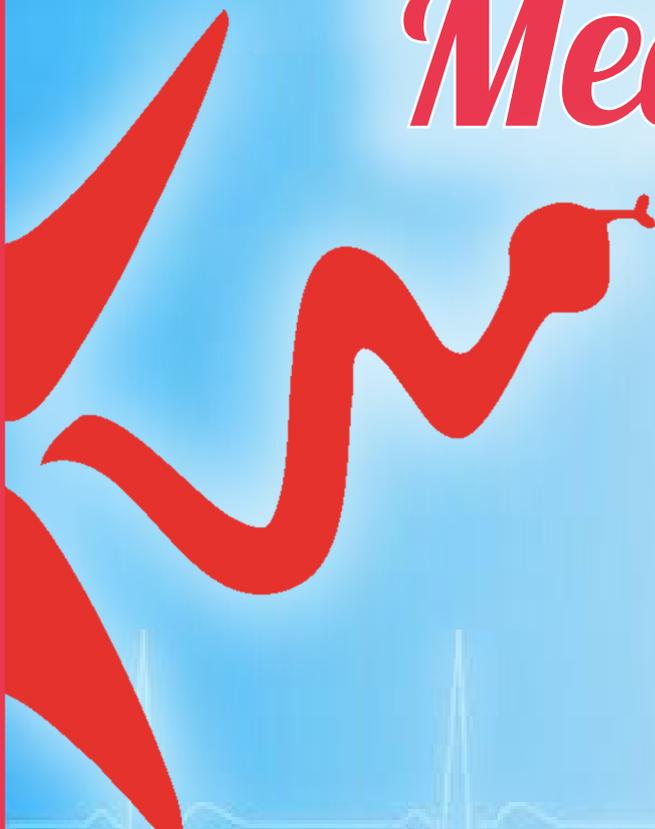


Minima Medicamentata



2016 - Issue 5



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Foreword from the Dean of Medicine & Surgery

The Malta Medical Students' Association (MMSA) is publishing another edition of Minima Medicamenta. The fact that the fifth edition has been compiled is an indication of its continuing success.

I believe that the main objective of medical education is to train students to learn to take a full history by talking to the patient, identify any abnormal physical signs, formulate a differential diagnosis and suggest possible options for treatment. Being knowledgeable about the commonly occurring mundane diagnoses is extremely important for day-to-day work. However, some understanding of the more uncommon, or possibly esoteric problems distinguishes the accomplished physician's mind and adds to intellectual interest.

This year the authors have embarked upon a number of interesting conditions which are uncommon in normal medical practice. These include topics such as infective endocarditis and Fournier's gangrene to name but two. It is perhaps pertinent to think of such uncommon conditions whilst formulating a differential diagnosis as such conditions may have long lasting consequences if missed. The positive features in the management of these conditions are eloquently highlighted in the cases presented. The two reviews on heavy metal intoxication and phantom pain make particularly interesting reading.

It is a pleasure and a privilege to have been asked to write this foreword for the fifth edition. I believe that the readers will find it stimulating and will particularly enjoy the style of presentation which will, without doubt, provide an excellent basis for learning. I wish it all the success it deserves.



Prof. Godfrey LAFERLA
Dean, Faculty of Medicine and Surgery,
University of Malta



Foreword from the Head of Physiology & Biochemistry

When I was invited to write this foreword, I searched for the publications that the Malta Medical Students Association published. Although I knew that MMSA has evolved in one of the most active Maltese university students' society, it was a pleasant surprise to find such an active group in the field of publications and the dissemination of students' scientific work. MMSA has really flourished since my time as its secretary in the mid-80's!

Apart from the usual case reports, this edition of the Minima Medicamenta is introducing the publication of medical students' physiology projects. The physiology project has till now taken the form of a literature review though from this year, we have introduced a pilot programme that shall also include projects with a practical and research component.

Looking at the numerous essays that have been produced in the past few years, one can find excellent ones that can and should be published. I would thus encourage our students in the preclinical years to take this opportunity to publish their work and use the facilities that MMSA has to offer.

As behind every successful endeavour there is an excellent team, I would like to congratulate the editorial team for their great work.

Enjoy this issue and I hope that the physiology project should kindle your interest in medical and scientific research.

Prof. Christian SCERRI

Head of the Department of Physiology and Biochemistry,
Faculty of Medicine & Surgery, University of Malta.



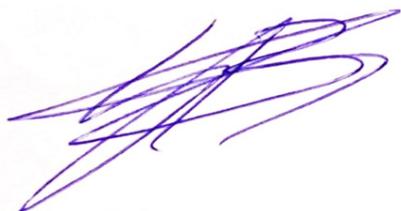
Foreword by the MMSA Medical Education Officer

The Standing Committee on Medical Education (SCOME), within the MMSA, aims at offering students the opportunity to participate and continue exploring different areas of their medical education. This is done by encouraging students to actively contribute to their own learning process and broadening their interests, by means of various seminars, workshops, and also publications. All in all, SCOME aims to make their education as well rounded as possible.

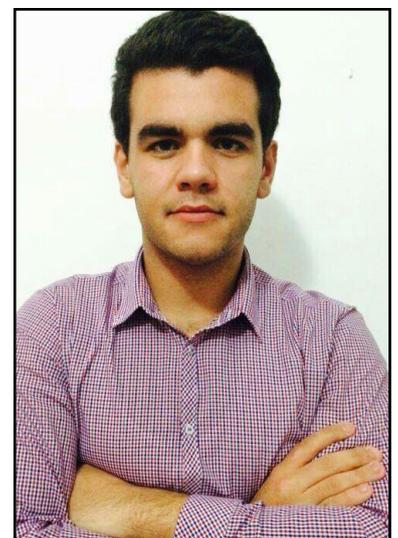
Minima Medicamenta is SCOME's main publication, which came about by the hard work and efforts of a very committed team of medical students and MMSA active members involved in the publication. Not only is this project useful to readers of these cases, but it has also allowed numerous students to take a more active interest in certain clinical rotations and given them an opportunity to try their hand at writing and publication, with impressive results. Furthermore, this journal provides a holistic approach to learning and help medical students to improve skills for becoming a better doctor.

My appreciation and admiration goes towards everyone involved in the Minima Medicamenta team, who were extremely dedicated and motivated towards this publication, which is evident from the end result. With this being the fifth edition of Minima Medicamenta, I would especially like to show gratitude towards the coordinator of this project, Georgiana Farrugia, for her constant effort in continuing upon the great work already done and her professional attitude in ensuring a high quality journal. In addition, I would like to also thank Christian Schembri for his preliminary commitment in this project.

I hope readers fully enjoy and benefit from this publication.



Saverio BIANCO,
MMSA SCOME Officer (2015/16)



The Editor's Letter

Dear research enthusiasts,

The story of the Malta Medical Students' Association's (MMSA) sole scientific journal – MINIMA MEDICAMENTA – continues, and one thing is sure: the work of issuing it annually, in print, is shifting towards increasing levels of professionalism. With a new editorial board and design team, each page of this publication is now being brought to you in a unique style. This year, on the occasion of the 5th anniversary from the official founding of this journal, a new layout has been introduced. Apart from the well renown case reports, a section dedicated to literature review papers has been included for the first time. The theme, however, remains the same as previous editions: RARE DISEASE.

The 2015/16 edition will bring you no less than four case reports, and two literature reviews, all of which have been compiled by medical students and reviewed by consultants, with the aim of raising awareness about a wide range of rare conditions presenting in our country. Above all, this publication is intended to act as a bridge between the pre-clinical and clinical journeys of medical school, by serving as a platform that encourages medical students to improve their clinical writing skills, and broaden their interest in research. In total, a team of over 25 persons have contributed in some way or another to produce yet another striking publication, and there will never be enough words to express the full extent of gratitude they deserve for their efforts. Hopefully, the diligent example set by all medical students who were eager to prepare their contributions today will encourage an even greater number of authors to contribute in future editions. I wish for nothing else but to see growing interest and vivid warm reactions towards one of the main MMSA publications.

In conclusion, I wish you all a great read, and would like to personally thank everyone who made this project come alive once more and who helped me lay another solid brick in MMSA's history.

Sincerest regards,



Georgiana FARRUGIA, BSc (Hons)
MMSA Minima Medicamenta Editor-in-Chief (2015/2016)



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Case Reports



Fournier's Gangrene

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□ Reviewer

Mr. Patrick Zammit,

Consultant Urologist at Mater Dei Hospital, Malta.

Mr. P.G., a 65-year-old male was referred to casualty by his family physician, following the complaint of a painful swelling in his left testicle, that was accompanied by a burning sensation on passing urine. Throughout the course of his admission at the local state hospital, a number of investigations were carried out. An ultrasound scan of both testicles, as well as a computed tomography scan of the abdomen and pelvis, delineated extensive thickening of the scrotal skin, as well as subcutaneous gas formation surrounding both testicles with extension to the penis and the right inguinal region. The patient was diagnosed with Fournier's gangrene, which is likely to be a complication of his uncontrolled Type II diabetes mellitus. This condition is classified as a rare and potentially life-threatening disease. Following the diagnosis, the patient received a right orchidectomy, circumcision, as well as subsequent rounds of scrotal debridement and wound cleaning. Pharmacological therapy was provided to relieve his symptoms.

Fact File on Fournier's Gangrene

Fournier's gangrene is classified as a fulminant form of infective necrotising fasciitis of the perineal, genital, or perianal regions, caused by both aerobic and anaerobic bacteria, including coliforms, Klebsiella, streptococci, staphylococci, clostridia, bacteroids, and corynebacteria (Johnin, 2000 & Yaghan, 2000). This rare, but potentially life threatening condition has been shown to have a predilection for male patients with diabetes, as well as long term alcohol misuse (Thwaini, et al., 2006). The synergistic activity of aerobes and anaerobes lead to the production of various exotoxins and enzymes which aid in tissue destruction, impaired phagocytic activity and spread of infection. The platelet aggregation and complement fixation induced by the aerobic flora, as well as the heparinase and collagenase produced by the anaerobic flora lead to microvascular thrombosis and dermal necrosis (Thwaini, et al., 2006). Although antibiotics and aggressive debridement have been broadly accepted as the standard treatment for Fournier's gangrene, the death rate from multiple organ failure remains high, averaging 20-30% of diagnosed cases (Pawlowski, 2004).

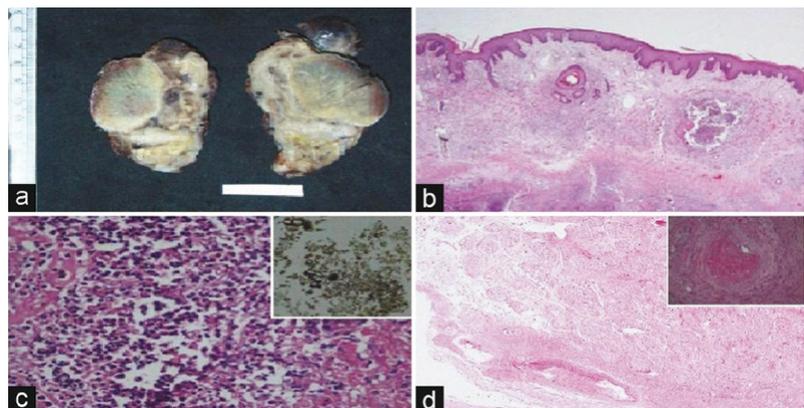


Figure 1: (a) Gross photograph of the testicles showing the cut surface containing extensive necrosis with haemorrhage just below the tunica; (b) Photomicrograph of scrotal skin showing necrotic areas in the dermis and subcutaneous tissue; (c) Photomicrograph showing broad aseptate fungal profiles with right angle branching; (d) Photomicrograph of testicles showing areas of necrosis and infarcted seminiferous tubules. (Retrieved from Kumar, et al., 2011).

This condition was named after the French venereologist, Jean Alfred Fournier, following his presentation of five cases in 1883 (Fournier, 1883). An estimated 2,476 cases of Fournier's gangrene have been reported in the literature worldwide (Vaz, 2006 & Burch, et al., 2007) however, it is difficult to quantify the epidemiology of this disease as the number of unreported cases remains unclear. The most historically prominent sufferers of Fournier's gangrene have been the king of Judea, Herod the Great, as well as the Roman emperor, Galerius.

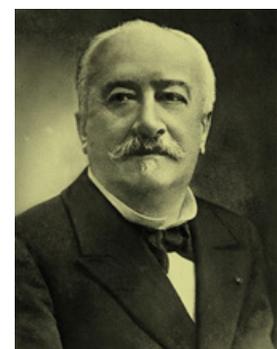


Figure 2: Jean Alfred Fournier (1832-1914), the French dermatologist who specialized in the study of venereal disease, after whom Fournier's gangrene was named.

Case Report on Fournier's Gangrene

Presenting Complaint

The patient was referred to casualty with a left testicular swelling, a right testicular mass and a burning sensation on passing urine. Moreover, these symptoms were accompanied by sudden pain, localized around the left testicle. The patient scored the severity of the pain as 6/10.

Past Medical & Surgical History

The patient is a known case of hypertension, hyperlipidaemia and Type II diabetes mellitus. He suffered from a perianal abscess 3 years ago. Furthermore, he underwent a left eye Schwannoma resection, circa 25 years ago. Recently, he received radiotherapy after having a tumour resected out of the right eye.

Drug History & Allergies

The patient is currently being prescribed the medications listed in Table 1. He is allergic to sulphonamide antibiotics.

