L; HIAA223 nmol/L, and folate 19.9 nmol/L. He was started on a low Phe diet at 2 weeks of age with Minaphlex, a special formula with a linoleic:α-linolenic acid ratio of 4:1, and was used to correct fatty acid imbalance associated with a PKU diet. Like his older brother, there was a very slow response in lowering Phe levels.

Despite the early diagnosis and treatment, this boy also manifested developmental delay, albeit milder when compared to his older brother. At 4 years of age he managed 5 to 6 word sentences, developed an early motor disorder with paucity of spontaneous movements, hypertonia and lead pipe rigidity reminiscent of symptomatic Parkinsonism. Neuro-imaging showed persistent prominence of the terminal myelination zone, but there were no definite white matter abnormalities.

He was managed with L-Dopa, 5-HT and folinic acid. At 4 years of age he developed significant behavioural disturbances, frequent falls, attention deficit and frequent temper outbursts during mealtimes. He was very fussy in his choice of food, making day to day management very difficult when considering the reduced choice of food available to him. This behavioural profile was very similar to that of his brother but improved in tandem with his improved epilepsy control.

Significant learning difficulties and neurodevelopmental delay necessitated a full time LSA in mainstream school (Table 2) and, as an adult, he will require sheltered and protected work placement and will also be unable to lead an independent existence without significant, long term support.

Case 6: The youngest brother of cases 4 and 5 was born and diagnosed in the UK after the family emigrated and clinical details of his condition are limited. He does, however, also have DHPR deficiency and manifests moderate global delay despite immediate diagnosis and initiation of therapy and a specialized diet shortly after birth. He remains on regular medication and a restricted diet as per his siblings. He has an LSA on a 1:1 basis at school and is likely to require long term support, even into adulthood (Table 2). This patient and his brothers are currently under the care and follow up of colleagues in the UK where they are now resident.

Discussion

Medical impact on patients and families

Dietary intervention

The goal of PKU treatment is to maintain plasma phenylalanine (Phe) levels with a 'normal' range that supports growth, development and mental function while providing a nutritionally complete diet. Phe is an essential amino acid and required for protein synthesis, therefore very low levels are also detrimental.

Individuals with hyperphenylalaninaemia require a low Phe diet that is based on two interrelated dietary modifications to achieve metabolic control of plasma Phe levels. Natural foods are severely restricted to limit protein intake while providing adequate amounts of Phe. This involves elimination of all sources of animal protein, legumes and nuts, as well as limiting amounts of bread, pasta, rice and some vegetables. Low protein bread and pasta products made from starch are used to provide energy.

Consumption of an amino-acid based, Phe-free formula milk or amino-acid medical food is required to provide adequate protein, vitamins, minerals and energy due to their restriction in natural foods. The UK Medical Research Council Working Party on PKU recommends a total protein intake of 3g/kg/day for children under 2 years of age and 2g/kg/day for children over 2 years of age. These amounts exceed recommendations for protein intake in the non-PKU population by 30%. A typical low phe diet is based on a system of exchanges. In the UK system, one 'exchange' amounts to 50mg Phe which is approximately 1g protein. Unfortunately, this assumption does not work for protein from fruit and vegetables, the content of which are calculated using special databases.³

Medication

In children with atypical PKU, CSF amino acids and neurotransmitter imbalance is common and need to be managed. This requires periodic lumbar punctures and daily supplementation with folinic acid, tryptophan and L-Dopa. Epilepsy and behaviour disturbance are frequent problems in this group of children and need to be managed appropriately with anticonvulsants, behavioural therapy and, if necessary, sedative medication.

Psycho-social and educational impact

A study by Di Ciommo et al⁴ focused on the lived experience of patients with PKU. This was a phenomenological study of 20 patients using a validated semi-structured interview in an Italian tertiary level metabolic centre. They looked at the personal experiences of these patients through (a) their knowledge and conceptualization of PKU, (b) their perception of being different and (c) their adherence to diet. It was shown that children and young adults with early treated PKU had a fair knowledge of their condition but did not feel that they were truly ill.⁴ Although they perceived no direct, immediate, adverse effects of their disease, they adhered to their diet. They reported a difference between themselves and their peers. The fear of stigmatization tended to prevent them from participating in social occasions during which food was shared. One coping strategy reported by these individuals to overcome isolation was to disclose their condition to their peers.

From the cognitive point of view, early diagnosis and treatment of PKU can prevent the severe neurocognitive consequences of this disorder. However, even early- and well-treated patients experience hidden disabilities, including subtle deficits in executive functioning, mild reductions in mental processing speed, social difficulties, and emotional problems that may remain unnoticed for years.

PKU has been shown to be associated with poor executive function that may impact treatment adherence and may lead to psychosocial deficits including difficulty in forming interpersonal relationships, achieving autonomy, attaining educational goals, and having healthy emotional development. A degree of depressive and anxiety symptoms may also be present. The combination of cognitive and psychiatric disturbances acts as a hidden disability.⁵ Patients with atypical and BH₄ disorders are more likely to be adversely affected with a greater incidence and degree of neurodisability.⁶ From the parental point of view, mothers of children with biochemical genetic disorders report greater stress and worry, less satisfaction with social support, greater difficulty meeting their child's extra care needs, and more impact on multiple aspects of their personal lives.⁷

Financial impact

A review of the cost of special dietary needs in 10 PKU specialist centres, reported that the mean annual cost of protein substitutes across 4 age groups (2, 8, 15 years and adults) ranged from €4,273 to €21,590 per patient. The cost of low-protein products also differed; the mean cost of low-protein bread varied from €0.04 to €1.60 per 100kcal. All protein substitutes were either fully reimbursed or covered by health insurance. However, reimbursement for low-protein products varied and state benefits differed between centres.⁸

In a cross-sectional study about time consumption and cost of PKU in the Netherlands, it was shown that the median out-of-pocket cost per patient was shown to be €604 annually (in all age groups)⁹. These costs were mainly due to expenditure on low-protein food products and for a small part on costs related to PKU testing equipment, postage of Phe blood tests, taking extra luggage on holiday to accommodate PKU equipment and attending PKU events. This study assessed whether these additional PKU-related costs are offset by the potentially cheaper natural diet imposed upon PKU patients that contains very little or no regular bread, dairy products or meat. In comparison to the general population, a Dutch adult on a normal diet will spend a mean amount of €1,200 annually on meat, cheese, milk, yoghurt and bread. For patients with PKU this expenditure is replaced by the costs of the low protein products. It may be expected that costs between protein containing and low protein food products will balance out in patients depending on disease severity and the need for low protein food products. Taking this into account, the authors concluded that it is unlikely that there will be a large burden of extra out-of-pocket cost for families of patients with PKU.⁹

It must be stressed, however, that the costs of the Phe free protein supplements in a mixture with vitamins and minerals, which are an essential part of the diet of patients with PKU, vary per country but may be as high as €30,000 annually. In most European countries these costs are reimbursed by the government, or as is the case in the Netherlands, by health insurance. To guarantee proper dietary treatment and compliance of patients with PKU and to avoid a disproportionate financial burden for patients and families, it is essential that costs of the

Phe free protein supplements are reimbursed in all countries.⁹

Impact on Health services

According to the National Institutes of Health Consensus Development Conference Statement about the management of phenylketonuria, health systems need to respond effectively in order to ensure metabolic control across the lifespan of individuals with PKU. Comprehensive, multidisciplinary, and integrated systems are needed to deliver this type of care to individuals with PKU. Consistent and coordinated screening, treatment, data collection, and patient support programs are necessary. Moreover, there should be equal access to culturally sensitive, age-appropriate treatment programs. They also state that uniform policies must be established to remove financial barriers to the acquisition of medical foods and modified low-protein foods and to provide access to support services needed to maintain metabolic control in individuals with PKU.¹⁰ In practical terms, the above requirements are best met by a coordinated, expert team.¹¹

Current challenges in management of PKU in Malta

Late diagnosis

The absence of neonatal screening in Malta is a major drawback that mitigates against early treatment. This is further compounded by the fact that, in Malta, atypical PKU appears to be more common than classical PKU where the prognosis is perhaps more heavily dependent on careful and early treatment. Given the absence of newborn screening in Malta, over the past 18 years, 4 children with PKU were diagnosed after the age of 5 months and, in some cases, much later in childhood, as shown in Table 1. Two siblings of the index case were screened immediately and diagnosed shortly after birth.

Paediatricians need to keep the possibility of PKU always in mind in those children with unexplained developmental delay, abnormalities in tone, movement disorders, or atypical cerebral palsy. Despite current literature stating that the use of 'metabolic screens' in the investigation of children with global developmental delay tends to have a low positive yield, this may be an argument in favour of performing a metabolic screen in such situations.

