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Matilda Naesström, Monika Kakol, Victoria Kamkar, Wioletta Baranksa-Rybak, Malgorzata Sokolowska-Wojdylo, Marta Stawczyk and Roman Nowicki

Abstract

Aims: Lesions of the skin are omnipresent in Internal Medicine practice. The varying etiopathology when facing multiple system involvement may pose a challenge when it comes to diagnostics and management, especially when faced with less common skin diseases. Dermatomyositis is a rare skin disorder that manifests on the skin and in muscle; it also comes with a higher risk of comorbid cancers. Therefore we present the cases of dermatomyositis diagnosed at our departmet during the last 17 years, with the specific attention to occurrence of oncological processes.

Method: A retrospective study was performed on 12 cases hospitalized between 1996 to 2011 due to dermatomyositis. The analysis was based on the course of the disease, clinical picture, treatment and frequency of neoplasms.

Results: Within those 12 patients (in addition to dermatomyositis) five patients had concomitant oncological process. The tumors of these five patients were located in discrete anatomical locations. The oncological process occurred before, during, or after the appearance of dermatomyositis.

Conclusions: The combination of hallmark signs and symptoms seen in dermatomyositis are specific for the disease. Physicians need to be better informed about this rare, yet important disease, because it can be considered a paraneoplastic process.

Keywords: skin diseases; neoplasms; dermatomyositis

Abbreviations: DM - Dermatomyositis, EMG - Electromyography, ANA - Antinuclear antibodies, CK - Creatine kinase, LDH - Lactate dehydrogenase, AST- aspartate transaminase, ALT - Alanine transaminase, CT - Computer tomography

Introduction

Dermatomyositis (DM) is a rare autoimmune process with not yet fully understood aetiology. It is characterised by a combination of striated muscle inflammation and cutaneous changes. The pathogenesis of the cutaneous manifestations of DM is not well understood either. DM occurs in all age groups. Therefore, two clinical subgroups of DM are described: adult and juvenile. The adult form is predominant among female patients with a clinical presentation which includes a Heliotrope rash (Fig. 1), Gottron’s papules (Fig. 2), nail fold telangiectasia and other various cutaneous manifestations in association with inflammatory myopathy. In addition to the previous mentioned symptoms, juvenile patients also commonly suffer from ulcerative skin and recurrent abdominal pain due to vasculitis. An increased occurrence of oncological processes in combination with adult DM has been observed with a slight predominance for the female gender. These patients carry a higher risk for comorbid cancers. The most common ones include malignant processes of the ovary, lung, pancreas, stomach, urinary bladder and haematopoietic system. The significance of these observations is that the development of DM should raise suspicion with regard to a possible parallel oncological process.

Materials and Methods

A retrospective consecutive case series was performed on a group of 12 patients that were hospitalised at the Department of Dermatology, Venereology and Allergology at the Medical University of Gdansk between 1996 and 2013. The diagnostic criteria for DM included: hallmark cutaneous lesions of DM, clinically significant muscle weakness evaluated by electromyography (EMG), indicative laboratory findings - muscle enzymes, muscle biopsy, autoantibodies. All 12 cases
had muscle biopsy, serum studies and EMG performed. The retrospective study analysed the age and sex of the patients, course of the disease, accompanying diseases, clinical picture and treatment. The patients with malignancies were analysed by the primary organs of origin, and the period between the diagnosis of DM and that of malignancy (Table 1).

Figure 2

Limitations

The small sample size is a significant limitation in this retrospective analysis. DM is a rare disease with a prevalence of 1:1000. Increasing sample size, by combining cases from multiple institutions, and implementing control would further strengthen the presented material.