Family History

The patient has a strong family history of diabetes mellitus. His mother developed gestational diabetes that ultimately progressed into Type II diabetes mellitus. She eventually died of multiple sclerosis. His sister is also affected with Type II diabetes mellitus.

Social History

The patient is an independent, retired civil servant, who lives with his wife who has been recently diagnosed with rectal carcinoma. He is an ex-smoker, and tends to engage in occasional alcohol intake during social events.

Systemic Inquiry

General Health: Obesity;

Cardiovascular System: Hypertension, hyperlipidaemia;

Respiratory System: Occasional shortness

of breath, pleural effusion, pulmonary atelectasis;

Gastrointestinal Tract: Diverticular disease;

Genitourinary System: Burning sensation on urination, left testicular swelling, right testicular mass, urinary incontinence;

Central Nervous System: Peripheral neuropathy;

Musculoskeletal System: Left foot hyperkeratosis;

Endocrine System: Uncontrolled Type II diabetes mellitus.

Physical Examination & Preliminary Investigations

Upon admission to casualty, the examinations and routine investigations listed in Table 2 were carried out on the patient.

Differential Diagnoses

1. Fournier's gangrene;
2. Varicocele;
3. Hydrocoele;
4. Strangulated inguinal hernia;
5. Testicular carcinoma.

Diagnostic Investigations

Requested investigation: **Ultrasound scan of both testicles;**

Justification for procedure: To exclude or confirm the presence of orchitis;

Result: The scrotal skin overlying both testicles is thickened, with accompanying extensive gas formation in the surrounding subcutaneous tissue. The right testicle is enlarged, measuring 2.2cm x 3.2cm, compared to the left testicle, which measures 1.4cm x 2.7cm. It contains an in-homogenous irregular mass, measuring 1.4cm x 1.7cm x 2cm, which demonstrates internal Doppler flow. The right epididymis is also enlarged with increased Doppler flow. A high grade varicocele and small hydrocoele are also present. The left testicle and epididymis are unremarkable (Figure 3).

Conclusion: A right testicular mass is present, in which a malignant process cannot be excluded; a less likely differential would include inflammatory changes involving the right testicle. Fournier's gangrene is suspected.

Generic Drug Name	Dosage	Frequency	Formulation	Reason for Prescription
Metformin	1g	Trice Daily, Indefinite	Oral Tablet	Control of Type II diabetes
Simvastatin	20mg	Once Daily, Indefinite	Oral Tablet	Prevention of hyperlipidaemia
Aspirin	75mg	Once Daily, Indefinite	Oral Tablet	Anti-coagulation
Valsartan	140mg	Once Daily, Indefinite	Oral Tablet	Anti-hypertensive
Clexane	40mg	Once Daily	Subcutaneous Injection	Prevention of thrombus formation
Oxybutynin	2.5mg	Twice Daily	Oral Tablet	Treatment of urinary incontinence
Bromhexine	10mls	Trice Daily	Oral Solution	Mucolysis

Table 1: Medications currently being prescribed to the patient.

Examination / Investigation	Result
Pulse Rate	100 bpm
SpO ₂	100 %
Blood Pressure	110/80 mmHg
Temperature	Afebrile
Heart Sounds	S1 + S2 + 0
Chest	Clear
Abdomen	Soft and non-tender
Electrocardiography	No abnormality detected
Chest X-Ray	No abnormality detected
Arterial Blood Gases	<ul style="list-style-type: none">• pO₂: 180 mmHg• pCO₂: 33 mmHg• pH: 7.4
Blood Analysis	<ul style="list-style-type: none">• Hb: 10.2 g/dL• Na⁺: 127 mmol/l• K⁺: 3.2 mmol/l• Cl⁻: 101mmol/l• Glucose: 7.9 mmol/l

Table 2: Examinations and routine investigations carried out on the patient upon admission to the casualty.

Requested investigation: Computed tomography scan of the abdomen and pelvis;

Justification for procedure: To determine the extent of spread of Fournier's Gangrene (if present);

Result: There is extensive thickening and gas bubbles in the wall of the scrotum extending to the penis and the right inguinal area. The right testicle is larger in size with heterogeneous enhancement. No free gas is detected in the pelvis. There is sigmoid colon diverticulosis.

Conclusion: The findings are in keeping with Fournier's Gangrene.

Diagnosis

The history of the presenting complaint, as well as the visibility of subcutaneous gas formation surrounding both testicles on the Computed Tomography scan of the abdomen and pelvis indicated a possible infectious disease process. The presence of a strangulated inguinal hernia was excluded upon the physical examination of the groin. Moreover, testicular carcinoma was excluded after an ultrasound scan of both testicles. Thus, it was concluded that the patient was experiencing complications of Type II diabetes mellitus, leading to Fournier's gangrene, with an accompanying high grade varicoele, and a small hydrocoele formation in the right testicle.

Management

Pharmacological Therapy

Upon admission to the hospital, the patient's glucose levels were excessively high so he was started on insulin injections to prevent further complications related to this condition. In light of his underlying infectious disease process, the patient was started on beta-lactamase antibiotics. Pain relief, anxiolytic and anti-emetic agents were also provided, as documented in Table 3.

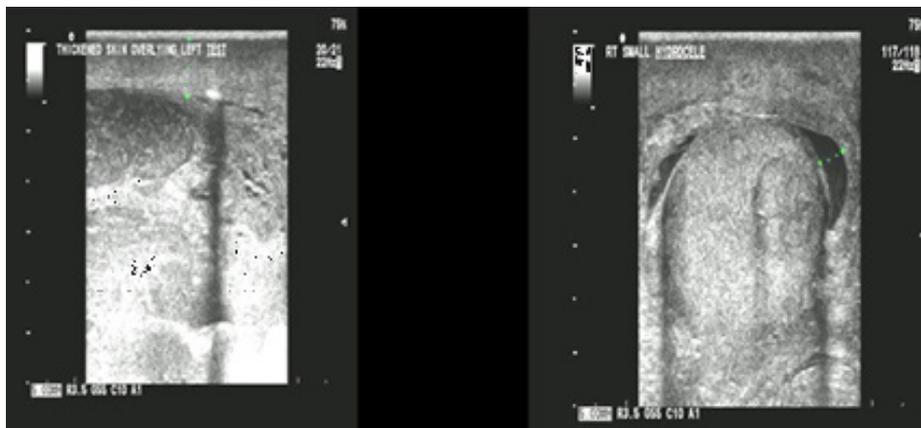


Figure 3: Mr. P.G.'s ultrasound scan images of the left and right testicles.

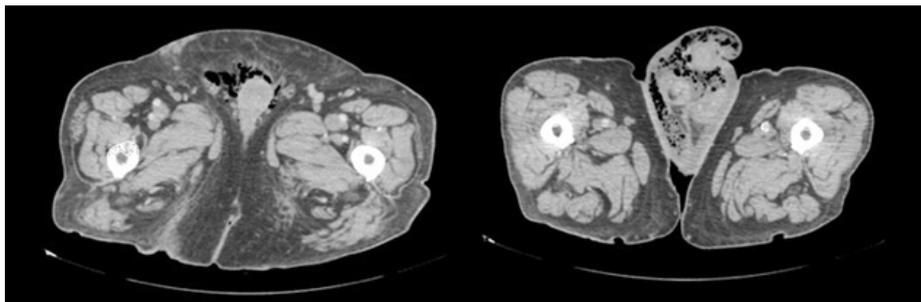


Figure 4: Mr. P.G.'s computed tomography scans of the abdomen and pelvis.

Generic Drug Name	Dosage	Frequency	Formulation	Reason for Prescription
Mixtard	56 units	Twice Daily	Subcutaneous Injection	Control of Type II Diabetes
Paracetamol	1g	PRN	Intravenous Injection	Analgesia
Pethidine	50mg	PRN	Intramuscular Injection	Analgesia
Haloperidol	5mg	Once Daily	Intramuscular Injection	Anxiolytic
Stematil	12.5mg	PRN	Intramuscular Injection	Prevention of nausea and vomiting
Amoxicillin	500mg	Twice Daily	Oral Tablet	Antibiotic
Tazocin	4g	Trice Daily	Intravenous injection	Antibiotic

Table 3: Medications given upon admission to the hospital.

Surgical Therapy

The patient has received subsequent rounds of scrotal debridement and wound cleaning, followed by a right orchidectomy. At the request of the plastic surgeons, circumcision was also performed, which involved penile skin excision along with elimination of oedematous foreskin and any underlying adhesions. Moreover, post-operative care following these procedures included monitoring of vital parameters and glucose levels every four hours, urinary catheter input/output charting, pain relief as well as nutritional planning of an improved diabetic diet.

Follow Up

As part of his continuous wound care re-

gime, the patient was educated on how to change the tight packing dressing around the scrotum using Calcium Manginate, and disinfect the genital area with Beta-dine spray. Moreover, the patient was advised to follow a strict diabetic diet following discharge from the hospital to reduce the risk of developing further complications. Furthermore, the patient and his wife were educated about self-administration of insulin and the importance of hypoglycaemia monitoring was emphasized. A follow-up appointment at plastic surgery outpatients was booked.

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Pemphigus Vulgaris

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4th Year Medical Students at the Faculty of
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□ Reviewers

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Hospital, Malta.

Dr. Liam Mercieca
Higher Specialist Trainee in Dermatology at Sir
Paul Boffa Hospital, Malta.

Mr. L.F. is a 53yr old gentleman who initially presented to his family doctor with mouth ulcers, hoarseness and odynophagia. He was given various treatments including antibiotics, anti-virals, non-steroidal anti-inflammatory drugs (NSAIDs) and oral steroids with no effect. His condition worsened and was associated with a 5kg weight loss. He subsequently developed skin blisters and erosions and was referred to the dermatology department. A clinical diagnosis of pemphigus vulgaris was made and he was started on high dose oral steroids. A skin biopsy sent for histology and immunofluorescence confirmed the diagnosis. On confirmation he was admitted for rituximab therapy and started on azathioprine.

Fact File on Pemphigus Vulgaris

Pemphigus vulgaris is a potentially life-threatening autoimmune disease with a number of clinical variants. This blistering disorder affects the mucosa and the skin. In up to 50% of cases, it initially presents with intra-oral lesions, and may remain so for about a year (Becker, et al., 2009). This emphasizes the need for dentists to be aware of this condition as it is most likely to present first in their practice. This is particularly important as early recognition results in a better prognosis (Shafer, et al., 2008). The age of presentation is often between 30-50 years, with a male predominance of 2:1. Pemphigus vulgaris is estimated to affect only 1-5 patients per million populations per year (Shamim, et al., 2008).

The aetiology of the disease is still largely unknown, however, it is characterized by the production of autoantibodies against desmosomes, particularly targeting desmoglein 3. Desmoglein 3 is predominantly expressed in the oral mucosa, hence explaining the reason why initial presentation is often with oral lesions. The loss of adhesion between these structural units gives rise to the manifestation of intraepidermal bullae (Robinson, et al., 2004).

Characteristically the oral blisters are prone to rupture, with ensuing painful erosions. There is a predilection for soft-palate, buccal mucosa and lip involvement but any site in the oral cavity can be affected (Neville, et al., 2008).

Initially pemphigus vulgaris presents with a positive Nikolsky's sign, which is a pressure-induced wrinkling of seemingly healthy skin. Clear-fluid containing bullae, occurring over both normal as well as erythematous skin, are the primary lesions. These bullae increase in size on application of pressure, with the fluid spreading to the surrounding epidermis (indirect Nikolsky's sign). Scarring is not a feature, though the healing process is slow (Pradeep, et al., 2010).

A lesional biopsy is necessary to confirm diagnosis of pemphigus vulgaris. On histology, intraepidermal clefting with acantholysis and Tzanck cells in the prickle cell layer is characteristic. Direct and indirect immunofluorescence can be used to further confirm the diagnosis of pemphigus vulgaris. On indirect immunofluorescence IgG antibodies are seen circulating in the serum whilst on direct immunofluorescence, intercellular IgG antibodies can be seen (Tamgadge, et al., 2010).

Pharmacological therapy is aimed at reducing the autoantibody production and the accompanying inflammatory response. Corticosteroids and immunosuppressants often make up the treatment regimen. Overall mortality has improved significantly with corticosteroid therapy. Despite this, steroid use is limited due to their significant side-effect profile which contributes to morbidity. Thus, steroid-sparing immunosuppressive drugs such as rituximab, are nowadays considered early on in treatment. Therapy is tailored to the patient's clinical picture, taking into consideration any other comorbidities (Bassam, et al., 2015).

Case Report on Pemphigus Vulgaris

Presenting Complaint

The patient initially complained of discomfort whilst eating accompanied with nausea for a few weeks. He was reviewed by an E.N.T. specialist and was found to have an oedematous and erythematous uvula which resolved following a short course of prednisolone. On stopping the steroids, he developed mouth ulcers and hoarseness, resulting in odynophagia and troublesome eating. A few days later, he noted a single skin lesion in the supraclavicular region which bled after showering, however the patient

thought nothing of it. In the ensuing days, the number of mouth ulcers increased. After seeking the advice of his general practitioner, he was diagnosed with herpes zoster and started on a five-day course of acyclovir. Despite this, the mouth ulcers continued to increase in number together with the appearance of skin erosions on his chest, prompting him to attend the E.N.T. clinic. The patient was prescribed metronidazole, clarithromycin and diclofenac, however, his symptoms did not improve. He had also visited his dentist who had prescribed mouth gargles with little effect. At a subsequent dental appointment, a mucosal biopsy was taken for histology due to worsening mouth ulcers. Throughout the course of this history, he noted a five-kilogram weight loss with no associated loss of appetite. The following morning, he visited his general practitioner in view of worsening mouth ulceration and skin erosions. This prompted his general practitioner to refer him to Boffa Hospital for dermatological review and investigation.