Furthermore, since PKU is a rare disease, medical practitioners will find it difficult to acquire enough experience to identify clinical signs suggestive of PKU early enough. This effectively strengthens the case for neonatal screening.

Shared care

PKU is best managed in a tertiary metabolic centre, and this type of management has been shown to be more effective in PKU when compared to management by general paediatric centres.⁵ Outside of these Centres, the level of experience in dealing with PKU is very limited. This scenario applies to Malta, whereby patient care is shared with a tertiary specialist centre in London. Phe levels need to be checked as often as needed/frequently, and communicated with the specialist team. Delays in the availability of results may not allow for appropriate titration of doses and changes in diet. Furthermore, CSF neurotransmitter levels may not be assayed often enough according to recommendations because of logistical problems with sampling and non-availability of laboratory assays at a local level. Indeed, CSF amine levels are obtained in London and necessitate an annual visit overseas. Despite this, local follow-up remains an important part of long term management with families still seeking advice about common problems in PKU such as doses of L-Dopa, 5-HT, seizure control and management of movement disorders.

Dietary supplies

The lack of specialist dietetic support is another important local drawback. This is regularly associated with and compounded by frustrating difficulties in procuring certain special food items, ensuring adequate stocks and avoiding 'out of date' issues, making provision and compliance with a low Phe diet very difficult. It would also seem that in contrast to other conditions requiring special dietary and/ or nutritional support, families of children with PKU struggle in order to secure timely delivery of the required special dietary items. These children only consume small amounts of specific food items that change from time to time, and are not widely available, thereby discouraging local pharmaceutical agents to stock these items.

Conclusion

National screening

PKU is a chronic condition with significant morbidity for affected patients and a burden on health care costs. It fulfils all criteria for newborn screening and is sufficiently prevalent in the local population such that an official report strongly recommended it's addition to the current National Programme in 2005.¹² There is no medical reason why neonatal screening should not be introduced in Malta in line with current international recommendations.¹³ Once introduced, infants who are found to have high phenylalanine levels will be recalled urgently to (a) confirm high Phe levels, and (b) depending on the level, plan further investigation, (c) liaise with tertiary centre and start a low Phe diet. It is important to keep in mind that failure to pick up PKU early on and any delay in starting effective treatment may carry medico-legal implications.

Central pooling of supplies

Although there are only very few children who require low Phe food products, they should receive the required products at the right quantity and at the right time. This is an important issue that has ethical as well as potentially serious medico-legal implications.

It is therefore time to push for appropriate changes in pharmacy service that effectively respond to the nutritional requirements of these children in real time. It may be possible to introduce a system whereby these families are given access to carefully-monitored credit that can be used to order and purchase their special foodstuffs directly from their tertiary centre. At this day and age, this is technically very feasible and convenient for all. It may also be more cost-effective as it eliminates expired / unused / surplus items.

Shared care

PKU, like other rare disease, needs to be managed under the direction of a specialist centre. Nonetheless, appropriate and effective joint care needs to be maintained between the local team and the tertiary team, and should incorporate dietetic input.

References

1. Office NS. Children 2010. Valletta, Malta: 2010.
2. Farrugia R, Scerri CA, Montalto SA, Parascandolo R, Neville BG, Felice AE. Molecular genetics of tetrahydrobiopterin (BH4) deficiency in the Maltese population. *Mol Genet Metab*. 2007; 90(3): 277-83.
3. Weetch E, Macdonald A. The determination of phenylalanine content of foods suitable for phenylketonuria. *J Hum Nutr Diet*. 2006; 19(3): 229-36.
4. Di Ciommo V, Forcella E, Cotugno G. Living with phenylketonuria from the point of view of children, adolescents, and young adults: a qualitative study. *J Dev Behav Pediatr*. 2012; 33(3): 229-35.
5. Gentile JK, Ten Hoedt AE, Bosch AM. Psychosocial aspects of PKU: hidden disabilities--a review. *Mol Genet Metab*. 2010; 99 Suppl 1: S64-7.
6. Jaggi L, Zurfluh MR, Schuler A, Ponzone A, Porta F, Fiori L, et al. Outcome and long-term follow-up of 36 patients with tetrahydrobiopterin deficiency. *Mol Genet Metab*. 2008; 93(3): 295-305.
7. Read CY. The demands of biochemical genetic disorders: a survey of mothers of children with mitochondrial disease or phenylketonuria. *J Pediatr Nurs*. 2003; 18(3): 181-6.
8. Belanger-Quintana A, Dokoupil K, Gokmen-Ozel H, Lammardo AM, MacDonald A, Motzfeldt K, et al. Diet in phenylketonuria: a snapshot of special dietary costs and reimbursement systems in 10 international centers. *Mol Genet Metab*. 2012; 105(3): 390-4.
9. Eijgelshoven I, Demirdas S, Smith TA, van Loon JM, Latour S, Bosch AM. The time consuming nature of phenylketonuria: a cross-sectional study investigating time burden and costs of phenylketonuria in the Netherlands. *Mol Genet Metab*. 2013; 109(3): 237-42.
10. National Institutes of Health Consensus Development Conference Statement: phenylketonuria: screening and management, October 16-18, 2000. *Pediatrics*. 2001; 108(4): 972-82.
11. Camfield CS, Joseph M, Hurley T, Campbell K, Sanderson S, Camfield PR. Optimal management of phenylketonuria: a centralized expert team is more successful than a decentralized model of care. *J Pediatr*. 2004; 145(1): 53-7.
12. Attard Montalto S, Zammit R, Felice A, Scerri C, Buhagiar G, Parascandolo R, et al. Report of the Committee for Review of Phenylketonuria and other diseases within the National Newborn Screening (PONNS) Programme. Malta: Department of Health, 2005.
13. Blau N, van Spronsen FJ, Levy HL. Phenylketonuria. *Lancet*. 2010; 376(9750): 1417-27.

A unique case of esophageal perforation caused by prickly pears

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Abstract

This is a report of a previously healthy 20-year-old male presenting with the sensation of a foreign object being stuck in the throat and difficulty speaking after the ingestion of 2 prickly pears. Tests were performed, confirming an esophageal perforation which was managed medically. The patient was discharged after 7 days in hospital with no complications.

Keywords

Perforation, esophageal, Boerhaave's, syndrome

Introduction

Esophageal perforation is a condition which is potentially life threatening and requires immediate monitoring and treatment.

It is most commonly caused iatrogenically, but other causes include spontaneous perforation (Boerhaave's syndrome), foreign body ingestion and trauma.¹

The esophagus lacks a serosal layer and is therefore more vulnerable to life threatening complications. Once a perforation (i.e., full-thickness tear in the wall) occurs, retained gastric contents, bile, saliva, and other substances may enter the mediastinum, resulting in mediastinitis.² This article describes a unique case of esophageal perforation caused by the ingestion of peeled prickly pears.

Case Report

A previously healthy 20-year-old male was referred to accident and emergency a few hours after eating 2 peeled prickly pears. The patient described a foreign body sensation in his throat with dyspnea, dysphagia and odynophagia. There was no history of alcohol ingestion. He had attempted to eat a piece of bread to dislodge the foreign body, to no effect.

On examination parameters were stable and the chest was clear. He was referred to ENT casualty where a flexible nasal endoscopy did not reveal any abnormalities. A soft tissue x-ray of the neck revealed subcutaneous emphysema.

A CT scan with water-soluble contrast of the neck was subsequently performed, revealing surgical emphysema of the skin up to the base of the skull and the presence of pneumomediastinitis due to a small perforation.

The patient was admitted for observation and was kept nil by mouth, with intravenous fluids, co-amoxiclav and metronidazole. The patient's parameters were stable for 3 days. On the fourth day he was allowed sips of water, progressing to a normal diet. On the seventh day he was discharged.

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Case Report

A repeat chest x-ray showed no abnormalities.

He was followed up at ear, nose and throat outpatients 2 weeks later. The oesophageal perforation healed without further complications and the pneumomediastinitis was successfully treated conservatively. A repeat chest X-ray showed the absence of the pneumomediastinitis and blood results showed normal results.

Discussion

Prompt diagnosis and treatment of esophageal perforation is critical for immediate patient care.³ A delay of greater than 24 hours in diagnosis and treatment of an esophageal perforation is associated with a higher mortality rate.