Results

The average age of onset of the disease was 48 years. All 12 subjects were female. Previous medical history included chronic eosinophilic leukaemia, diabetes mellitus type II, hypertension, leiomyomas, hypo- and hyper-thyroid disease, chronic obstructive pulmonary disease, peptic ulcer disease, autoimmune hepatitis and osteopenia. The two most common are diabetes mellitus type II and hypertension. The clinical picture of each case was similar in that all of the patients presented with some form of muscle weakness. In addition, typical features of DM with Gottron’s papules, periorbital oedema, facial oedema and erythema were noted in five patients. Antinuclear Antibodies (ANA) Hep-2 of values >1:160 were identified in nine patients. Additional laboratory markers such as creatine kinase (CK), lactate dehydrogenase (LDH), aspartate transaminase (AST) and alanine transaminase (ALT) were elevated in five patients. Two patients had muscle biopsies performed. The immunohistopathology picture consisted of Immunoglobulin G (IgG), fibrinogen, C1q, and C3 deposition around the perimsysum and granular deposits of Immunoglobulin M (IgM) in the dermal epidermal junction. Of the 12 patients, four had neoplasms in addition to the diagnosed DM. The primary cancers were originating from the cervix, breast, stomach and ovary. Of these four patients, all had the diagnosis of DM prior to the diagnosis of a malignancy.

Discussion

The diagnosis of DM is made by combining the clinical picture with the results of various laboratory findings: skin and muscle biopsies, EMG, serum enzymes and ANAs.

The clinical picture varies. The typical dermatological presentation consists of a erythematous and oedematous periorbital rash - the Heliotrope rash (Fig. 1). Symmetrical redness and flaking can be observed on the elbows and dorsal sides of the phalanges, especially over the distal metacarpal joints - Gottron’s papules (Fig. 2). Erythematous lesions can also be found on other locations such as the face, upper chest and knees. The dermatitis heals with atrophy, leaving behind areas that resemble radiation-damaged skin. The striated muscle inflammation most often involves the shoulder and hip area, leading to muscle weakness and atrophy. The intercostal muscles and the diaphragm may be involved causing alarm with regards to respiratory compromise. Dysphagia can be present due to inflammation of the smooth and skeletal muscles of the oesophagus. These inflammatory processes often lead to muscle calcification. The sum of all these changes clinically is seen most often as weakness, weight loss and subfebrile temperatures. All patients in our study had co-existing muscle and cutaneous symptoms, with variation in severity and localisation. Five patients had the classical picture of shoulder and hip area weakness. The rest of the patients had a more general muscle weakness. Two patients had atypical complaints of hand paraesthesia and extremity pain respectively.

Subtypes of DM exist for the purpose of epidemiological research and sometimes prognosis. They are categorised by the clinical presentation and presence or absence of specific laboratory findings. These subtypes are as follows: Classic DM, Amyopathic DM, Hypo-amyopathic DM and Clinically Amyopathic DM. These subtypes have little impact on routine diagnosis. Common laboratory findings in DM are enzymatic elevation of CK, AST, ALT and LDH; these mainly reflect the muscle involvement. Amyopathic DM lacks both abnormal muscle enzymes and weakness. Enzymatic elevation may sometimes precede the clinical symptoms of muscle involvement. Hence, an enzymatic raise in a patient with a history of DM, should raise suspicion of recurrence. Positive ANA findings are frequent in DM but not necessary for diagnosis. More myositis-specific antibodies include anti-Mi 2 and anti-Jo 1. A typical histopathological examination shows: myofiber necrosis, perifascicular atrophy, patchy endomysial infiltrate of lymphocytes and occasionally the capillaries may contain membrane attack complexes.

Cutaneous changes and muscular complaints can correspond to: 1. Systemic sclerosis which often has a positive ANA; 2. Trichinosis, in which periorbital swelling and myositis occurs, but there is a prominent eosinophilia and a history of consuming undercooked swine or bear meat; 3. Psoriasis with joint involvement which may give a clinically similar picture to DM. However, the skin changes in psoriasis have a more