Past Medical & Surgical History

The patient is a known case of hypothyroidism (diagnosed five years ago) and borderline hypercholesterolaemia. He wears dentures as a consequence of an extensive history of periodontal gum disease. Surgical history included two nasal polypectomies in 1991 and 2004.

Drug History & Allergies

The patient has no known drug allergies. Drug history is listed in Table 1.

Family History

The patient's father had a history of type II diabetes mellitus (TIIDM), and hypertension. He had a stroke aged 48 and died of natural causes. His mother had a history of ischaemic heart disease, heart failure, deep vein thrombosis, and died aged 81. He has five siblings. One of his brothers suffers from TIIDM and hypercholesterolaemia. His sister developed hypertension at 34 years and also suffers from hypercholesterolaemia.

Generic Drug Name	Dosage	Frequency	Formulation	Reason for Prescription
Levothyroxine	75 mcg	Once Daily	Oral Tablet	Control of hypothyroidism
Omeprazole	30mg	Once Daily	Oral Tablet	Control of dyspepsia

Table 1: Drug History.



Figure 1: Mr. L.F.'s supraclavicular skin erosions.



Figure 2: Mr. L.F.'s erosions on the inside of the lower lip.

Social History

The patient is married and lives at home with his wife and two healthy children. He is independent and works as an electrician in a residence for the elderly. He has no alcohol or smoking history.

Systemic Enquiry

General Health: Anxiety;
Cardiovascular System: Borderline hypercholesterolaemia;
Respiratory System: Nil to note;
Gastrointestinal Tract: Dyspepsia;
Genitourinary System: Nil to note;
Central Nervous System: Nil to note;
Musculoskeletal System: Nil to note;
Endocrine System: Hypothyroidism.

Upon dermatological consultation, the patient's lesions were examined (Figures 1 and 2).

Differential Diagnoses

1. Pemphigus vulgaris;
2. Pemphigus foliaceus;
3. IgA pemphigus;
4. Pemphigus erythematosus;
5. Bullous pemphigoid.

Diagnostic Investigations

Requested investigations: **Liver function tests & hepatitis screen;**

Justification for procedure: Possible deterioration of liver function on rituximab, and the use of rituximab in the presence of chronic viral hepatitis

may lead to worsening of pre-existing hepatitis;

Result: Normal.

Conclusion: No contraindication to rituximab therapy with respect to liver function.

Requested investigations: **Tuberculosis (TB) Quantiferon test & Chest X-Ray (CXR);**

Justification for procedure: To investigate for latent TB as rituximab therapy needed to treat pemphigus vulgaris may reactivate latent TB;

Result: CXR and Quantiferon test both normal.

Conclusion: No evidence of previous infection with TB.

Requested investigations: **Anti-nuclear antibody (ANA), extractable nuclear antigens (ENA) antibody and immunoglobulin tests;**

Justification for procedure: Possible other associated autoimmune disorders apart from pemphigus vulgaris;

Result: Normal.

Conclusion: Other associated autoimmune disorders highly unlikely.

Requested investigations: **Skin incisional biopsy for histology and direct immunofluorescence;**

Justification for procedure: Necessary for definite diagnosis of pemphigus vulgaris

Result:

Histology: Intraepidermal clefting with acantholysis in the prickle cell layer. A sparse chronic inflammatory cell infiltrate, which includes scattered eosinophils, is present in the papillary dermis. A perivascular lymphocytic infiltrate involves the superficial plexus and vessels in the mid dermis.

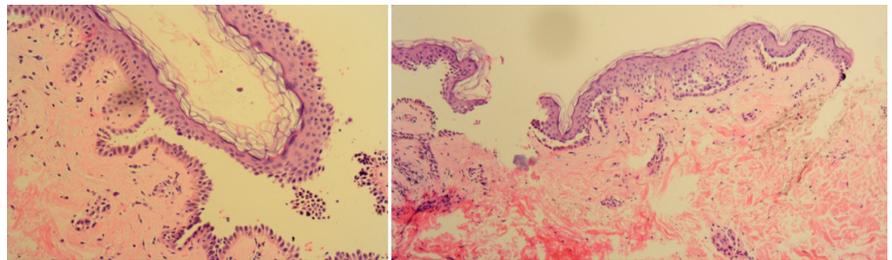


Figure 3: Mr. L.F.'s histology microscopy slides of the skin incisional biopsy.

Direct Immunofluorescence: Intercellular deposition of IgG and of C3 within the epidermis, outlining the cell membranes of keratinocytes in the prickle cell layer.

Conclusion: Diagnosis of pemphigus vulgaris confirmed.

Diagnosis

The characteristic nature of the skin lesions, coupled with the definite findings on histology and direct immunofluorescence, confirmed the diagnosis of pemphigus vulgaris. The investigations conducted revealed no contraindications to treatment with rituximab and high-dose steroids, thus, the patient was started on these two medications.

Management

Pharmacological Therapy

Following investigations, the patient was started on the following:

Follow Up

The patient received his weekly dose of intravenous (IV) rituximab for four weeks, with routine bloods and glucose monitoring. There was a partial response to treatment with some improvement but he was still getting new mouth ulcers. He will be followed up regularly at the outpatient department and will be continued on oral steroids and an

Generic Drug Name	Dosage	Frequency	Formulation	Reason for Prescription
Prednisolone	40mg	Once Daily	Oral tablet	To induce remission
Rituximab	500mg	Once Weekly	Intravenous injection	To induce remission
Azathioprine	50mg	Once Daily	Oral tablet	As a steroid sparing agent for maintenance.

Table 2: Pharmacological Therapy.

increasing dose of azathioprine. Further courses of rituximab are planned in view of active disease.

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Becker's Muscular Dystrophy

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Mr. K.B., a 23 year old gentleman, presented with difficulty climbing stairs, changes in posture and toe walking. Significant calf hypertrophy was seen on examination. A muscular dystrophy was the probable diagnosis and to confirm, this various investigations were carried out, including: genetic testing, electromyography (EMG), and creatinine kinase (CK) levels. The doctors' suspicions were confirmed and the patient was diagnosed with a de novo mutation of Becker's Muscular Dystrophy (BMD). A cardiac work up followed to assess for dilated cardiomyopathy which is associated with BMD, although Mr. K.B. was still asymptomatic. BMD is a very rare disease with an incidence in males as low as 1 in 30,000 people. The prevalence in females is extremely low, as BMD is an X linked disorder. Apart from this, Mr. K.B's case is particularly more rare due to the fact that genetic studies have shown a de novo mutation, furthermore no other family member is affected by the disease, nor is a carrier. Under Dr. Aquilina's care, only one other family has been reported in Malta.

Fact File on Becker's Muscular Dystrophy

Becker's Muscular Dystrophy (BMD) is one of the various Muscular Dystrophies having a male distribution due to its X linked inheritance. The condition is significantly rare, with an incidence as low as 1 in 30,000 people and with a prevalence of 17-27 cases per 1 million population. BMD is a rarer, milder form of muscular dystrophy compared to Duchenne Muscular Dystrophy (DMD), and presents later in life between the ages of 14-20. BMD is an X linked recessive mutation and most cases involve exon deletions in the dystrophin gene Xp21. This mutation leads to the translation and production of a semi-functional dystrophin gene (unlike DMD where the resulting dystrophin gene is non functional; 30-80% normal dystrophin in BMD compared to only 5% in DMD). Nicolas et al suggested that different exon deletions resulted in different disease severity and hence, different disease progression. Nicolas et al studied four prevalent in- frame

exon deletions (45-47, 45-48, 45-49, 45-51) and showed differences in the rate of disability progression to the point of being wheelchair bound (reached earlier in deletions 45-47 and 45-49 compared to deletion 45-48), as well as differences in the age of onset of dilated cardiomyopathy (onset delayed by 11 years in deletion 45-48 and by 14 years in deletion 45-49, in comparison to exon deletions 45-47)(Nicolas et al, 2015).

BMD presents within the ages of 14 and 20 with various signs and symptoms. The most common presentation is symmetrical proximal muscle weakness and classically the patient presents with difficulty climbing stairs. Apart from this, the patient may complain of increasing clumsiness with resulting falls and toe walking. On examination a rather characteristic sign in BMD (as well as DMD) is pseudo-hypertrophy of the calves, which may be quite obvious on inspection. However, it is known that the pseudohypertrophy is realistically a combination of actual muscle hypertrophy

together with fatty deposition (Mauro et al, 2014). A sign which helps differentiate DMD from BMD is the preservation of strength of the neck flexors.

A rather serious manifestation of BMD (and DMD) is dilated cardiomyopathy, which is not necessarily related to the skeletal signs and symptoms (Mavrogeni et al, 2015). Dilated cardiomyopathy is not only seen in affected males with BMD, however it may also present in female carriers of BMD (females carry two X chromosomes, compared to males which carry one X chromosome, the other being Y. Therefore, a female will be a carrier if only one of her two X chromosomes carry the mutation of BMD). It is for this reason that BMD patients require regular cardiological work up in order to diagnose and treat such a condition. The work up includes electrocardiogram (ECG) which may show certain arrhythmias, conduction defects and hypertrophy among other electrical changes. Another important investigation is an echocardiogram which is basically an ultrasound of the heart which assesses

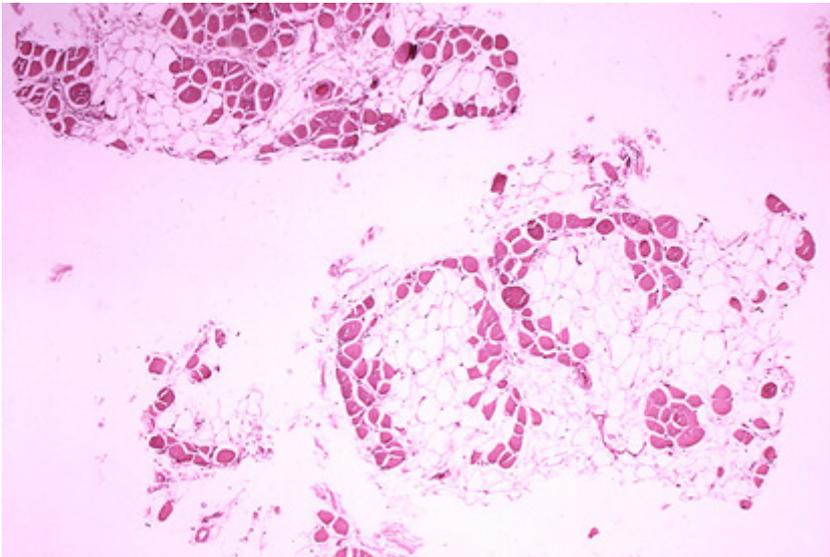


Figure 1: Histopathology of a DMD patient's Gastrocnemius muscle showing the extensive replacement of muscle fibres by adipose cells.

the heart function as well as visualises any functional defects of the heart. It is important to assess for heart failure as early as possible to avoid life-threatening conditions. Yilmaz A. et al have shown that more recent investigation approaches, mainly Cardiovascular Magnetic Resonance, have proven more efficient in detecting cardiac involvement when compared to other methods.

Regarding treatment, there is no cure for BMD. Therefore, the main aim of treatment is to control patients' symptoms as they arise, as well as a supportive approach with a multidisciplinary team in order to improve the health-related quality of life. The team should include physiotherapy, occupational therapy, as well as speech therapy. Physiotherapy focuses on strengthening muscles as well as helping the patients to be as physically functional as possible. Occupational therapy focuses on aiding the patient with activities of daily living, as well as education and job difficulties encountered due to the disease. Speech therapy is needed in BMD patients if dysphagia (difficulty swallowing) becomes a concern with increasing severity of the condition (Grootenhuus et al, 2007).

Treatment is important for cardiology and respiratory deterioration. Once the muscles used in respiration start to weaken, non-invasive respiratory intermittent positive-pressure ventilation is helpful in the care of these affected patients. With regards to cardiological

treatment the regular treatment used in heart failure is advantageous, and includes diuretics and angiotensin converting enzymes among others. The use of a pacemaker is also beneficial in the treatment of heart failure.

Surgical treatment may be considered in situations where scoliosis becomes a prominent problem and it may be beneficial to undergo spinal fusion procedure. Another surgical procedure considered in BMD patients is an Achilles tendon section for patients with severe ankle contractures in need of muscle release.

New approaches to treating DMD and BMD include stem cell transplants. Gussone E. et al have shown that intravenous injection of either normal haematopoietic stem cells or muscle-derived stem cells into mdx mice (mice models of DMD) have resulted in the partial restoration of dystrophin expression in the affected muscles. Another approach is gene therapy; Norma B. R. et al carried out an experiment on 9 patients with DMD/BMD were injected with a full-length human dystrophin plasmid into the radialis muscle. Dystrophin expression was observed in six out of the nine patients and therefore the results showed that exogenous dystrophin expression can be obtained after intramuscular transfer of the plasmid.

Case Report on Becker's Muscular Dystrophy

Presenting Complaint

A 23-year-old male presented with difficulty walking up stairs for the past two years. Mr. K.B. also complained of fatigue in the lower limbs and problems with running. The patient also described occasional falls. These symptoms have been present for the previous two years. The patient described difficulty with running and difficulty going up stairs. He explained that it is easier to go down the stairs. The symptoms came on gradually and have been slowly progressing and the patient now expressed that he is apprehensive in walking as he fears he might fall. Mr. K.B. also explained that he has problems getting up from a sitting position. Upon further questioning, there were no associated muscle cramps, no visual or swallowing problems, no active speech difficulty and no dark urine. However, the patient said he experiences some pain on walking, mainly in both calves and feet.