The frequency of esophageal perforation varies, but in the United States it is approximately 3 in 100,000 people.⁴ The majority of perforations are

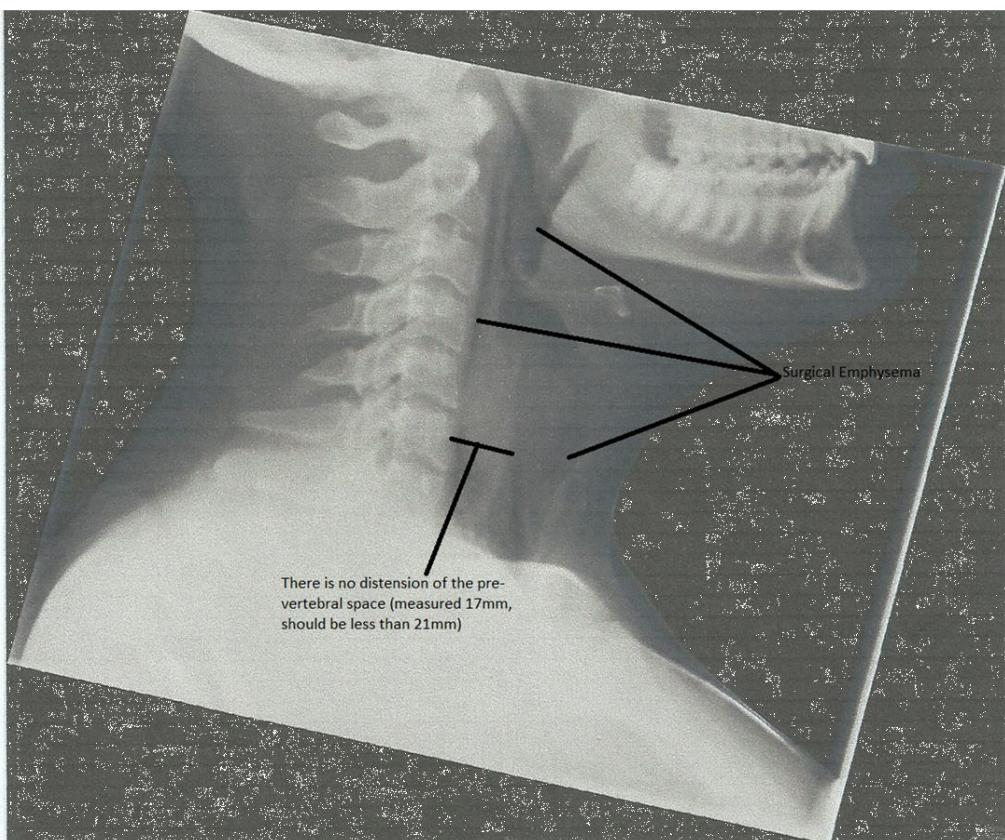
caused by medical instruments during a procedure, although other causes include trauma to chest and esophagus, tumours and previous surgery.⁵

What makes this case unique is the etiology of this perforation being an innocuous, edible fruit. The location of the perforation may depend on the cause.

In some cases, esophageal perforation may be managed surgically, although contraindications exist. These include a cervical perforation that cannot be assessed (but can be drained), an esophageal malignancy and also diffuse mediastinal necrosis.²

In this case, however, while pneumomediastinitis was present, the tear was small enough for the esophagus to heal on its own, resulting in the decision to continue with conservative management of the patient.

Figure 1: X-Ray of neck, lateral



Case Report

Figure 2: Soft Tissue X-Ray, PA

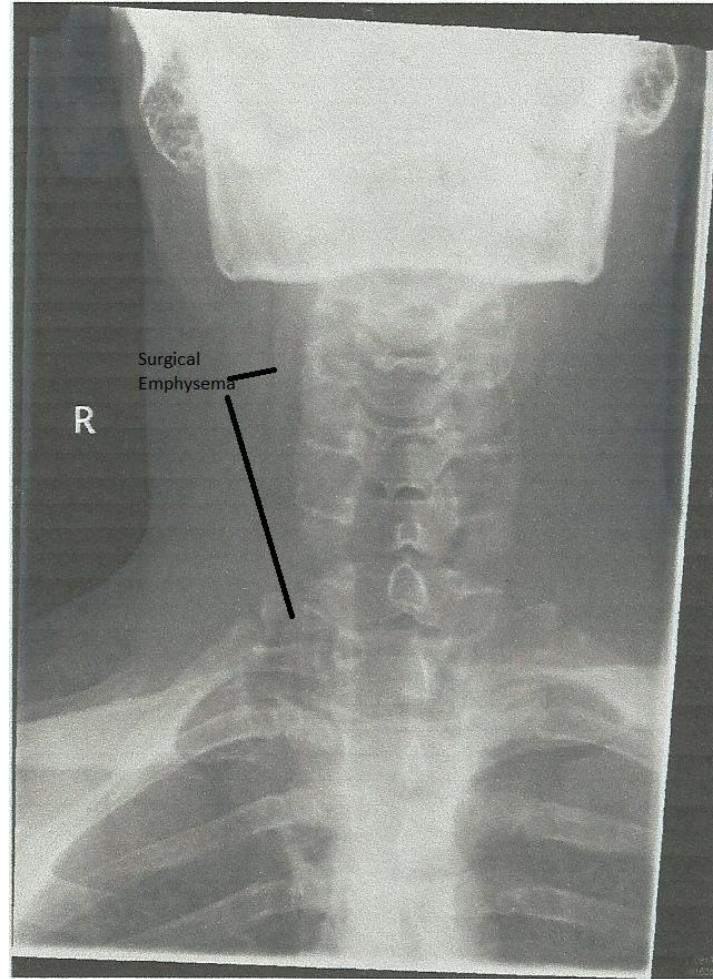
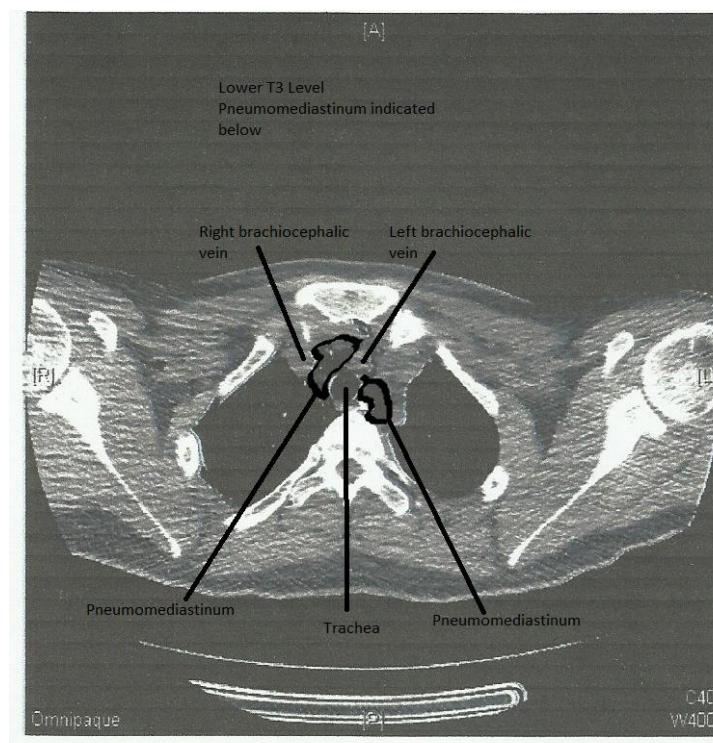