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<table>
<thead>
<tr>
<th>No.</th>
<th>Sex</th>
<th>Previous medical history</th>
<th>Age of onset of DM</th>
<th>Clinical picture</th>
<th>Diagnostics</th>
<th>Treatment</th>
<th>Malignancy and age at diagnosis</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>F</td>
<td>Chronic eosinophilic leukaemia</td>
<td>54</td>
<td>Muscle weakness of shoulder and hip area, facial oedema and erythema, palmar erythema</td>
<td>CK 2550, ANA Hep-2 1:640, LDH 901, AST 69, ALT 143, X-ray = N, USG = N, EMG = N</td>
<td>Azathioprine, Prednisone</td>
<td>Stage IIA ovarian cancer at 55</td>
</tr>
<tr>
<td>2</td>
<td>F</td>
<td>Peptic ulcer disease</td>
<td>66</td>
<td>Facial erythema, Gottron’s papules on the hands, muscular weakness creating difficulty in movement, weight loss, decreased appetite</td>
<td>ANA Hep-2 1:1280, CT = N, EMG = N</td>
<td>Glucocorticoids</td>
<td>Small cell carcinoma at 66</td>
</tr>
<tr>
<td>3</td>
<td>F</td>
<td>None</td>
<td>23</td>
<td>Muscular weakness of shoulder and hip area; difficulty in standing up and walking up stairs, Gottron’s papules, Heliotrope rash, upper chest erythema</td>
<td>ANA Hep-2 1:2580, CPK 12022; AST 595, ALT 210, CK-MB 534; Jo 1 = N, Mi = N</td>
<td>Azathioprine, Prednisone, Methotrexate</td>
<td>None</td>
</tr>
<tr>
<td>4</td>
<td>F</td>
<td>Chronic obstructive pulmonary disease</td>
<td>42</td>
<td>Muscle weakness of shoulder and hip area, facial oedema and erythema</td>
<td></td>
<td>Cyclophosphamide, Methyl-prednisolone</td>
<td>Stomach tumour at 43</td>
</tr>
<tr>
<td>5</td>
<td>F</td>
<td>None</td>
<td>22</td>
<td>Muscle weakness, painful extremities, facial oedema and erythema</td>
<td>ANA Hep-2 = N, CT = N</td>
<td>Cyclophosphamide, Prednisone</td>
<td>None</td>
</tr>
<tr>
<td>6</td>
<td>F</td>
<td>None</td>
<td>42</td>
<td>Muscle weakness, paraesthesia of hands, facial oedema and erythema</td>
<td>ANA Hep-2 1:640</td>
<td>Cyclophosphamide, Prednisone</td>
<td>None</td>
</tr>
<tr>
<td>7</td>
<td>F</td>
<td>Hypertension, diabetes type II, osteopenia, leiomyoma.</td>
<td>65</td>
<td>Muscle weakness of shoulder and hip area, facial oedema and erythema</td>
<td>ANA Hep-2 1:1280, LDH 650</td>
<td>Cyclophosphamide, Prednisone</td>
<td>None</td>
</tr>
<tr>
<td>8</td>
<td>F</td>
<td>Hyper-thyroiditis</td>
<td>46</td>
<td>Muscle weakness; difficulty in moving, facial oedema and erythema</td>
<td>ANA Hep-2 1:160</td>
<td>Ciclosporin A, Prednisone</td>
<td>None</td>
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<tr>
<td>9</td>
<td>F</td>
<td>Autoimmune hepatic disease, leiomyoma.</td>
<td>45</td>
<td>Muscular weakness of shoulder and hip area, facial oedema and erythema</td>
<td>ANA Hep-2 1:2560, CK 3700, Mi-2 = P</td>
<td>Azathioprine, Methylprednisolone</td>
<td>None</td>
</tr>
<tr>
<td>10</td>
<td>F</td>
<td>Hypertension, diabetes type 2, hypo-thyroidism, ovarian cysts</td>
<td>57</td>
<td>Muscle weakness of shoulder and hip area, facial oedema and erythema, upper chest erythema, Gottron’s papules, Gottron’s papules, fatigue, dysphagia</td>
<td>ANA Hep-2 1:640, CK 747, LDH 363, AST 78, Ro52 = P, Mi 2 = N, Jo 1 = N, PM/Scd = N, CT= two pulmonary lesions that were biopsied and diagnosed as pneumoconiosis</td>
<td>Prednisone, Methotrexate</td>
<td>Cervical Carcinoma at 51, Breast Cancer at 57, Pulmonary Metastasis at 58</td>
</tr>
<tr>
<td>11</td>
<td>F</td>
<td>Hypertension</td>
<td>80</td>
<td>Muscle weakness, Heliotrope rash</td>
<td>ANA Hep-2 = P; Mi = N, CK 171.5, AST 45.22</td>
<td>Azathioprine, Prednisone</td>
<td>None</td>
</tr>
<tr>
<td>12</td>
<td>F</td>
<td>Hypertension, diabetes Type 2, hypo-thyroidism</td>
<td>42</td>
<td>Muscle weakness, Heliotrope rash, upper chest erythema</td>
<td>ANA Hep-2 1:320, Jo 1(-), Mi(-), CT=N</td>
<td>Ciclosporin A, Methyl-prednisolone, Methotrexate</td>
<td>None</td>
</tr>
</tbody>
</table>