Past Medical & Surgical History

The patient suffered from croup as an infant, and severe acne as a teenager, which was treated successfully. He also suffered from speech difficulties as a child and was taken to a speech therapist for a few months and had a pure tone tympanogram performed to ensure that there were no auditory problems. There was also a history of lower back pain, which was investigated via plain thoracolumbar and pelvic radiography and no notable anatomical cause was found.

Drug History & Allergies

The patient takes daily multivitamins and Omega 3. Mr. K.B. was previously taking Isotretinoin (Decutan) 0.5 mg/kg/daily. After diagnosis, it was recommended he takes the influenza vaccine yearly as well as the Pneumovax vaccine. He has no known drug allergies.

Family History

There are two known cases of cerebral

palsy in Mr. K.B.'s distant family, i.e. his first cousins.

Social History

The patient is a non-smoker and does not consume any alcohol on a daily basis and has never taken any illicit drugs. He lives with his family and is currently working as an IT technician. The patient manages to drive and carry out activities of daily living. Mr. K.B. is in a stable relationship and has been for several years now.

Systemic Inquiry

Nil to note.

Physical Examination & Preliminary Investigations

Mr. K.B. had a full neurological examination carried out.

On examination of the upper limbs:

- Cranial nerves: Intact;
- Tone: Normal;
- Power: 5/5;
- Reflexes: Normal;
- Sensation: Normal.

On examination of the lower limbs:

- Tone: Normal;
- Power: 5/5;
- Reflexes: Normal;
- Sensation: Normal.

The patient was noted to have visible bilateral calf hypertrophy and a lordotic posture. On examination of the patient's gait, he also had a mild, bilateral foot drop and a waddling gait. The patient's waddling gait was more prominent on walking up stairs.

Mr. K.B. also had a cardiovascular examination:

- Pulse: 60 beats/minute;
- Blood Pressure: 130/70;
- Heart Sounds: Normal;
- Chest: Clear;
- No lower limb oedema was present.



Figure 2: Mr. K.B.'s photographs delineating bilateral calf hypertrophy.

Differential Diagnoses

1. Becker's Muscular Dystrophy;
2. Glycogen Storage Disorder.

Diagnostic Investigations

Requested Investigation: **Creatinine Kinase (CK);**

Justification for procedure: Elevated CK levels may indicate a muscular pathology;

Result & Conclusion: The CK levels were 1800 U/L, which are much higher than the normal range.

Requested Investigation: **Electromyogram (EMG);**

Justification for procedure: This test will measure muscle activity at rest and during contraction and will show any abnormality in the motor neuron unit;

Result & Conclusion: Shows a chronic, myopathic process with small, short polyphasic potentials.

Requested Investigation: **Electrocardiogram (ECG);**

Justification for procedure: To look for any arrhythmias or electrical conduction abnormalities, for example sinus tachycardia or complete left bundle

branch block;

Result & Conclusion: ECG showed narrow QRS SR segments.

Requested Investigation: **24- Hour Holter ECG;**

Justification for procedure: To exclude any cardiac electrical abnormalities;

Result & Conclusion: No ventricular arrhythmias were noted.

Requested Investigation: **Echocardiogram;**

Justification for procedure: To show any evidence of dilated cardiomyopathy or any ventricular failure;

Result & Conclusion: Showed good global left ventricular function and an ejection fraction of 55%.

Requested Investigation: **Family Genetic testing;**

Justification for procedure: To look for specific axons deletions in the dystrophin gene and to establish whether the condition was inherited from his mother;

Result & Conclusion: Tests showed a deletion of the axons 45-47 in the dystrophic gene, which is compatible with the suspected diagnosis of BMD.

However, Mr. K.B.'s mother marked negative for the gene mutation.

Diagnosis

The history of presenting complaint, with difficulty walking and getting up from chairs and occasional falls, points to the diagnosis of a Muscular Dystrophy. The characteristic features of toe walking, waddling gait and marked calf hypertrophy were also seen on examination. The test results also confirmed a chronic myopathic process, and the genetic testing confirmed the diagnosis of Becker's Muscular Dystrophy.

Management

Physiotherapy

Mr. K.B. attends physiotherapy and occupational therapy once a month and was given a series of exercises, including squats, bicycle and weighted stair lifts to perform at home daily.

Genetic Counselling

The patient was counselled about the inheritance pattern of the condition. Becker's Muscular Dystrophy is an X-linked recessive inherited disorder, meaning that Mr. K.B. was informed that there is a 100% chance that any female offspring he has will be a carrier for the disease.

Follow Up

The patient is being followed up by both the Neurology and Cardiology Departments. A yearly echocardiogram and full cardiovascular and neurological examination is done to monitor the progression of the disease.

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Septic Emboli

Secondary to Infective Endocarditis

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Ms. Y.Z. is a 31 year old lady brought to casualty by a friend, unconscious and incontinent of urine and faeces. She was responsive to verbal stimuli with a Glasgow Coma Scale (GCS) of 10 and noted to have a fever of 39.6°C. She had a blood pressure (BP) of 116/65 mmHg and a pulse rate of 160 bpm. She was allegedly unresponsive for two days prior to admission. She is a known intravenous drug user (IVDU). Physical examination revealed bilateral puncture wounds in the groin. In view of her poor general condition she was admitted to the intensive therapy unit (ITU). She was started on empirical antibiotics which included both G+ and G- coverage. Blood culture eventually grew a methicillin sensitive staphylococcus aureus (MSSA), and the antibiotics were eventually downgraded to flucloxacillin. A transoesophageal echocardiogram (TOE) showed a massive infective endocarditis of the mitral valve, which was rendered incompetent. An MRI scan of the brain revealed multiple septic emboli resulting in several cerebral infarcts.

Fact File on Infective Endocarditis

Infective Endocarditis (IE) is an infection of the endocardial lining of the heart, which may involve one or more heart valves. The valve most commonly implicated is the mitral valve (Murdoch & David, 2009). Common signs and symptoms include fever, night sweats, and a new or changed heart murmur. The intracardiac consequences include severe valvular insufficiency, which may result in intractable congestive heart failure and myocardial abscesses. As many as 40% of IE patients develop neurological complications, as a result of septic emboli arising from endocardial vegetations. Such complications include embolic stroke, intracerebral haemorrhage and microabscesses.

IE is a major cause of morbidity in intravenous drug users, in which case it usually affects the tricuspid valve, with the most common infective organism being *Staphylococcus aureus*. It is generally accepted practice to suspect right-sided

endocarditis in active IVDU presenting with fever and radiologic pulmonary infiltrates, whether or not a murmur is detected clinically. The prognosis of IE in IVDU largely depends on the side of the heart involved, as well as the particular causative organism. When treated, the outcome of staphylococcal right-sided IE is usually good, with a mortality of less than 5% (Miró & José, 2003).

Case Report on Septic Emboli Secondary to Infective Endocarditis

Presenting Complaint

The patient was found by a friend of hers, unconscious, incontinent of urine and faeces. Once the patient was able to give a history, she reported a prior 3 week history of altered mental status, loss of balance and a low grade fever.

Past Medical & Surgical History

The patient was known to be Hepatitis C positive. She was previously treated

for leg ulcers that arose secondary to intravenous (IV) drug use. She also had kyphoscoliosis (L2/L3) secondary to methicillin resistant staphylococcus aureus (MRSA) discitis. The patient delivered her daughter by caesarian section. She also had plastic surgery to treat her leg ulcers. The surgery was unsuccessful as she used the graft for intravenous drug abuse.

Drug History & Allergies

The patient is currently being prescribed the medications listed in Table 1. She is allergic to rifampicin.

Family History

The patient's medical family history is unremarkable except for the fact that her father is an alcoholic.

Social History

Ms. Y.Z., originally from Ukraine, now

lives with her husband. She describes her housing as a regular house. She has a ten pack year smoking history but does not smoke more than 2-3 cigarettes a day now. She has been using illicit drugs since she came to Malta. She is a social drinker and does not gamble. She has not had any trouble with the police apart from them finding needles in her car. She has not worked in Malta since she has been here because of her drug problem, her pregnancy, looking after her daughter and her vertebral problem. She has a ten year history of illegal drug abuse. She started snorting coke socially and proceeded to injecting. She later started injecting heroin. She had been off heroin for three years prior to admission apart from the month before admission where she had a relapse. She says that she relapsed because she was suffering from a depression brought about by marital friction which stemmed from her vertebral problems.

She describes a happy childhood; she was a high achiever at school and went to university to study ecological engineering. She came to Malta in 2003 and entered a relationship with a cocaine user. She subsequently adopted the habit herself. She became pregnant with his child and gave birth to a girl who lives in Ukraine. She left her previous relationship and is now married to another man who abuses drugs but does not inject. She does not have any children with her husband. She describes her marriage negatively and does not wish to remain with her husband.

Systemic Inquiry

General Health: Pallor, dehydration;
Cardiovascular System: Nil to note;
Respiratory System: Patent airway;
Gastrointestinal Tract: Nil to note;
Genitourinary System: Nil to note;
Central Nervous System: Loss of consciousness;
Musculoskeletal System: Kyphoscoliosis (L2/L3) secondary to MRSA discitis;
Endocrine System: Nil to note.

Physical Examination & Preliminary Investigations

Table 2 lists the examinations and routine investigations that were carried out on the patient upon admission to casualty.

Generic Drug Name	Dosage	Frequency	Formulation	Reason for Prescription
Diclofenac Potassium	50mg	Trice Daily	Immediate Release Tablet	Back pain relief
Methadone	40ml	Once Daily	Intravenous Injection	Opioid replacement therapy

Table 1: Medications prescribed to the patient.

Examination / Investigation	Result
Pulse Rate	160 bpm
SpO ₂	100 %
Blood Pressure	116/65 mmHg
Temperature	39.6 °C
Heart Sounds	S1 + S2 + 0
Chest	Clear, good air entry
Abdomen	SNT
Neurological System	GCS 10, E 3, M 5, V 2 Both pupils reactive, Unable to assess cranial nerves, limbs, cerebellum. No rashes or neck stiffness.
Chest X-Ray	The heart is enlarged even for an AP projection; There is a right central line with its distal tip in the projection of the right atrium. There is a lobulated right pleural effusion on the right; No signs of consolidation or collapse in either lung noted; Severe mid-thoracic scoliosis noted. See Figure 1
ECCG	Sinus tachycardia
Arterial Blood Gases	<ul style="list-style-type: none"> pO₂: 206.3 mmHg pCO₂: 24.8 mmHg pH: 7.619
Blood Analysis	<ul style="list-style-type: none"> Hb: 8.0 g/dL Na⁺: 141 mmol/l K⁺: 2.6 mmol/l Cl⁻: 92.4 mmol/l Glucose: 8.2 mmol/l

Table 2: Examinations and routine investigations that were carried out on the patient upon admission to casualty.



Figure 1: Chest X-Ray

Differential Diagnoses

1. Septic emboli secondary to infective endocarditis;
2. Meningitis;
3. Sepsis secondary to infected leg ulcers;
4. Encephalitis.

Diagnostic Investigations

Requested investigation: **Blood culture and sensitivity;**

Justification for procedure: To detect bacteremia, identify organism and obtain sensitivities;

Result: MSSA cultured;

Conclusion: Antibiotics were changed according to sensitivity

Requested investigation: Trans-oesophageal echocardiogram;

Justification for procedure: To diagnose infective endocarditis;

Result: Gross vegetation attached to the mitral valve leaflets with resulting severe mitral regurgitation;

Conclusion: Investigation is diagnostic of infective endocarditis.

Requested investigation: **MRI (brain) with contrast;**

Justification for procedure: To identify focal lesions causing neurological deficit;

Result: Multiple embolic infarcts;

Conclusion: Septic emboli from infective endocarditis confirmed.

In conclusion, the trans-oesophageal echocardiogram confirmed the presence of infective endocarditis of the mitral valve. Moreover, the MRI scan of the brain allowed for the diagnosis of septic emboli to be made.

Generic Drug Name	Dosage	Frequency	Formulation	Reason for Prescription
<i>Teicoplanin</i>	400mg	Initially 12hrly for 3 doses, then once daily.	Intravenous infusion	Empirical antibiotic therapy
<i>Meropenem</i>	1g	8hrly	Intravenous infusion	Empirical antibiotic therapy
<i>Vancomycin (replacing teicoplanin)</i>	1.5g	12hrly	Intravenous infusion	Empirical antibiotic therapy
<i>Septrin</i>	960mg	12hrly	Intravenous infusion	Empirical antibiotic therapy
<i>Dexamethasone</i>	4mg	6hrly	Intravenous infusion	Suppression of cerebral inflammation
<i>Flucloxacillin</i>	2g	6hrly	Intravenous infusion	Targeted antibiotic treatment for MSSA

Table 3: Pharmacological Therapy.