Figure 3: T3 level CT scan



Case Report

Figure 4: T1 level CT scan

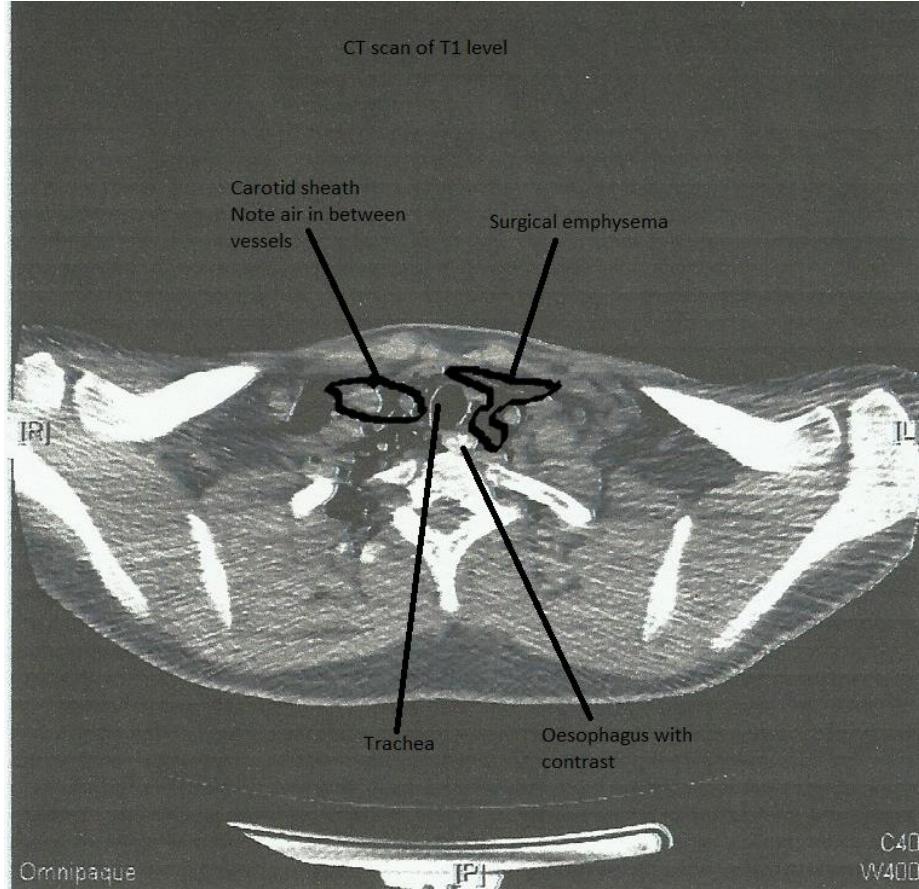
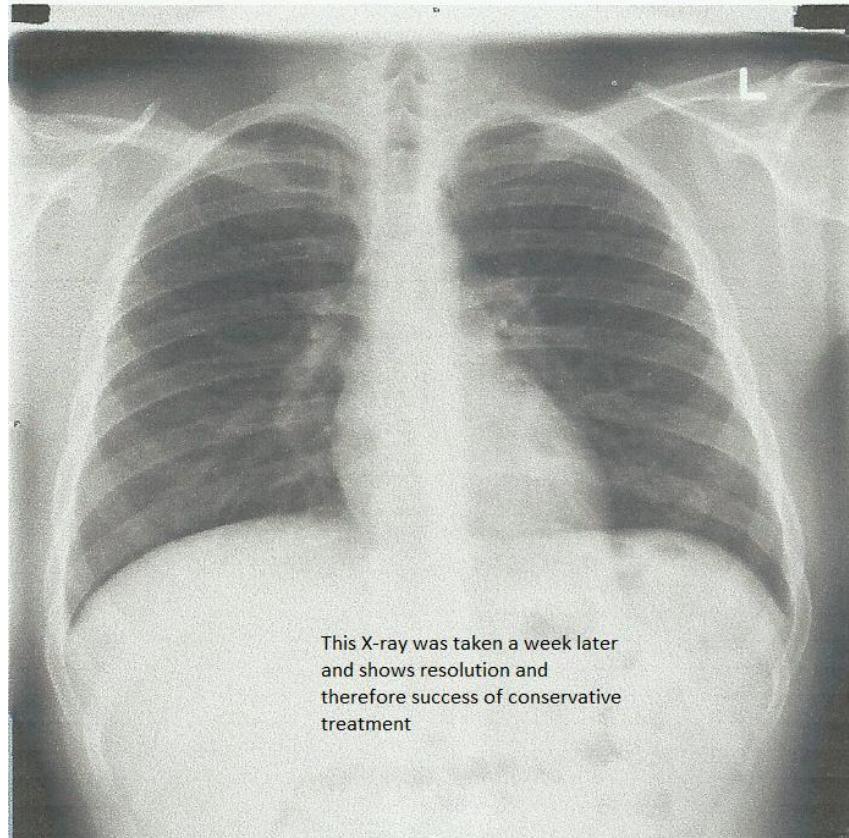


Figure 5: Normal X-Ray, PA



Case Report

References

1. Søreide JA, Viste A. Esophageal perforation: diagnostic work-up and clinical decision-making in the first 24 hours. *Scandinavian Journal of Trauma, Resuscitation and Emergency Medicine* 2011; 19(66): . <http://sjtrem.biomedcentral.com/articles/10.1186/1757-7241-19-66> (accessed February 2015).
2. Raymond DP, Jones C. *Surgical management of esophageal perforation*. <http://www.uptodate.com/contents/surgical-management-of-esophageal-perforation> (accessed May 2015).
3. Lehrer JK. *Esophageal perforation*. <http://umm.edu/health/medical/ency/articles/esophageal-perforation> (accessed May 2015).
4. Mueller DK. *Esophageal Rupture*. <http://emedicine.medscape.com/article/425410-overview> (accessed May 2015).
5. Vogel SB, Rout WR, Martin TD, Abbott PL. Esophageal Perforation in Adults. *Annals of Surgery* 2005; 241(6): . <http://www.ncbi.nlm.nih.gov/pmc/articles/PMC1357179/> (accessed June 2015).

An unusual case of intertrigo in an adult caused by purely cutaneous Langerhans cell histiocytosis

Godfrey Baldacchino, Michael J. Boffa, Alexandra Betts, Alex Gatt

Abstract

We report a case of persistent intertrigo in an adult, eventually diagnosed as cutaneous Langerhans cell histiocytosis (LCH). It is known that LCH has a predilection for intertriginous areas, however purely cutaneous disease as in our case, is uncommon and usually other systems are affected. Following the report, literature of similar cases is reviewed to determine possible outcomes and to decide on the best possible treatment options.

Keywords

Intertrigo, Langerhans cell histiocytosis

Case report

A 29-year old obese Maltese man was referred to the Dermatology Department in March 2012, with a one month history of worsening burning sensation in both axillae and groins, not responding to topical antifungal creams. A similar episode had apparently occurred a few months earlier and settled after application of a topical steroid/antifungal cream. He had a history of schizoaffective disorder and was on fluphenazine 25mg depot injection every 5 weeks but had no previous history of skin or other medical problems. No positive symptoms were elicited on systemic enquiry.

On examination there were striking, symmetrical, well-circumscribed, non-scaly erythematous-violaceous areas of induration in both axillae extending towards the proximal medial aspect of the arms (fig 1a). The affected areas were warm to touch and slightly tender. There were similar changes beneath the abdominal apron and in the groins extending towards the anterolateral thighs (fig 1b), and over the lateral right foot and ankle (fig 1c). There was no palpable lymphadenopathy, no hepatosplenomegaly and no visible abnormality in the scalp, external ears, mouth and nails.

An incisional biopsy from the right axilla was taken at presentation and empirical treatment with clarithromycin for 2 weeks for possible cellulitis was prescribed, with only minimal reduction in erythema at review 3 weeks later. Histology showed papillary dermal and deep dermal perivascular clusters and sheets of large ovoid cells with abundant pale cytoplasm and irregular, grooved reniform nuclei. These cells were accompanied by a variably dense inflammatory infiltrate composed of lymphocytes, eosinophils, and occasional plasma cells. Immunohistochemistry showed diffuse expression of S100 and CD1a by the large ovoid cells (fig 2). These features were consistent with

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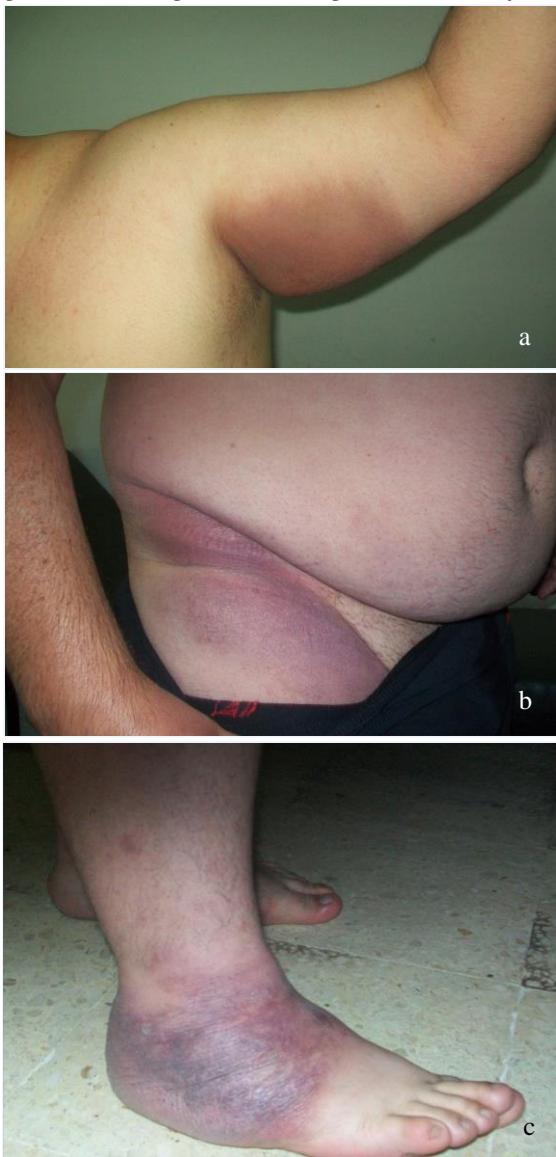
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Case Report

Langerhans cell histiocytosis (LCH).