No. = number (patient), DM = dermatomyositis, F = female, M = male, CK = creatine phosphokinase, ANA = antinuclear antibodies, LDH = lactate dehydrogenase, AST = aspartate transaminase, ALT = alanine transaminase, N = negative, P = positive, USG = ultrasonography, EMG = electromyography, CT = computerised tomography
flaking pattern. In doubtful cases, a skin and muscle biopsy together with an electromyography will set the diagnoses apart. A facial rash may also be observed in systemic lupus erythematosus together with nail fold telangiectasia. They are usually distinguished by a clinical picture with more organ system involvement in systemic lupus and by serological studies. A drug-induced picture of DM exists and is particularly associated with statins and hydroxyurea.8

It is estimated that around 25% of DM cases are associated with a neoplastic process that can occur prior, during or after the episode of DM. The risk of developing a malignancy is highest in the first year of DM and remains elevated for years after diagnosis.9, 10, 11 This was the case with patient number 1, 2 and 4 in our study, where the malignant process appeared in the first year following onset of DM. Risk factors seen in DM patients include male gender, advanced age and symptoms of dysphagia.12 The age range of the four patients in our study with malignancy was between 43 and 66. Symptoms that clinically raised suspicion of a malignant process included weight loss, lack of appetite and dysphagia. All neoplasms were discovered within one year after the diagnosis of DM was made. One patient had a previous history of cervical cancer, six years prior to the onset of DM.

The most common neoplasms seen in patients with DM vary in the world. In Europe the malignancies are located mainly in the ovaries, lungs, and stomach. The cancer types associated with the DM correlate with common cancers seen in the same area. For instance, in Asia, nasopharyngeal carcinoma (which is a rare malignancy in Europe) is a frequent occurrence in DM.1, 3 The location of neoplasms seen in our study varied from gastric, breast, ovary and pulmonary. The screening in regards to malignancies in patients with DM is individualised and should be based on risk factors such as previous malignancies, alarming symptoms such as weight loss or dysphagia, or abnormal findings on physical exam. This was the case with patient number 10 in our study who had a previous history of cancer, and patient number 2 who had symptoms of weight loss and decreased appetite. Initial screening was negative for patient number 1 and 2, where the malignancy developed first after the onset of DM. Age-appropriate screening with mammography, faecal-occult blood test and Papanicolaou smear should be considered. Additional investigations with chest films, computerised tomography (CT) scanning of chest, abdomen or pelvis; colonoscopy, cancer antigens; and gynaecological ultrasonography should be done when indicated.