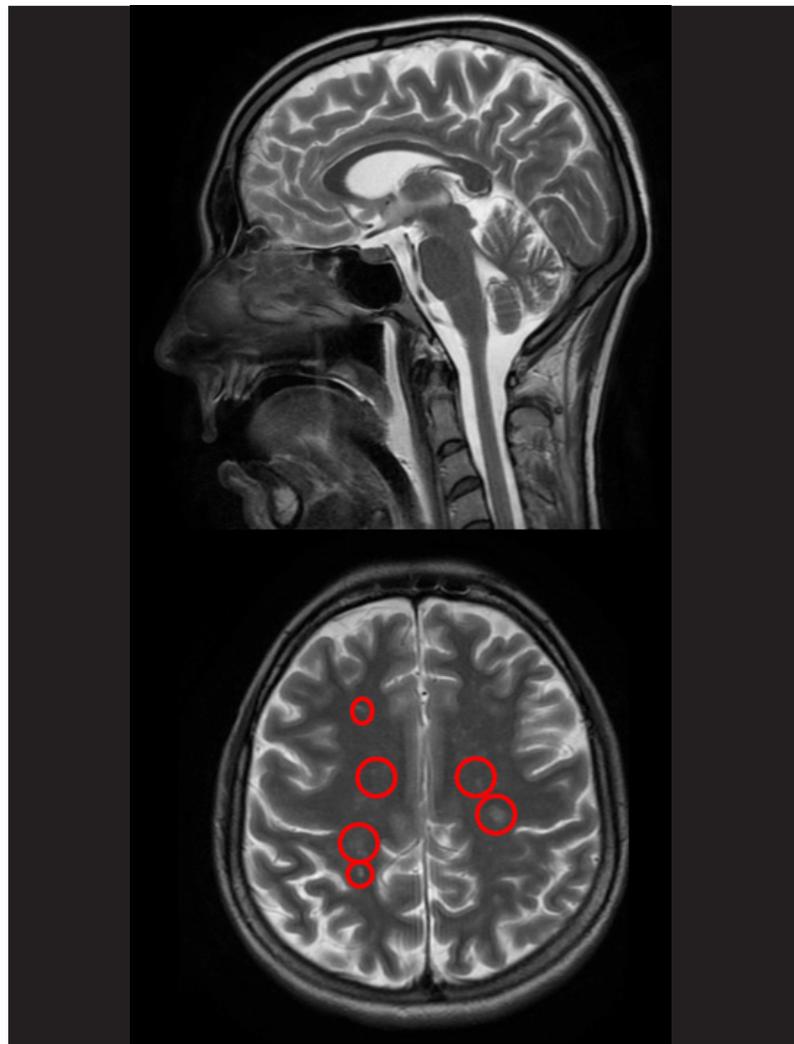


Figure 2: Ms. Y.Z.'s MRI brain scan, demonstrating septic emboli.

Requested investigation: **MRI Vertebral Column;**

Justification for procedure: To assess extent of kyphoscoliosis and discitis for orthopaedic review;

Result: Severe kyphoscoliosis and MRSA discitis of L2/L3;

Conclusion: Extensive kyphoscoliosis and MRSA discitis of L2/L3 confirmed.

Diagnosis

In conclusion, the trans-oesophageal echocardiogram confirmed the presence of infective endocarditis of the mitral valve. Moreover, the MRI scan of the brain allowed for the diagnosis of septic emboli to be made.

Management

Pharmacological Therapy

The patient was admitted to ITU where she was intubated and sedated and given supportive care; Table 3.

Surgical Therapy

The patient was not initially a candidate for valve replacement surgery.

Follow Up

The patient is now awaiting valve replacement surgery. Hepatitis C is to be treated. She is also being followed up by orthopaedics as she will eventually need spinal stabilisation.

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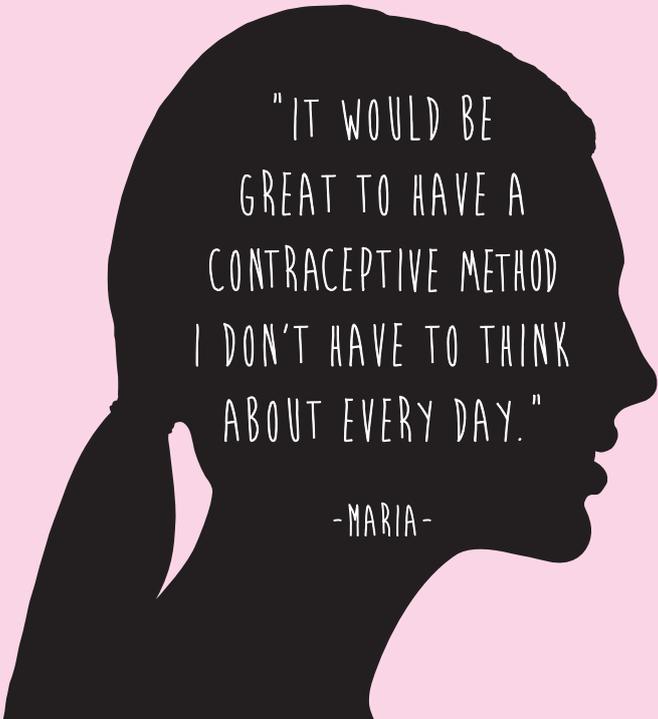


Figure 3: Ms. Y.Z.'s MRI scan of the vertebral column.



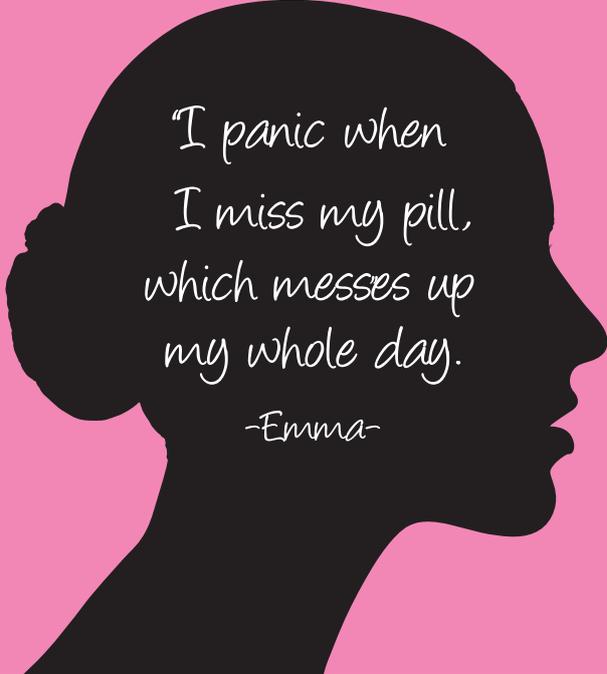
The Strength of Experience

motor | boat | travel | professional | business | health



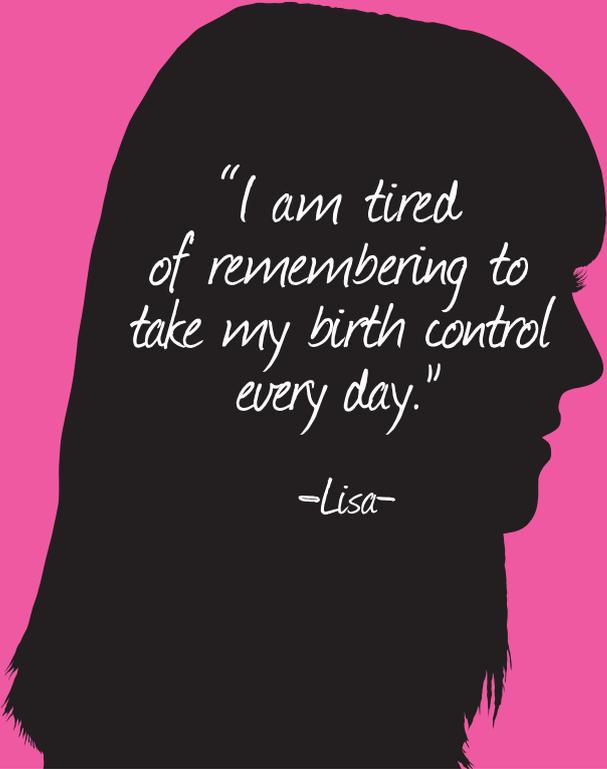
"IT WOULD BE
GREAT TO HAVE A
CONTRACEPTIVE METHOD
I DON'T HAVE TO THINK
ABOUT EVERY DAY."

-MARIA-



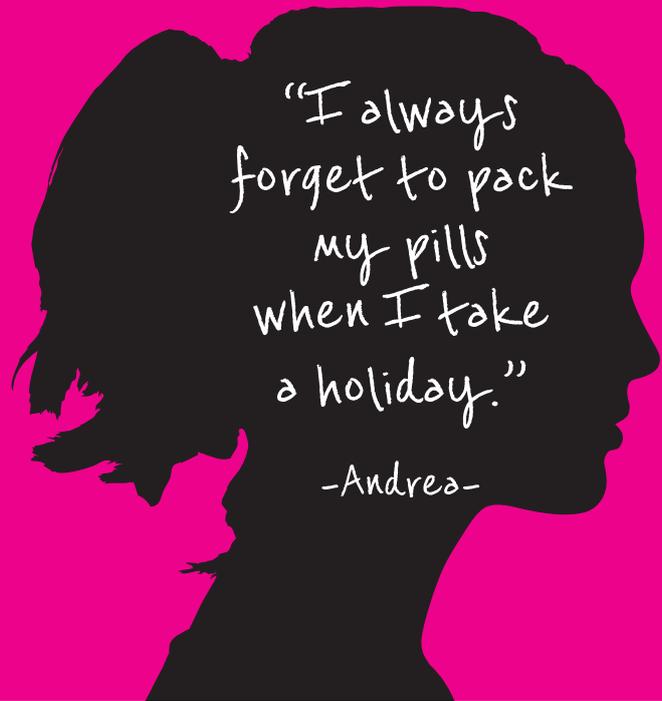
"I panic when
I miss my pill,
which messes up
my whole day."

-Emma-



"I am tired
of remembering to
take my birth control
every day."

-Lisa-



"I always
forget to pack
my pills
when I take
a holiday."

-Andrea-

Daily pills may not always be the right solution for your contraceptive needs.

Ask your doctor for more information about the **new, non daily, long acting** and **reversible** intrauterine contraceptive system.

Literature Reviews



Heavy Metal Intoxication

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Although some debate exists with regards to the subject, elements which are classified under 'heavy metals' have come to be those which pose a threat to humans in terms of toxicity. Intoxication with heavy metals is not a typical diagnosis as it is fairly uncommon. This can impose a risk on people who fail to be diagnosed and removed from the source of exposure, increasing morbidity and mortality.

For the purposes of this review, Cadmium and Mercury will be discussed. A brief introduction of each element's chemical and physical properties will be given, as well as its sources in the environment and any uses. Each metal's toxicity will be illustrated using actual cases of poisoning. Any treatments for intoxication will be explained at the end of each section.

Overview on Cadmium

Cadmium (chemical symbol Cd) is a transition metal element. Although the pure metal is not typically found in nature, it is associated with zinc ores, and to a certain extent to the ores of lead and copper. For this reason, it is difficult to eliminate the by-product of Cd from the metallurgy of the aforementioned elements. Other industrial sources of Cd include smelting of other metals, combustion of fossil fuels, incineration of waste and the utilization of phosphate and sewage sludge fertilizers (Alexandar et al., 2009).

The uses of Cd in industry include the production of coatings, pigments, plastics, plastic stabilizers, batteries, photovoltaic devices and nonferrous alloys. When it is released in the environment it can contaminate the air, water and soil. Cd is released from natural mechanisms including forest fires, marine aerosol production and volcanic eruptions among other natural phenomena (Faroon et al., 2012).

Typically found in its +2 oxidation state, Cd ions exist in their hydrated forms as well as complexed to organic or inorganic

substances. The more soluble forms have the ability to migrate in water, whereas insoluble forms tend to adsorb to sediments and become immobilized (Faroon et al., 2012).

According to data collected in the European Union (EU), it is estimated that 90% of Cd exposure in non-smokers occurs from food, particularly cereals and vegetable crops. Plants can take up Cd salts from the soil. This uptake depends on factors such as the type of soil, the solubility of Cd in it and the species of the plant in question. Other sources of exposure include meat and fish, although these are less significant. However, consumption of organs such as liver and kidneys from exposed animals contributes a more noteworthy source of Cd, as the element tends to accumulate in these organs. For non-smokers, air and water pose negligible threats in terms of exposure as very low levels are present (Alexandar et al., 2009).

Data collected in the United States (US) complies with the report issued by the European Food Safety Authority. Exposure to non-smokers in the US is largely from the diet, with females exhibiting a larger uptake of Cd from their gastrointestinal

tract than males. The highest amounts of Cd were found in leafy vegetables such as spinach and lettuce, and in staple foods like potatoes and grains. Naturally high levels of Cd can be found in peanuts, soybeans and sunflower seeds (Faroon et al., 2012).

Smokers showed an overall high mean blood Cd compared to non-smokers. This could be measured as high as 1.58µg/L, compared to the average value for adults, 0.38µg/L. The reason for this markedly high value is the fact that tobacco leaves naturally accumulate Cd more readily than other plants. It was also noted that non-smokers exposed to second-hand smoke were also at risk for Cd accumulation (Faroon et al., 2012).

Cd biomarkers are typically detected in blood, urine, hepatic tissue, faeces, renal tissue, hair and other tissues (Faroon et al., 2012). Blood Cd levels tend to be more closely related to recent Cd exposure, whereas urine Cd levels reflect body burden over lengthy exposure, and tend to increase with renal tubular dysfunction. Liver Cd levels are also related to duration and intensity of exposure regardless of renal function (Roels et al., 1981).

Cadmium Toxicity

This metal ion can pose numerous health risks. Cd²⁺ does not have any known use in animal or human biology, however its divalent nature can assimilate roles performed by other essential metals. It can cross membranes using metal transporters. When it gains entry within the cell, Cd²⁺ can bind ligands with a particularly high affinity. Clearance is difficult, explaining the long term storage of Cd in intestinal, hepatic and renal tissues. The biological half life of this metal is estimated to vary from 10 to 30 years. Its toxicity stems from its interference with iron, calcium or zinc homeostasis, which are necessary for basic cellular functions (Alexandar et al., 2009).