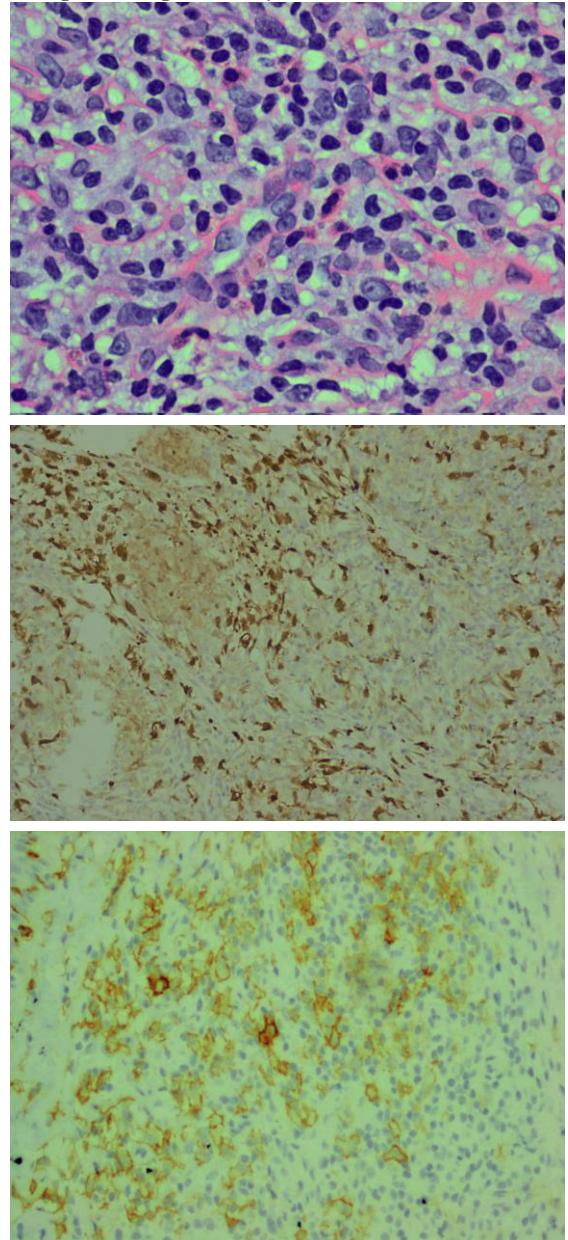
Figure 1: Indurated warm erythematous-violaceous plaques of LCH affecting the a) left axilla, b) right groin and thigh, and c) right ankle and foot



During follow up, topical hydrocortisone butyrate cream twice daily gave some symptomatic relief. However the skin lesions persisted. Another infiltrated area was noticed on the right temple in May 2014, and this was also confirmed to be LCH on biopsy. General physical examination never showed any other abnormalities. Routine blood tests showed a mildly elevated erythrocyte sedimentation rate ranging between 33 and 19 mm/hr (normal <15mm/hr), raised blood glucose, slightly deranged liver function tests, and combined hyperlipidaemia. Abdominal ultrasound showed a fatty liver and left renal pelviureteric dilatation

with a small stone.

Figure 2: Histology of a biopsy taken from the right axilla A) H&E showing clusters and sheets of large ovoid cells with abundant pale cytoplasm and irregular, grooved reniform nuclei. B) CD1a and C) S100 protein positivity on Immunohistochemistry



The patient was referred to a haematologist for further investigation of the LCH and to a diabetologist for better glycaemic and lipaemic control.

Hormone profile showed an elevated prolactin level attributable to fluphenazine. Complete blood count (CBC), serum protein electrophoresis, and specific gravity, remained

normal throughout. Skeletal survey, computerized tomography scans of brain, thorax, abdomen and pelvis, and magnetic resonance imaging of the pituitary, failed to detect any other foci of LCH other than in the skin.

In view of previous reports of cutaneous LCH responding to phototherapy, the patient was started on twice weekly narrow band ultraviolet B treatment (NB-UVB-TL01) in June 2014. Over the first 9 months of treatment, the lesions of LCH softened and faded slightly. However, no further improvement was observed by March 2015. The patient was subsequently offered psoralen combined with ultraviolet -A treatment (PUVA), but refused further treatment except topical hydrocortisone butyrate. He remains well apart from his persistent skin lesions and is being followed up regularly by dermatologists and a haematologists.

PET scan performed in June 2015, confirmed disease was still limited to the affected areas of skin.

Discussion

Intertrigo is a dermatosis involving the skin folds. Epithelial loss caused by friction of moist apposing skin is the commonest cause of intertrigo. Secondary growth of opportunistic organisms such as yeasts, bacteria, and dermatophytes at such sites, account for most other causes. Seborrhoeic dermatitis, contact dermatitis, atopic dermatitis and psoriasis are also fairly common causes.¹ This case adds LCH as another cause to be considered in cases of refractory intertrigo.

LCH is an enigmatic condition characterized by tissue invasion and damage by Langerhans cells (LHCs). These cells are large, with abundant pale cytoplasm and a reniform nucleus. They immunohistochemically stain for langerin (CD207), CD1a and S100, and ultrastructurally contain Birbeck granules. The aetiology is unclear. Debate whether LCH is a neoplastic process, an immune disorder or a genetic condition is ongoing.

Recent literature favours the theory that LCH is a neoplasm with monoclonal proliferation of bone-marrow-derived monocytes exhibiting CD1a+ and langerin on immunohistochemistry (langerin denoting the presence of Birbeck granules where electron microscopy is not available). This particular pattern of immunohistochemistry staining

correlates with consistent X chromosomal mutations on human androgen receptor genes (HUMARA) of lesional LC.²⁻⁴ Further support that LCH is a neoplastic condition is the presence of BRAF V600E mutations in 57% of subjects with LCH.⁴ The detection of chromosomal fragility on chromosomes 1, 4, 6, 7, 9, 16, 17 and 22 together with telomere shortening in lesional Langerhans cells further supports a neoplastic origin.⁶

A reactive immune process is suggested by the presence of multiple inflammatory markers such as TNF- α and others in lesional tissue in response to an unidentified stimulus.⁷ However, LCs remain immature both morphologically and functionally, with non-dendritic roundish cells which fail to stimulate an effective T-cell immune response. Such LCs express CD83 and CD40 which denote immaturity. Cytokines enhancing maturation such as TNF- α and IL-1 β , and others preventing maturation like TGF β 1 and IL-10 are detected but lesions tend to contain immature LCs.⁶⁻⁸ These cells can be transformed to functional maturity by the addition of CD40+ ligand but their morphology is not altered.⁷

Some evidence advocating that LCH is a genetic condition is obtained from studies that demonstrated an 86% concordance in monozygotic twins with LCH and that LCH occurs more often in families where there is one affected member.⁹ However it is not clear which mechanisms are involved.

Chu postulates the involvement of D-retrovirus in the pathogenesis.¹⁰ Again no definite proof is currently available.³

Adult LCH is uncommon with an estimated yearly incidence of 1-2 per million.¹¹ It usually, but not exclusively affects Caucasians, is commonest between 30-50 years of age, and becomes rarer with advancing age.¹² LCH can affect one or more organ systems and in any combination. The nomenclature of specific LCH syndromes such as Letterer-Siwe disease, eosinophilic granuloma, and Hand-Schuller-Christian disease has been abandoned because of inconsistency of the clinical pictures. Instead LCH is classified by the Histiocyte Society into three categories according to the organ systems affected: (i) single system disease, (ii) multisystem disease, and (iii) multisystem disease with organ failure.¹⁰

The clinical course of LCH is unpredictable.

Case Report

Barres et al. suggested that BRAF-V600e mutations in bone marrow dendritic cells favour high risk for multisystem disease with organ failure, whereas if the mutation occurs only in lesional dendritic cells this would represent the low risk type of LCH.¹³ Unfortunately, BRAF-V600e mutations are only detected in about half of the cases of LCH. Single system disease may remain confined to the respective system (low risk) or may progress to involve other organs (multisystem disease). Multisystem disease, with liver, spleen, bone marrow, lung and skeletal involvement, is considered as high risk with increased mortality.¹⁴ In our patient, to date no extension to other organ systems has been noted. He is thus considered as a case of purely cutaneous LCH and classified as low risk for developing multisystem disease with organ failure.

Cutaneous lesions of LCH occur in at least 50% of adult cases of LCH and are usually associated with multisystem disease involving bone, lungs, pituitary gland and reticuloendothelial system. Purely cutaneous LCH occurs in only 7% of all patients with LCH.¹⁵ This highlights the singularity of our case which occurred in Malta with a population of 440 000.