The acute effects of Cadmium

Metal fume fever is a condition which develops within 48h of exposure to metal fumes and is typically caused by cadmium oxide, although other metal oxides can also cause it. Patients present with flu-like symptoms, with resolution within 24-48h of onset. The pathogenesis is not fully understood; however it is hypothesized that upregulation of protein release in response to stress occurs. An example could be heat shock proteins, which are chaperone proteins released in response to hypothermia and other environmental stresses. The advised treatment is immediate removal from the source of Cd exposure, bed rest, antipyretics and treatment for osteoporosis (Malaguarnera et al., 2013).

The chronic effects of Cadmium

Metallothioneins are sulfur-containing proteins rich in the amino acid

cysteine, which typically bind metal ions in the body; with the example of haemoglobin. These chelators have numerous important functions including transport, detoxification, sequestering and metabolism of metal ions. Metallothioneins bound to Cd are reabsorbed in kidney tubules (Nordberg & Nordberg 2009). Renal cortex Cd accumulation results in tubular proteinuria with measurable loss of low molecular weight proteins. These include retinol binding protein, β -1-microglobulin and β -2-microglobulin. Progression of renal damage results in glucose, amino acids and minerals being lost in the urine. Long term exposure eventually damages the renal glomeruli and results in a drop in glomerular filtration rate. Uraemia can develop in serious cases. Reversibility of Cd-induced tubular dysfunction depends on the severity of proteinuria, which is quantified by the amount of β -2-microglobulin (B2M) in the urine (Table 1.1) (Nordberg 1998).

Itai-Itai disease (IID) is a painful disease which presents with multiple distortions and fractures of the long bones. It is the most severe form of chronic Cd poisoning by ingestion. Due to a zinc mine located upstream from Toyama Prefecture, the Jinzu River was contaminated with Cd. People who lived in the river basin showed the symptoms of Itai-Itai (Baba et al., 2014).

A study was conducted on post-menopausal women living in this area. The aim of the study was to link osteomalacia with renal tubulopathy. Two methods for cause of development of osteomalacia were considered; a direct and an indirect pathway. In the direct pathway, osteomalacia is thought to be caused by the direct interference of Cd with bone metabolism. In the indirect

pathway Cd causes Fanconi syndrome, which is the damage of the renal proximal tubule resulting in loss of calcium and phosphate in the urine and the subsequent development of osteomalacia. Although the study does not entirely dismiss the direct pathway, histopathological analysis showed that osteomalacia development was linked to the Cd concentration in the renal cortex but not in bone. Figure 1.1 shows the damage caused by Cd; in comparison to the normal subjects, there is notable atrophy in the renal cortex of IID patients, as well as osteoid lesions in their bones (Baba et al., 2014).

Cd exposure by inhalation has been linked to lung cancer in studies based on men who were exposed to Cd at their workplace; however, these studies did not account for other significant factors such as the possibility of other carcinogens or the smoking habits of the subjects. Considering different studies, it was concluded that Cd was not a cause of lung cancer; rather, cigarette smoking and exposure to arsenic were to blame (Faroon et al., 2012).

Treatment for Cadmium Toxicity

Treatment of Cd exposure is largely symptomatic. Patients exposed to oral Cd salts should be given a gastric lavage or induced to vomit. Inhalation exposure treatment consists of removing the subject from exposure and giving oxygen as necessary. Chelating agents are contraindicated as they are nephrotoxic in combination with Cd (Nordberg, 1998).

In a study using a rat model, administration of *Chlorella vulgaris* was observed to increase excretion of Cd in the urine and faeces, as well as preventing its uptake from the gastrointestinal tract. The

B2M in urine (μ g/g creatinine)	Clinical interpretation
<300	Within the reference interval.
300-1,000	Incipient cadmium tubulopathy, possibly reversible upon cessation of exposure or forerunner a) of accelerated decline of GFR; increased incidence of renal stones.
1,000-10,000	Irreversible tubular proteinuria. GFR may still be normal.
> 10,000	Overt cadmium nephropathy and usually decreased GFR.

^{a)} this refers to values that have been confirmed in the same subject at least twice in two repeated measurements over a six-month period.

Table 1: Levels of B2M in the urine compared with the level of damage achieved and the possibility for reversal (Nordberg 1998).

precise mechanism by which excretion is increased is unknown. Prevention of Cd uptake is thought to be due to dietary fibre found in *Chlorella*, which traps Cd in the intestinal epithelium. Epithelial cells are then lost in the faeces by desquamation (Shim et al., 2009).

Overview on Mercury

Mercury (chemical symbol Hg) is a transition metal which occurs in three variations; the elemental form and in inorganic and organic compounds. In its elemental form Hg is a liquid at room temperature. Depending on how high the temperature, colourless and odourless vapours are emitted (Risher & DeWoskin, 1999).

In its inorganic form, Hg occurs as salts of chloride, sulfide or oxides. A large majority are white salts, with the exception of cinnabar. Cinnabar is mercury sulfide, a red salt which converts to black following light exposure. Organic Hg compounds are also known as organomercurials. The most common organomercurial is methylmercury, a crystalline white solid. Other compounds include dimethylmercury, a colourless

liquid, and phenylmercury, a white solid (Risher & DeWoskin, 1999).

In nature the commonest forms of Hg are elemental, mercuric chloride, cinnabar ore and methylmercury. Liquid elemental Hg has multiple uses, such as the production of caustic soda, gaseous chlorine, as well as the extraction of gold from it ore or gold-containing items. Elemental Hg is used in measuring devices like thermometers and barometers, and also batteries and electric switches. Inorganic Hg is used in fungicides, skin-lightening creams, paints, tattoo dyes, topical antiseptics as well as disinfecting agents. Prior to 1991, organic Hg compounds were used in antifungal agents, but this use was discontinued after it became known that Hg vapours were released from these products (Risher & DeWoskin, 1999).

Hg constitutes about 50% of the components of dental amalgam. Other metals include silver, copper, tin and trace metals. Dental amalgam is used to treat dental cavities. Its continued use till today is mainly due to its quality and the fact that most dentists are trained to use it, as opposed to other modern substitutes. These fillings leach Hg when

they are being inserted, removed, as they deteriorate with time and from the buried or cremated remains of people who had these fillings. According to the final report prepared for the European commission, the phasing out of Hg-containing dental amalgam would be difficult for a number of reasons, including the expense of dental amalgams that do not contain Hg. Also, dentists would require training to insert these amalgams as well as new equipment with it. Health services in the EU do not always cover these costs; dental fillings are not covered by the national health insurance schemes in Malta (Mudgal et al., 2012).

Mercury Toxicity

Hg poisoning in the clinical setting is largely due to suicide attempts by ingestion of mercury cyanide or other compounds. Accidental poisoning is unusual, although reports of Hg exposure by youngsters from broken mercury thermometers and barometers have been reported. Inorganic Hg compounds in their pure powder form are the cause of non-fatal poisoning in adults (Triunfante et al., 2009).

Chronic exposure of methylmercury from bioaccumulation in fish is a cause of concern (Triunfante et al., 2009). Hg in trace amounts dissolves in water and is converted into toxic methylmercury, which is absorbed by fish through the gills and by consuming smaller aquatic organisms contaminated by Hg. Larger fish carry the largest amounts of Hg due to predation. A study conducted in Ghana analysed the content of heavy metals including Hg in several canned fish products. Canned tuna brands showed the highest Hg levels from the fish analysed (Okoye et al., 2015).

Intoxication from inhalation of metallic Hg vapour typically results in respiratory distress, which can result in death if severe (Triunfante et al., 2009). When Hg is inhaled, 74-80% of the dose is absorbed via the alveolar membrane in the lungs. It is then transported to a number of tissues including the liver, central nervous system and especially the kidneys. In a case report by Gul Oz et al. (2012), a family of four suffered varying

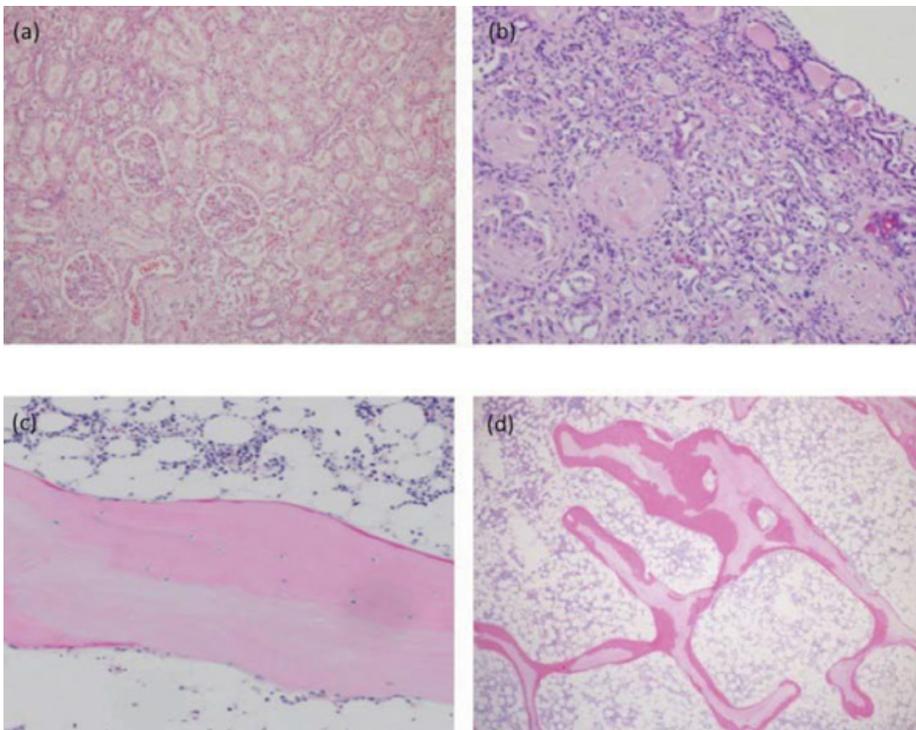


Figure 1: Histological sections of normal renal cortex (a), IID patient renal cortex (b), normal iliac bone (c) and IID patient iliac bone (d). Renal cortex atrophy in (b) and iliac bone osteoid lesions in (d) can be observed following prolonged exposure to Cd (Baba et al., 2014).

degrees of Hg poisoning after one of the children brought home a minute piece of Hg in a glass from school, which broke and was vacuumed up by the mother in a non-aerated room.

Nephrotic syndrome due to Hg intoxication developed in the mother following 3 months from exposure. Kidney malfunctions present with proteinuria, which can be for one of two reasons: antigen-antibody complexes that form as a result of excess Hg are not effectively cleared and result in damage to the glomeruli (Figure 2.1); alternatively Hg ions cause direct damage in renal tubules (Gul Oz et al., 2012).

The initial effects of Hg poisoning are flu-like symptoms within 1 to 3 days of exposure. These effects include excess salivation, oedematous gingiva, fever, dry cough, diarrhoea, nausea and vomiting. Later effects include non-cardiogenic pulmonary oedema as well as pneumothorax. In post-mortem analyses of Hg-exposed lungs, damage such as intense corrosion of the bronchiolar epithelium and necrotizing bronchiolitis with fluid accumulation in the alveoli and the interstitium. Dysfunctions in other systems such as the kidneys, liver, blood and skin have also been reported (Gul Oz et al., 2012).

The final phase of Hg poisoning is typically a progressing hypoxic state which can lead to death. If the patient survives the intoxication, there may be residual damage in the form of gingivostomatitis, tremors as well as erethrism, which can manifest as loss of memory, emotional instability, insomnia, depression and shyness (Gul Oz et al., 2012).

Injection of metallic Hg with the intent of suicide is also reported. Intravenous injection leads to pulmonary embolization by globules of Hg, and patients present with chest pain, dyspnoea, fever and cough. Other signs include changes in the patient's electrocardiogram, impairment of renal function and dermatological symptoms. Subcutaneous Hg injections results in inflammation that is localised, granulation tissue and the formation of abscesses. Eventual systemic involvement is also expected (Alhamad et al., 2012).

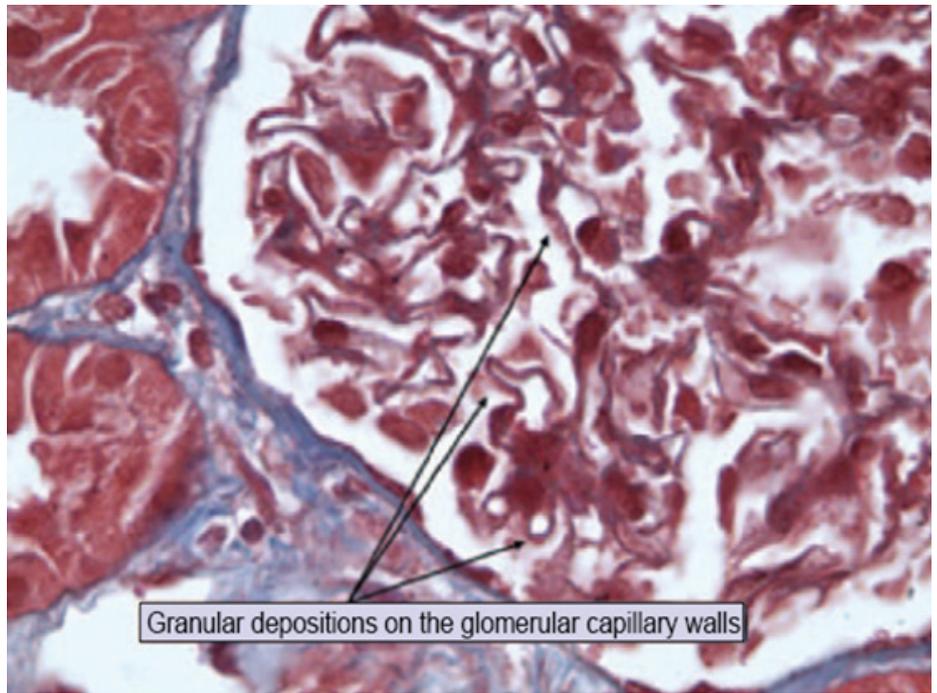


Figure 2: Histological section showing depositions on the capillary walls of glomeruli made up of granules formed by antibody-antigen complexes that did not clear successfully, (Gul Oz et al., 2012).