Cutaneous LCH has a predilection for intertriginous and seborrhoeic areas. Multiple reports of LCH affecting groins, perineum, perianal area, genitalia, axillae, inframammary folds, scalp and retro auricular areas have been published.^{10-11,14,16-18,20} In spite of this, there is no published literature to explore why LCH preferentially affects such sites. We postulate that these sites may harbour low-grade non-specific inflammation, either due to friction of opposing skin surfaces or superficial infection which could induce the release of chemoattractants to LCs.

Cutaneous manifestations of LCH are diverse and often pose diagnostic difficulty during physical examination. The commonest types of lesions include yellow-brown scaly patches, papules and nodules with or without exudate. Rarer manifestations of cutaneous LCH include lesions clinically similar to pyoderma gangrenosum, bruising, amoebiasis, eruptive xanthomata, prurigo nodularis, arthropod bites, vesicles, pustules, cherry spots, plane warts, Darrier's disease, and pyogenic granuloma. Nail involvement with paronychia, nail grooving and onycholysis are also

documented.^{1,14,16} Our patient had uniform, mildly infiltrated red-violaceous plaques without petechiae, scaling or ulceration in the intertriginous areas, scalp and ankle. Although these sites are commonly involved in LCH, this type of lesion appears rarely, if ever documented.

The possibility that single system LCH may progress to multisystem disease always needs to be considered. Diabetes insipidus due to pituitary invasion by LCH is one of the best-known complications.¹⁷ Haematological malignancies such as chronic myelomonocytic leukaemia, acute lymphatic leukaemia and lymphomas are also possible complications.¹⁸

In our case, the condition so far appears to be progressing only as cutaneous LCH with new lesions on the right ankle and right temple developing over a period of two years. No other abnormality attributable to LCH or haematological malignancy has been found in other systems despite thorough investigation.

In our patient, NB-UVB had a noticeable but short-lived effect, thus further therapeutic modalities were considered to try to halt the condition. Such modalities would include PUVA, local radiotherapy, imiquimod, systemic isotretinoin, low dose methotrexate, cyclosporine, topical nitrogen mustard, thalidomide and intralesional interferon- α or interferon- β .^{18-23,27} This order of single-agent treatment offers successive options of treatment with the intention of limiting adverse effects. However, the efficacy of individual treatments was inconsistent with several reports of treatment failure and relapse.²⁷ Our patient refused PUVA and other treatments, despite his concern about the cosmetic appearance of the lesion on the scalp.

For resistant cases of LCH or multisystem disease affecting vital organs, chemotherapy regimens are often used. These include combinations of chlorodeoxyadenosine, vincristine, vinblastine, cytarabine, 6-mercaptopurine, cyclophosphamide, etoposide and systemic steroids.^{18,20,25-27}

Our patient needs lifelong follow-up in order to monitor any extension of his condition, relapses and any other arising complications.

References

1. Burns T, Breathnach S, Griffiths C, Cox N. Rook's textbook

Case Report

- of dermatology, 8th edition, 71.2-71.4.
- topical nitrogen mustard. *Clin Exp Dermatol.* 1986; 11(2):183-7.
2. Hage C, Willman CL, Favara BE, Isaacson PG. Langerhan's cell histiocytosis (histiocytosis X): immunophenotype and growth fraction. *Human Pathology*, 1993; 24: 840-5.
 3. Willman CL, McClain K. An update on clonality, cytokines and viral aetiology in Langerhans cell histiocytosis. *Haematol Oncol Clin North Am* 1998; 12: 407-16
 4. Yu RC, Chu C, Buluwela L, et al. Clonal proliferation of Langerhans cell histiocytosis. *Lancet* 1994; 343: 767-8
 5. Badalian-Very G, Vergilio J, Degar BA, MacConaill L, Brandner B, Calicchio M et al. Recurrent BRAF mutations in Langerhans cell histiocytosis. *Blood* 2010; 116: 1919-23
 6. Abla O, Egeler RM, Weitzman S. Langerhans cell histiocytosis: Current concepts and treatments. *Cancer Treat Rev* 2010; 36: 354-9
 7. Ruco LP, Stoppacciaro A, Vitolo D, Uccini S, Baroni CD. Expression of adhesion molecules in langerhan's cell histiocytosis, *Histopathology* , 1993; 23: 29-37.
 8. Geissman F, Lepelletier Y, Fraitag S, Valladeau J, Bodemer C, Debre M et al. Differentiation of Langerhans cells in Langerhans cell histiocytosis. *Blood* 2001; 97: 1241-8
 9. Arico M, Danesino C. Langerhans cell Histiocytosis: Is there a role for Genetics? *Haematologica* 2001; 86: 1009-14
 10. Chu T. Langerhans cell histiocytosis. *Australas J Dermatol.* 2001; 42:237-42.
 11. Liu YH, Fan XH, Fang K. Langerhans' cell histiocytosis with multisystem involvement in an adult. *Clin Exp Dermatol.* 2007; 32 : 765-8.
 12. Fichter J, Doberauer C, Seegenschmiedt H. Langerhans Cell Histiocytosis in Adults: An interdisciplinary Challenge. *Dtsch Arztebl* 2007; 104: 2347-53.
 13. Berres ML, Lim KP, Peters T, Price J, Takizawa H, Salmon H et al. BRAF-V600E expression in precursor versus differentiated dendritic cells defines clinically distinct LCH risk groups. *J Exp Med.* 2014; 211: 669-83.
 14. Querings K, Starz H, Balda BR. Clinical Spectrum of Cutaneous Langerhans' Cell Histiocytosis Mimicking Various Diseases. *Acta Derm Venereol.* 2006; 86: 39-43
 15. Weedon D, Weedon's Skin Pathology, 3rd edition, 965-970.
 16. Wang P, Wang X, Hong J, Wang Z. Extensive cutaneous Langerhans cell histiocytosis in an elderly woman. *J Dermatol.* 2011; 38(8): 794-7.
 17. Hoeger P.H, Janka-Schaub G, Mensing H. Late manifestation of diabetes insipidus in ``pure" cutaneous Langerhans cell histiocytosis. *Eur J Pediatr.* 1997; 156(7):524-7.
 18. Wollina U, Kaatz M, Krönert C, Scholebe J, Schmalenberg H, Schreiber G et al. Cutaneous Langerhans cell histiocytosis with subsequent development of haematological malignancies. *Acta Dermatovenerol Alp Pannonica Adriat.* 2006; 15(2): 79-84.
 19. Imafuku S, Shibata S, Tashiro A, Furue M. Langerhans cell histiocytosis in an elderly man successfully treated with narrowband ultraviolet B. *Br J Dermatol.* 2007; 157(6):1277-9.
 20. Campanati A, Simonetti O, Marconi B, Giuliodori K, Ganzetti G, Brandozzi G et al. Purely Cutaneous Langerhans' Cell Histiocytosis in an Adult Woman *Acta Derm Venereol.* 2009; 89(3): 299-301.
 21. Steen A.E, Steen K.H, Bauer R, Bieber T. Successful treatment of cutaneous Langerhans cell histiocytosis with low-dose methotrexate. *Br J Dermatol.* 2001; 145(1): 137-40.
 22. Wong E, Holden C.A, Broadbent V, Atherton D.J. Histiocytosis X presenting as intertrigo and responding to topical nitrogen mustard. *Clin Exp Dermatol.* 1986; 11(2):183-7.
 23. Matsushima Y, Baba T. Resolution of Cutaneous Lesions of Histiocytosis X by Intralesional Injections of Interferon Beta. *Int J Dermatol.* 1991; 30: 373-4.
 24. Meunier L, Marck Y, Ribeyre C, Meynadier J. Adult cutaneous Langerhans cell histiocytosis: remission with thalidomide treatment. *Br J Dermatol.* 1995; 132:168.
 25. Conias S, Stratton G and Stephenson G. Adult cutaneous Langerhans cell histiocytosis. *Australas J Dermatol.* 1998; 39:106-8.
 26. Park L, Schiltz C, Korman N, Langerhans cell histiocytosis, *J Cutan Med Surg.* 2012; 16:45-9.
 27. Grischikosky M, Arico M, Castillo D, Chu A, Doberauer C, Fichter J et al. Management of adult patients with Langerhans cell histiocytosis: recommendations from expert panel on behalf of Euro-Histio-Net. *Orphan J Rare Dis.* 2013;8:72

Syndrome of inappropriate anti-diuretic hormone secretion (SIADH) and posterior cerebral artery ischaemic event: two uncommon complications following posterior fossa decompression

Simon Mifsud, Emma Louise Schembri, Antoine Zrinzo

Abstract

Neurosurgical procedures in cases of Type 1 Arnold Chiari Malformation (ACM) may result in a wide spectrum of complications.¹ We report a case of a sixty-four year lady who underwent an elective posterior fossa decompression for Type 1 ACM. The procedure was complicated by syndrome of inappropriate anti-diuretic hormone secretion (SIADH) and an ischaemic cerebrovascular event affecting the posterior cerebral artery. The association of these complications with the procedure is rarely described in the literature. In spite of the poor prognosis associated with such complications, the patient made a relatively quick and uneventful recovery.

Keywords

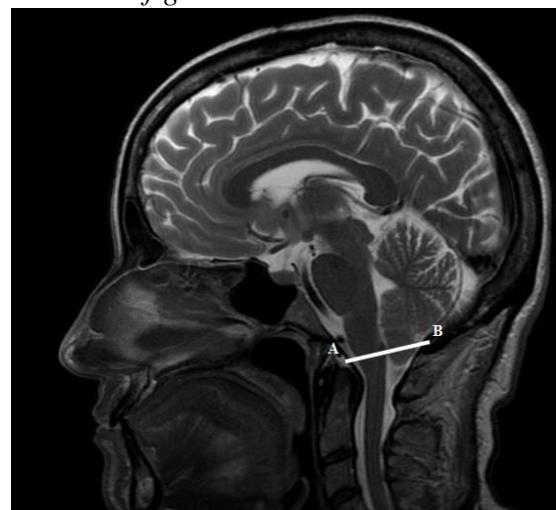
Neurosurgery, Arnold Chiari Malformation (ACM), Hyponatraemia, Syndrome of inappropriate anti-diuretic hormone secretion (SIADH), Cerebrovascular accident

Case Presentation

A sixty-four year old lady was admitted for an elective posterior fossa decompression for Type 1 Arnold Chiari Malformation (ACM). The patient had presented with a longstanding history of headaches and lower limb weakness and numbness. The only positive finding on neurological examination was clonus. The diagnosis of Type 1 ACM was confirmed on magnetic resonance imaging (MRI) of the brain which revealed low lying cerebellar tonsils associated with cervicomedullary kinking (Figure 1). The patient had a past medical history of hypothyroidism and hypertension which were well controlled on medications.

Figure 1: MR Head: Sagittal T2 view showing the cerebellar tonsils lying 7mm below McRae's line consistent with Type 1 Arnold Chiari Malformation.

McRae's line is a radiographic line drawn on a mid-sagittal section of an MRI joining the basion (A) and opisthion (B) which is depicted in this figure as a white line.



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Posterior fossa decompression was carried out uneventfully. Following the procedure, the patient was well and did not have apnoeic episodes throughout the night. On the first post-operative day, she was tolerating oral liquids and solids and her speech was normal. All of the former were indicative of intact brainstem function. However, by the second day post-operatively she started to complain of persistent headaches, nausea and fatigue.

Physical examination revealed a drowsy patient who was afebrile, normotensive and was not tachycardic. She was not cooperative for a full neurological examination; however there was no pronator drift and no apparent focal neurological deficit. The rest of the examination was unremarkable.

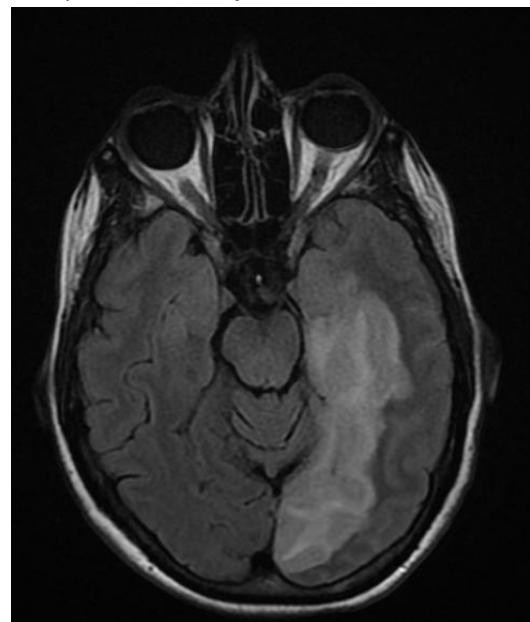
Peripheral blood investigations revealed a serum sodium level of 120mmol/L (normal values: 135-145mmol/L). This had dropped from 140mmol/L overnight. Serum osmolality was 253mOsm/kg (normal values: 275-299mOsm/kg), urine osmolality was 728mOsm/kg (normal values: 50-1200mOsm/kg) and urine sodium was 291mmol/L (normal values: 54-190mmol/L). Serum cortisol level was elevated at 1804nmol/L (119-618nmol/L). Complete blood count, thyroid function tests, lipid profile, and total protein and albumin levels were normal. The aforementioned blood tests in addition with the patient's normal blood pressure satisfied the Bartter-Schwartz Diagnostic Criteria for the syndrome of inappropriate anti-diuretic hormone secretion (SIADH).² An urgent computed tomography (CT) scan of the brain revealed hypo-density in the left occipito-temporal region but no haemorrhage.

In view of the hyponatraemia, the patient was kept nil by mouth and started on 0.9% saline infusion which was restricted to 1.5 litres daily. Despite this management, the patient's sodium level was on the decline. After four hours, the sodium level decreased further to 115mmol/L and clinical symptoms worsened. In view of the risks of seizing, the patient was transferred to the intensive therapy unit for administration of intra-venous 1.8% hypertonic saline.

Twelve hours after the administration of hypertonic saline, the patient's clinical condition improved and her serum sodium level increased to 120mmol/L. Neurological examination was

repeated since the patient was now more cooperative. The only positive finding was a right sided homonymous hemi-anopia. She underwent an urgent MRI brain which revealed an acute ischaemic stroke in the left posterior cerebral artery territory with a small focus in the medial aspect of the right cerebellar hemisphere (Figure 2). A magnetic resonance angiogram (MRA) revealed that a thrombus had occluded the left posterior cerebral artery. She was therefore started on aspirin and dipyridamole.

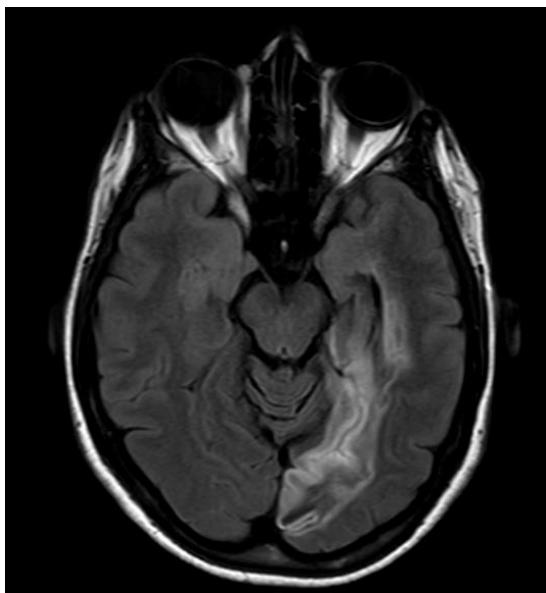
Figure 2: MR Head: Axial FLAIR view showing hyper-intensity in the left posterior cerebral artery territory indicative of an acute ischaemic stroke.



After four days of hypertonic saline administration, the serum sodium level gradually increased to 136mmol/L. At this point, the patient was transferred to the neurosurgical ward. She made a steady recovery with the help of the multidisciplinary team. The patient was discharged fifteen days post-operatively with a serum sodium level of 137mmol/L and a visual field assessment which revealed right sided superior quadrant-anopia. By the time of discharge she was completely independent.

The patient was reviewed one month later at an outpatient appointment. She remained well. Her serum sodium level was 144mmol/L. A repeat MRI brain revealed post-infarct macrocystic encephalomalacia in the left posterior cerebral artery territory (Figure 3).

Figure 3: MR Head: Axial FLAIR view showing post-infarct macrocystic encephalomalacia in the left posterior cerebral artery territory.



Discussion

Arnold Chiari Malformation (ACM) is a group of congenital hindbrain and spinal cord abnormalities, characterized by herniation of the posterior fossa contents into the spinal canal through the foramen magnum. Type 1 ACM is characterized by the caudal descent of the cerebellar tonsils through the foramen magnum by at least 3-5mm. It may be associated with an elongated fourth ventricle, syringomyelia and medullary kinking.¹

Type 1 ACM classically presents in adult life with symptoms of headaches and neck pain which are made worse with coughing and the Valsalva manoeuvre.³ Other symptoms may include weakness, numbness and unsteadiness.⁴ Presenting signs consist of a foramen magnum compression syndrome, a central cord syndrome or a cerebellar syndrome.⁴ Diagnosis is confirmed on MRI as this reveals essential details on the anatomy of the crano-cervical junction and any associated syringomyelia.^{1, 5} In symptomatic patients, treatment involves posterior fossa decompression. Complications following such a procedure may include: respiratory depression, cerebrospinal fluid (CSF) leak, aseptic meningitis, wound infection, failure of procedure and pseudo-meningocele formation.^{4, 6}

In our case, posterior fossa decompression resulted in two complications, these being hyponatraemia secondary to SIADH and an

ischaemic cerebrovascular event outside the brainstem. These are both uncommon complications of the procedure. Hyponatraemia is particularly common in neurosurgical patients. Its incidence is generally reported following subarachnoid haemorrhage, traumatic brain injury, intracranial tumours and hypophysectomy; however it is rarely seen in patients undergoing spinal procedures such as posterior fossa decompression.⁷ In addition, ischaemic events following posterior fossa decompression usually involve the brainstem following injury to the vertebral arteries or posterior inferior cerebellar arteries (PICA). The vertebral artery is at increased risk of injury during dissection of the posterior arch of cervical vertebra 1. The PICA can be damaged during extra-dural exposure or during intra-dural dissection.⁸ In this case, the ischaemic event involved a thrombus occluding the posterior cerebral artery.