Treatment for Mercury intoxication

British Anti-Lewisite, also known as BAL, was developed in warfare as an antidote to lewisite, which is an arsenical vesicant. BAL's chemical name is 2,3-dimercaptopropanal, and it is an oil which is freely absorbed by the skin. It binds lewisite to form a stable compound, therefore removing this toxin's effect on the enzyme pyruvate. BAL can also prevent the vesicant effects of lewisite if applied before exposure, but can reverse the initial symptoms up to two hours after exposure. The resulting compound is then excreted in the urine. This drug was also used to treat Hg poisoning. (Peters 1949).

In rats, intravenous BAL proved effective in preventing the acute systemic poisoning caused by mercury chloride. When BAL was supplied by injection as well as oral dosage, it also safeguarded the rats from fatal doses (Stocken 1946).

In the 1950s, chemically similar dithiols which could also dissolve in water were produced; unithiol (DMPS) and succimer (DMSA). Treatment with these substances is required as early as possible following Hg exposure, as their

as their effectiveness decreases with time. In chronic intoxication, DMPA and DMSA chelation appears to reduce the inorganic Hg burden on some organs. However, in morbidity and mortality terms, the benefit has not yet been concluded. Some observed side effects of DMPS and DMSA include allergic reactions with widespread rashes in 1 to 10% of subjects in certain studies. Other effects include gastrointestinal issues and reversible rises in hepatic transaminases and drops in white blood cell count (Kosnett 2013).

Conclusion

Diagnosis of heavy metal intoxication is not one of the first which comes to mind when presented with a case, and therefore achieving a good standard of care requires understanding the sources of exposure of each metal as well as the pathophysiology of poisoning. This is also true from the point of view of researchers looking for possible prevention treatments.

Exposure can occur from medication, diet, the environment and on the workplace. For this reason, a thorough history of possible heavy metal intoxication cases should be gathered and scrutinized

before any attempt at a diagnosis is made. When multiple patients present with similar symptoms, it can be advisable to further investigate any linking factors. The possibility of intentional poisoning as a means of suicide or murder cannot be excluded.

The primary treatment is removing the patient from the source of exposure as soon as possible. Further follow-up depends on the type of metal poisoning; chelating agents discussed in the essay are used at the discretion of the physician in charge, due to side effects and the chance of nephrotoxicity especially when the kidneys have already been implicated.

Future research should be based on the prevention as well as treatment. New and better chelators are a good avenue, however other studies have focused on substances like Vitamin E and NAC, as well as organisms like *Chlorella vulgaris* for preventing the toxic effects of specific metals when administered concomitantly. More studies would be required before any conclusions can be reached; however, current studies are showing promise.

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Phantom Pain

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Almost anyone with a limb amputation experiences phantom sensations. Moreover, the majority of amputees experience pain. This phenomenon is known as 'Phantom pain' and is described as the pain felt from a body part, usually a limb, which is no longer present. Several mechanisms have been proposed in attempt to explain this phenomenon with some being more prevalent than others. Cortical remapping seems to explain a substantial part of the occurrence of phantom pain and will be focused upon throughout this review. Since the exact mechanism underlying phantom limb pain is unknown, treatment for this condition is still quite primitive and is mostly by trial and error. However, 'Mirror Therapy' has recently been suggested which seems to show promising results for the effective treatment of phantom pain.

Overview on Phantom Pain

Allegedly, one might think that amputation or complete denervation of a body part would result in immediate disembodiment of that part, however, this is rarely the case (Melita J. Guimarra and G. Lorimer Moseley, 2011). As a matter of fact between 90 and 98 percent of amputees experience a vivid impression that the amputated limb is still present. This phenomenon is known as 'Phantom Sensation'. In 75 percent of cases, phantoms appear immediately after surgery as soon as the anaesthetic wears off. In the remaining 25 percent, the appearance of the phantom is delayed, usually by a few days or weeks (V.S Ramachandran and William Hirstein, 1998).

In 80 percent of the cases the phantom limb is painful (Melita J. Guimarra and G. Lorimer Moseley, 2011). Phantom pain is defined as a painful or unpleasant sensation in the distribution of the lost or deafferentated body part. (Eugene Hsu and Steven P Cohen et al., 2013). It is also referred to as 'Post-amputation Pain'. Pain, together with touch, vibration, temperature and pressure, makes up the exteroceptive perceptions of phantom

(Sharon R. Weeks, Victoria C. Anderson-Barnes et al., 2010; Eugene Hsu and Steven P Cohen et al, 2013).

Phantom pain can be present for a couple of days, weeks or else it can persist for years. The longest duration reported is that of 57 years (Browder and Gallagher, 1948). Phantom pain can be a constant dull throbbing pain which lasts several hours, or else it can be a sharp shooting pain which lasts only a few seconds, the latter one being the most common (V.S Ramachandran and William Hirstein, 1998; K.Maclver, D.M Lloyd et al., 2008). It can take several forms including tingling, itching, stabbing, burning, cramping and even feeling 'pins and needles' (Sharon R. Weeks, Victoria C. Anderson-Barnes et al., 2010). Moreover, the pain could be present all over the missing limb or else localised to just one area. It is most often localised on the hands and feet where there is a high degree of cortical mapping (Eugene Hsu and Steven P Cohen et al, 2013). Post-amputation pain may also result as the phantom takes up an awkward and uncomfortable position. This is known as a kinaesthetic sensation which can be painful (Sharon R. Weeks, Victoria C. Anderson-Barnes et al., 2010; Eugene Hsu and Steven P Cohen et al, 2013). These amputees usually have

very specific sensations, for example a reported case of a soldier who had a grenade explode in his hand leaving behind a phantom hand cramped in that position (Browder and Gallagher, 1948). This habitual posture taken up by the phantom may be temporary or even permanent.

The occurrence of phantom pain is regardless of the cause, level and location of the amputation. Gender, age, social and marital status do not affect the incidence of phantom pain in any way (V.S Ramachandran and William Hirstein, 1998).

Factors which do enhance the appearance of phantoms include firstly the pre-amputation history. Amputation following a pre-existing painful limb pathology or a traumatic limb loss usually results in a vivid, persistent and painful phantom. This is especially in contrast to pre-planned amputations where the limb is not painful which are far less likely to result in post-amputation pain. The reason for this may be due to 'pain memories' of the existing painful limb which persist in the phantom. A second factor which effects the appearance of phantoms is the condition of the stump. If there is

no stump pathology such as scarring or neuromas and the stump heals nicely and quickly, the phantom is dulled rapidly. Hitting the stump can also elicit phantom pain. Resting, tranquility and distraction can alleviate the pain whereas stress and emotional turmoil will make it worse (V.S Ramachandran and William Hirstein, 1998). Phantom limb pain has also been found to be more prevalent in upper extremity amputees than lower extremity amputees (Bishnu Subedi and G.T. Grossberg, 2011).

Phantom pain has not just been reported in limbs, although this is the most common, but also in other body parts. There have been several reports of phantom menstrual cramps following hysterectomy, acute appendicitis following appendectomy (V.S Ramachandran and William Hirstein, 1998), phantoms following mastectomy (Aglioti, 1994; Björkman B. et al., 2008) phantom ulcer pains following partial gastrectomy (Szasz, 1949) and even phantom facial pain after parts of the face have been removed (Hoffman, 1955). Phantom sensations of flatus and faeces as well as sensation of haemorrhoids and hard stool that would rupture the rectum have been reported after resection of the rectum or the sigmoid colon (Oversen P. et al., 1991; Reategui C. et al., 2013). Patients with their penis removed have also reported having phantom erections and ejaculation (Fisher CM., 1999; Wade NJ. and Finger S., 2010).

Phantom pain may also be experienced by children with congenital amputations although these are far less common. This is because the brain has already developed several neural connections (but not all) involving the perception of the body. Congenital phantoms are experienced in 20 percent of child amputees. Apart from this, 50 percent of children who lose a limb at the age of 5 years or younger develop a phantom limb. In amputees over 8 years of age the incidence is the same as in adults (V.S Ramachandran and William Hirstein, 1998).

There are numerous proposed mechanisms underlying the pathophysiology and aetiology of phantom limb pain with some theories being more prevalent than others. In this next section I will discuss the most

prevalent ones.

Mechanisms Underlying Phantom Pain

Post-amputation pain was primarily thought to be a form of mental disorder (Bishnu Subedi and George T. Grossberg, 2011) until in the mid-16th century, French military surgeon Ambrose Pare introduced the concept. Years after, this concept was described and given the term 'Phantom Pain' by Mitchell in 1871. It is only until recent decades that this condition was researched and given more importance, and this is due to the ongoing conflicts in Iraq and Afghanistan which have caused a significant rise in amputee patients (Sharon R. Weeks, Victoria C. Anderson-Barnes et al., 2010).

Over time there have been several proposed theories of the mechanisms underlying phantom pain. Some of these have been discarded whilst others are being supported but still need further research to be confirmed and accepted by all scientists. One of the strongest and most supported model is that proposed by Ramachandran and Hirstein. This hypothesis includes several sources which these scientists believe provide a contribution to the occurrence of phantom pain and in fact, describe phantom pain as a multifactorial phenomenon (Sharon R. Weeks, Victoria C. Anderson-Barnes et al., 2010; V.S Ramachandran and William Hirstein, 1998).

The Multifactorial Model

According to Ramachandran and Hirstein, a number of factors are involved in the pathophysiology of phantom pain and all of these factors reinforce one another.

Residual Limb Neuroma

One of the factors, that of residual limb neuroma was the first standard explanation for the occurrence of phantom pain. A neuroma is a non-neoplastic tumour which occurs as the nerves supplying the limb are lacerated (Sharon R. Weeks, Victoria C. Anderson-Barnes et al., 2010; Melita J. Guimarra and G. Lorimer Moseley, 2011). Although residual limb pain, or more commonly called stump pain, does contribute to the

occurrence of phantom limb pain, it is not the causative agent producing the pain (V.S Ramachandran and William Hirstein, 1998). In fact, as has been discussed, congenital amputees also experience phantom limb pain which shows that there is a much more complex representation of the limb. Apart from this, administration of local anaesthesia to the stump or surgical removal of the neuroma does not always relieve the pain. Ramachandran and Hirstein believe that the sympathetic nervous system contributes highly to the intensified phantom pain in the presence of neuromas. Spontaneous activity or excitation of the cortex, which could be due to several factors including emotional instability as well as weather changes, causes an increase in firing rate of the pre-ganglionic sympathetic neurons. At the sympathetic ganglion the pre-ganglionic sympathetic neurons synapse with the post-ganglionic sympathetic neurons and these fibres fire. The post-ganglionic sympathetic fibres could either be noradrenergic or cholinergic. The noradrenergic (vasomotor) fibres innervate the blood vessels and when excited cause vasoconstriction whilst the cholinergic (sudomotor) fibres innervate sweat glands. Apart from this the release of noradrenaline and acetylcholine at the stump causes excitation of primary afferent fibres trapped in the neuroma. These afferents synapse at the dorsal horn and from here the impulses can either reach and synapse at the sympathetic ganglia or else reach the cortex, either way, this sympathetic cycle can be repeated (V.S Ramachandran and William Hirstein, 1998). If this cycle keeps on going, the pain will also continue to be perceived, once it stops, the pain will go away.

Cortical Factors

A second factor which contributes highly to phantom pain is cortical remapping. It is only until recent decades that the concept of cortical remapping was accepted amongst a number of researchers and scientists. Primarily, it was believed that the cortex remains stable throughout life and that one will die with the neural connections that were established in infancy. The first clear experimental study of cortical plasticity was demonstrated by Patrick Wall and his

team. After a case of partial denervation, these scientists managed to record changes in the receptive field size of a single neuron in the dorsal column (Wall, 1977). Nowadays, thanks to advances in technology, we are able to observe this phenomenon of cortical remapping using Magnetoencephalogram (MEG).

We now know that the somatosensory cortex comprises a complete map of the body. Parts of the body which have a higher sensory function than others, such as the lips and hands have more cortical representation. This is represented by the sensory homunculus. After amputation there is a decrease in the sensory input from the lost limb to the cortex. The area which once corresponded to the hand is now taken over by adjacent areas, these being the face and also the shoulder in upper limb amputation. Therefore, the sensory input from the face is received by the cortical areas of the face itself and also that of the hand (V.S Ramachandran and Wiliam Hirstein, 1998). This can happen even just a few hours after the amputation (V.S Ramachandran, 1998). This phenomenon could be observed in several studies performed by Ramachandran and Hirstein. In one case, a 17-year old boy who was involved in a car accident had his left arm amputated above the elbow. Tactile stimuli using a cotton swab were applied to the boy's left side of the face with his eyes closed at all times. The boy could accurately perceive the stimuli as coming from the face and also simultaneously mis-localised the stimuli as tingling sensations coming from his phantom hand. When the cotton swab was stroked along the boy's face, he could feel a sensation of stroking along his phantom hand. The areas on the face which corresponded to the areas on the phantom hand were very specific and stable over successive tests. Apart from this, these mis-localised stimuli were only perceived when touching the face, whilst other body parts such the tongue, neck and shoulder did not produce the same effect. These tests were performed again a week after and the results were found to be exactly the same. In another case these same results were obtained but conversely a second map present on the deltoid was observed. This was also stable and topographically organised. Other tests were done but this time using the sensations of warmth and cold.

When a drop of warm water was placed on the amputee's face he felt the warm sensation on his phantom arm. When this drop trickled down his face he could also feel the warm water trickling down his phantom arm. The topographical arrangement of the sensation of warmth and cold was found to be roughly the same as that of the tactile stimulation. This referral from the face or deltoid to the phantom arm/hand is quite common and one might assume that the same thing would happen with phantom legs or feet, although this is not the case. Ramachandran and Hirstein have reported only two cases of lower limb amputees experienced sensation of their phantom leg during sexual intercourse. In addition to this form of referral there have also been a few reported cases of referral from the other intact arm. This referral occurred for touch but not for pain and temperature. In fact, a painful prick on the intact arm was perceived as an indentation on the phantom. These results propose that there are connections linking the two hands conveying the sensation of touch. These may be too weak when both limbs are intact but when one limb is amputated the input may be strengthened resulting in this referral of touch (V.S Ramachandran and Wiliam Hirstein, 1998).

Ramachandran and Hirstein also discussed the reasons why the referral of pain is not always constant as could be seen in the two cases mentioned above. The first reason for this is that the hypothesis of cortical remapping could be totally wrong or missing some parts. Also, in this hypothesis we are assuming that the remapping takes place only at the primary somatosensory cortex but in actual fact, it could be occurring anywhere in the cortex including the thalamus. Another reason could be that the somatosensory maps vary from one person to another. Moreover, this referral is also influenced by external factors. For example, some patients may learn to disregard the referred sensations. Apart from this, certain patients continually use their stump for everyday activities and this may encourage cortical reorganisation of the hand to be referred to the stump instead of the face or shoulder (V.S Ramachandran and Wiliam Hirstein, 1998). This process of cortical reorganisation may cause pain

in a number of amputees because it is a pathological process. These sudden maladaptive changes in the cortex may be labelled as pain or paraesthesiae in the phantom by the nervous system (V.S Ramachandran and Wiliam Hirstein, 1998). In fact scientists have found out that there is actually a relationship between the extent of cortical remapping and the potency of the phantom limb pain; the higher the extent of cortical remapping the more potent is the phantom pain (Flor et al., 2006). This hypothesis of cortical remapping is partially supported by a study in which 9 patients who had a focal lesion of the parietal lobe had a complete disappearance of the phantom. Even though this theory manages to give us several answers on phantom pain, it fails to explain a number of things such as the phantom movements perceived by the subject, the paralysis of the phantom and the presence of phantoms in several cases, including those with a congenital absence of a limb. In fact congenital phantoms may strongly suggest that the brain constructs a body image which is partly genetically determined but can also be modified to undergo drastic changes, since it is affected by sensations such as touch, vision, hearing, balance and proprioception. The body image may also explain the rest of the cases because although the body image is subject to change the brain is predisposed to retain a complete body image, regardless of the actual appearance (Sharon R. Weeks, Victoria C. Anderson-Barnes et al., 2010; V.S Ramachandran and Wiliam Hirstein, 1998). The mechanism underlying cortical remapping, which is still primitive, is thought to be mediated by N-methyl-D-aspartate (NMDA) receptors. These receptors intensify the connection between two inputs coming together which will eventually result in a long-term Hebbian (neurons that fire together, wire together) potentiation of synapses (LTP) (V.S Ramachandran and Wiliam Hirstein, 1998). They are most commonly found at the anterior cingulate cortex, which is an area that controls pain and cognition. Glutamate is the major fast excitatory neurotransmitter present in the anterior cingulate cortex whilst gamma-amino butyric acid (GABA) is the major inhibitory neurotransmitter. When there is a reduction in the sensory activity, as in the case of amputation, the amount of GABA neurotransmitter will be reduced.

Therefore, NMDA receptors have a greater chance of being activated. This increased activation will cause calcium ions, an intracellular messenger, to be released in the dendritic spines. At the cells calcium binds to calmodulin and activates calcium-stimulated signalling pathways. This will cause synapses which were previously inhibited to be disinhibited. This will result in more long-term Hebbian connections to be set up which will in turn contribute to cortical remapping. At the anterior cingulate cortex, long-term depression of synapses (LTD) can also be set up but unlike the LTP's, this ability is thought to be lost after amputation. The ability to reset any enhanced synapses is lost after amputation (Min Zhuo, 2012; V.S Ramachandran and William Hirstein, 1998). The enhanced LTP's together with the diminished LTD's may be involved directly with the occurrence of phantom pain due to the maladaptive plasticity. In fact a promising treatment for phantom pain is resetting the enhanced synapses or recovering the ability for neurons to undergo LTD's (Min Zhuo, 2012).

Another cortical factor which is thought to contribute to the perception of phantom pain is corollary discharge. Corollary discharge is defined as the copy of a motor output in order to inform various parts of the brain that a movement will be performed. After amputation, the brain still continues to provide motor input to the missing limb, but after some time the brain realises that it is not receiving any sensory or proprioceptive inputs from the limb and thus discontinues the signals to that limb. Thus the phantom disappears over time. However, this is not the case in every individual, in congenital amputees the phantom limb usually persists longer. This is because the brain has never relied on any sensory inputs from the phantom as it has never received any. There is also the concept of 'learned paralysis', which most commonly happens when the limb is paralysed before the amputation. The brain has already learned that the arm is immobile through repeated messages from the motor cortex in effort to move limb. The visual stimulus will then inform the brain that the limb is paralysed. This concept happens as well after amputation but in this case the brain does not receive visual or any other stimulus input as the limb is missing. Thus, the ability to control the phantom is lessened to such a great

extent which results in paralysis (V.S Ramachandran and William Hirstein, 1998; Sharon R. Weeks, Victoria C. Anderson-Barnes et al., 2010).

Proprioceptive Memory

Even though the visual stimuli are not present after amputation it is thought that proprioceptive stimuli still exist. This is because the proprioceptive memory remains in the individual. This may also further explain the concept of learned paralysis. In most of the investigated cases, patients undergoing surgery perceive the phantom to be in the last position as it was just before local anaesthesia was administered. Memories of motor and sensory information could still be recalled in the limb through proprioceptive memory. The proprioceptive memory of the paralysed limb after amputation together with the absence of visual stimuli, causes the proprioceptive memory to perceive the phantom as being paralysed. The proprioceptive memory is also thought to be involved in the underlying mechanisms of several experiences reported by patients. These include reports of patients who still feel their wedding ring on their phantom finger. Apart from this, a number of patients have reported the sensation of a clenched fist and the feeling that their nails are digging into their palm. In all of these patients this sensation was accompanied by agonising pain which in some lasted for a couple of minutes, while in others lasted for hours. It is thought that the motor cortex sends signals to the phantom hand to clench the fist. This action is normally lessened by proprioceptive feedback, but in this case it is only the proprioceptive memory which remains and this has no control over the signalling from the motor cortex. Thus the motor cortex fires more and this overflow of motor input to the phantom may be interpreted as pain (V.S Ramachandran and William Hirstein, 1998; Sharon R. Weeks, Victoria C. Anderson-Barnes et al., 2010).

Pain Memory

Apart from the proprioceptive memory Ramachandran and Hirstein also believe that the actual pain memory in the spinal cord remains intact after the amputation,

possibly due to the process of central sensitisation. Since the amputation in itself results in severe tissue injury hyperalgesia takes place. There is an increase in the activity of nociceptive afferents which causes an increase in the excitability of neurons present in the dorsal horn. Moreover, nociceptive afferents which were once sub-threshold are now active which results in an increase in pain sensitivity and thus, more firing of the dorsal horn neurons. This hyper-excitability state is not influenced in any way by a local anaesthetic but it has been found that NMDA antagonists can block the spinal cord and prevent this central sensitisation process (V.S Ramachandran and William Hirstein, 1998). NMDA antagonist are sometimes given to patients before and during surgery to prevent the occurrence of phantom pain after amputation (Melita J. Guimarra and G. Lorimer Moseley, 2011).

Peripheral Nervous System Theory

A peripheral nervous system theory for the development of phantom pain due to stump neuroma suggests that the severe tissue and nerve injury after the amputation causes abnormal peripheral activity. Intracellular sodium at the neuroma increases as there is build-up of molecules that increase the expression of sodium channels. This results in loss of inhibitory control at the dorsal horn and therefore hyper-excitability (Sharon R. Weeks, Victoria C. Anderson-Barnes et al., 2010; Melita J. Guimarra and G. Lorimer Moseley, 2011; Bishnu Subedi and George T. Grossberg, 2011). Peripheral injections which alter the intracellular sodium concentration at the stump have been used for research and also as part of treatment. Peripheral injection of gallamine increases the sodium concentration in the neuroma by blocking acetylcholine. This has shown to increase phantom limb pain. Furthermore, injection of lidocaine showed a decrease in phantom limb pain as it blocks the sodium channels (Sharon R. Weeks, Victoria C. Anderson-Barnes et al., 2010). This hypothesis only attempts to explain part of the cause of phantom pain and therefore cannot be regarded as an effective theory.

Conclusion

If the discussed hypothesis on phantom pain is true, that is it includes several number of factors, most significantly cortical and physical factors that reinforce each other to cause pain, then both pharmacological and behavioural methods of treatment need to be taken into consideration in order to effectively treat phantom pain. This formula of carefully combined methods of treatment in order to effectively and consistently treat phantom pain in a majority of patients has not yet been established and much more work still needs to be done. One could say that treatment options for phantom limb pain depend upon the level of understanding of the mechanisms and nature of phantom limb pain. Since this comprehension is still relatively poor, phantom limb pain continues to be a ghostly phenomenon.

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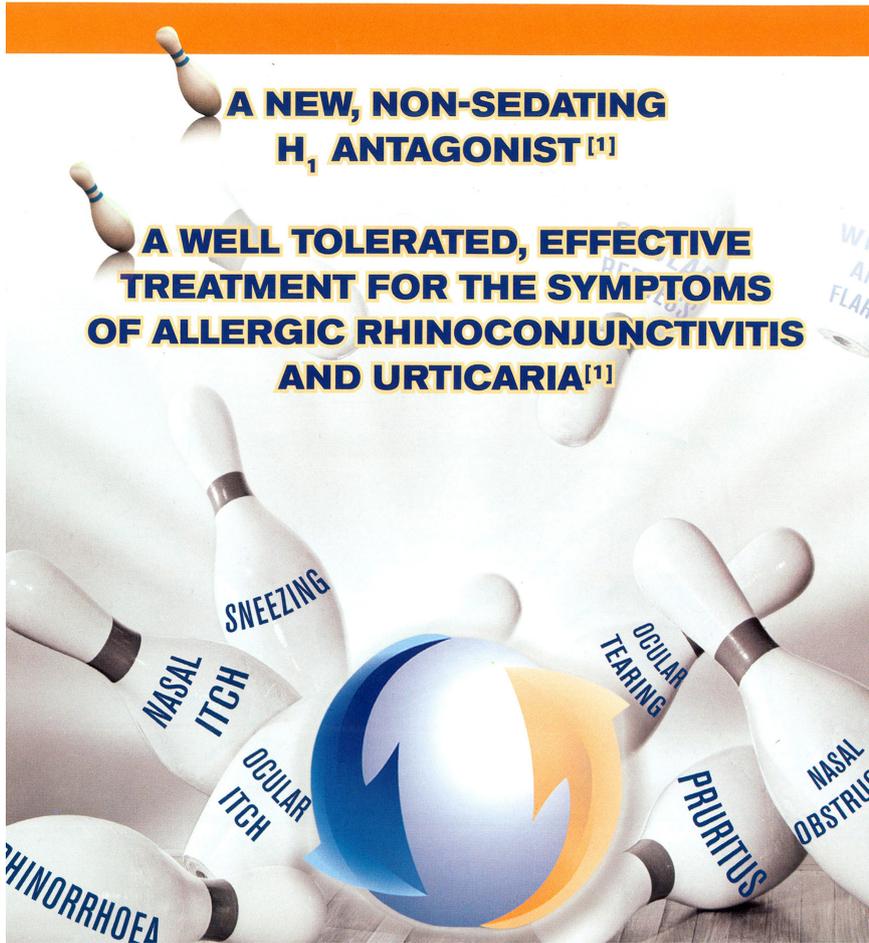
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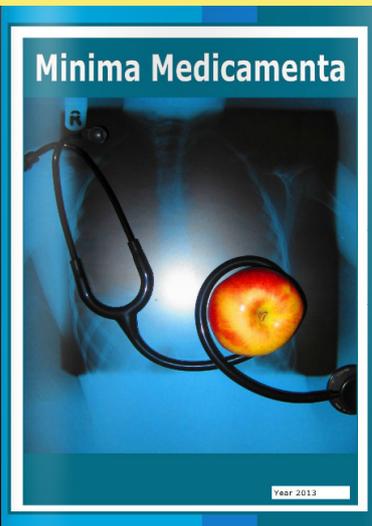
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