Hyponatraemia is an important electrolyte disorder in neurosurgical patients. Signs and symptoms of hyponatraemia may be more pronounced in such patients due to the presence of co-existent factors that may cause cerebral irritation. In this case, breathing assessment and close monitoring of the patient's oxygenation were of paramount importance in view of the close relationship of the procedure with the brainstem. Hyponatraemic seizures may occur at higher than usual plasma sodium concentrations in the presence of cerebral irritation from hypercapnia, hypoxia and/or cerebral oedema.⁷ The two most common causes of hyponatraemia following neurosurgical procedures are SIADH and cerebral salt wasting (CSW).⁹ Differentiating the two conditions is essential, as their treatment is different.¹⁰

In SIADH, there's excessive unbalanced free water retention secondary to inappropriate anti-diuretic hormone (ADH) secretion. In CSW, the exact mechanism is still not completely understood, however natriuretic peptides play an important role. SIADH and CSW share common features i.e.: high urine osmolality, low plasma osmolality, low serum sodium level and high urine sodium level. The main distinguishing feature is the extracellular fluid volume state of the patient.¹⁰ In SIADH, there's a volume expanded state resulting in a euvolaeemic or hypervolaemic patient. In fact, a euvolaeemic status is one of the Bartter-Schwartz Diagnostic Criteria for SIADH (summarized in table 1). On the other

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hand, in CSW, there's renal salt wasting resulting in a contracted extracellular fluid volume, hence a hypovolaemic patient. Table 2 summarizes some of the differences between SIADH and CSW.

Table 1: Bartter-Schwartz Diagnostic Criteria for SIADH

Bartter-Schwartz Diagnostic Criteria for SIADH ²	Patient's Case
Hypo-osmolality (Plasma osmolality <280mOsm/kg)	253mOsm/kg
Inappropriate urine concentration (Urine osmolality >100mOsm/kg)	728mOsm/kg
Elevated urinary sodium (>40mmol/L) despite normal water and salt intake	291mmol/L
Patient is clinically euvoalaemic	Normotensive with good urinary output
No diuretic use	None used
Exclude hypothyroidism and glucocorticoid deficiency	None present

Table 2: Biochemical and clinical features of SIADH and CSW¹¹

Characteristic	SIADH	CSW
Extracellular Fluid Volume	Normal, Increased	Decreased
Urine Osmolality	High	High
Plasma Osmolality	Low	Low
Serum Sodium	Low	Low
Urine Sodium	High	Very high
Urine Output	Normal or Low	High
Treatment	Fluid Restriction	Fluids &/or mineralocorticoids

Hyponatraemia is a serious co-morbidity in neurosurgical patients as untreated this may lead to seizures, apnoea, coma and death. Hence identifying and treating the cause is essential. SIADH is managed according to the severity of the symptoms. Initially in mild to moderate severity, the patient should be managed with fluid restriction, however if symptoms worsen, hypertonic saline should be administered.¹¹ Fluid restriction should not be used in CSW as these patients are hypovolaemic and their blood pressure can drop

further if they are deprived of intra-venous fluids. Instead they require 0.9% or hypertonic saline to maintain circulation.¹² In both situations, hyponatraemia should be corrected slowly at a rate of < 8mmol/L in 24 hours so as to avoid the risk of central pontine myelinolysis.¹³

This case also highlights the importance of having a low threshold to perform a CT brain scan in hyponatraemic patients after neurosurgical procedures. This is useful so as to assess the level of cerebral oedema and exclude any haemorrhagic or ischaemic insults. In this patient, the CT brain revealed hypodensity in the left occipito-temporal region indicating that an ischaemic stroke had occurred. This was valuable since the patient's confused state secondary to hyponatraemia, made visual field and neurological assessment challenging. Following the confirmation of an acute ischaemic event due to thrombus formation in the left posterior cerebral artery, the patient was started on anti-platelet agents to prevent further neurological sequelae.

Most posterior cerebral artery ischaemic events are caused by emboli from cardiac or proximal vertebral-basilar arteries. Local arteriothrombotic stenosis or occlusions of the posterior cerebral artery, as in this case, are less common causes of infarction.^{14 - 15}

In conclusion, both hyponatraemia and ischaemic strokes outside the brainstem are uncommon complications following posterior fossa decompression. Studies have also shown that the development of hyponatraemia is a negative prognostic marker in patients with ischaemic stroke resulting in a longer hospital stay and an increased mortality rate.¹⁶ Despite this, our patient was discharged fifteen days post-operatively with the only clinical deficit being superior quadrant-anopia, making this case noteworthy.

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References

1. Siasios J, Kapsalaki EZ, Fountas KN. Surgical Management of Patients with Chiari I Malformation. *Int J Paediatr.* 2012; 2012:640127.
2. Grant JF, Cho D, Nichani S. How Is SIADH Diagnosed and Managed? *The Hospitalist* [Internet]. 2011 Jul [cited 2016 Feb 03]. Available from: <http://www.the-hospitalist.org/article/how-is-siadhs-diagnosed-and-managed/2/>.

Case Report

3. Taylor FR, Larkins MV. Headache and Chiari I malformation: clinical presentation, diagnosis, and controversies in management. *Curr Pain Headache Rep.* 2002; 6(4): 331-7.
4. Paul KS, Lye RH, Strang FA, Dutton J. Arnold-Chiari malformation. Review of 71 cases. *J Neurosurg.* 1983; 58(2): 183-7.
5. Nash J, Cheng JS, Meyer GA, Remler BF. Chiari Type I malformation: overview of diagnosis and treatment. *WMJ.* 2002; 101(8): 35-40.
6. Menger R, Connor DE Jr., Hefner M, Caldito G, Nanda A. Pseudomeningocele formation following Chiari decompression: 19-year retrospective review of predisposing and prognostic factors. *Surg Neurol Int.* 2015; 6: 70.
7. Hannon MJ, Thompson CJ. Neurosurgical Hyponatraemia. *J Clin Med.* 2014; 3(4): 1084-1104.
8. Bejjani GK, Cockerham KP. Adult Chiari Malformation. Greater Pittsburgh Neurosurgical Associates (GPNA) [Internet]. 2001 [cited 2016 Feb 03]. Available from: <http://www.neurosurgery-web.com/Chiari.pdf>
9. Cole CD, Gottfried ON, Liu JK, Couldwell WT. Hyponatraemia in the neurosurgical patient: diagnosis and management. *Neurosurg Focus.* 2004; 16(4): 1-10.
10. Palmer BF. Hyponatraemia in a neurosurgical patient; syndrome of inappropriate antidiuretic hormone secretion versus cerebral salt wasting. *Nephrol Dial Transplant.* 2000; 15: 262-268.
11. Zaki SA, Lad V, Shanbag P. Cerebral salt wasting following tuberculous meningoencephalitis in an infant. *Ann Indian Acad Neurol.* 2012; 15(2): 148-50.
12. Gross P. Clinical Management of SIADH. *Ther Adv Endocrinol Metab.* 2012; 3(2): 61-73.
13. George V, Mullhi D, Jones AF. Central pontine myelinolysis following 'optimal' rate of correction of hyponatraemia with a good clinical outcome. *Ann Clin Biochem.* 2007; 44(5): 488-90.
14. Brandt T, Steinke W, Thie A, Pessin MS, Caplan LR. Posterior cerebral artery territory infarcts: clinical features, infarct topography, causes and outcome. Multicenter results and a review of literature. *Cerebrovasc Dis.* 2000; 10(3): 170-82.
15. Yamamoto Y, Georgiadis AL, Chang HM, Caplan LR. Posterior cerebral artery territory infarcts in the New England Medical Center Posterior Circulation Registry. *Arch Neurol.* 1999; 56(7): 824-32.
16. Rodrigues B, Staff I, Fortunato G, McCullough LD. Hyponatraemia in the prognosis of acute ischemic stroke. *J Stroke Cerebrovasc Dis.* 2014; 23(5): 850-4.