The main objective of treatment in DM is to improve muscle strength and obtain remission, or at least clinical stabilisation. No specific protocol exists with regard to treatment of DM. Treatment is individualised and adapted to the specific condition of the patient. High-dose corticosteroids are the basis of treatment. However, randomised placebo clinical trials failed to show their efficacy. Clinical efficacy of corticosteroid therapy demonstrates itself and hence is the initial treatment of choice. Doses start at around 1 mg/kg/day depending on the corticosteroid of preference. This dosing is maintained for approximately two months until clinical regression is achieved, followed by approximately 10 mg decrease in dose for the coming three months. A maintenance dose of approximately 5-10 mg should be achieved. The exact parameters are patient-specific. In the case of a severe flare of dermatomyositis, 1 g per day for three days of methylprednisolone intravenous pulses can be administered. The systemic effects of long term therapy with corticosteroids have to be kept in mind. Hence, yearly dual-energy X-ray absorptiometry bone scans can be administered to monitor the development of osteopenia.

Further treatment options are offered in situations where the initial disease presentation is severe, involves internal organs, if relapse occurs during steroid dose reduction, and steroid side-effects. It has been proposed that combination therapy is a better method of approach due to lower reported relapse rates and lower need to use high-dose corticosteroids. Methotrexate is second-line therapy when steroids fail alone. Methotrexate is used with a maximum dose of 25 mg per week plus folate supplementation. The limitations of Methotrexate are immunosuppression and pulmonary fibrosis. Methotrexate is considered preferable to Azathioprine because the latter has a longer onset of efficacy. Azathioprine is administered at doses ranging from 1.5 - 3 mg/kg/day and has a side-effect profile is similar to that of other immunosuppressants. Cyclosporin A is a T-cell cytokine moderator that has a similar efficacy profile to Methotrexate. Side-effects include renal impairment, gingival hyperplasia, and hypertrichosis. Dosing of Cyclosporin A ranges from 2 - 3 mg/kg/day.

An expensive but effective and rather low side-effect alternative is intravenous immunoglobulins. The dosage of this medication has not been officially established in the treatment of DM, but options are: 2 g/kg given either in 1 g/kg/day for two days every four weeks; or 0.4 mg/kg/day for five days initially, and then for three days monthly for three to six months. Other alternatives include Mycophenolate Mofetil, Cyclophosphamide, Chlorambucil, Fludarabine, Eculizumab, Rituximab.2 Further options might be treatment targeted toward malignancy when associated with DM. This was observed in our patient number 10, where full remission of DM was obtained first after lobectomy and chemotherapy for the mammary carcinoma.

Conclusion

DM mainly affects women and all 12 cases presented in our study were female. One third of our cases had malignancies associated with their course of DM. We conclude that it is reasonable to screen these patients, especially in those with already established cancer risk factor. Age-appropriate screening and beyond is indicated by high risk factors or clinical presentation. High suspicion should be raised in patients with a previous history of oncological treatment since DM can be the first clinical sign of cancer recurrence.
Competing Interests
None declared

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References

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Hypertensive Crises – the Acute Take

Andrew Kristian Grech

Abstract
Despite chronic hypertension affecting over one billion individuals worldwide, presentation with acute hypertensive crises has been associated with low rates of appropriate management. According to established guidelines this includes lowering of pressure by 25% over the first hour following diagnosis, with target definition and treatment options described hereunder. Oral treatment can prove sufficient in many instances, with potential precipitous pressure drop and inherent detriment to patients borne in mind. Female gender, coronary artery disease and history of antihypertensive therapy (particularly with poor adherence to the latter) are thought to represent risk factors for acute crises. Presenting symptomatology includes headache, chest pain and shortness of breath, dizziness and nausea and emesis. End organ damage is a distinguishing feature in the subtypes of hypertensive crises, with investigation of presenting crises focusing on making this distinction.

Keywords: hypertension crisis emergency acute

Introduction
The Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure has long reported chronic hypertension as affecting over one billion individuals worldwide. While the role of primary care providers in the long term management of this ubiquitous condition cannot be overstated, the hypertensive patient can also present challenges to an acute physician when the control of arterial blood pressure reaches crisis level.

The What
The clinical entity extravagantly referred to as a hypertensive crisis describes an elevated systolic blood pressure of >180mmHg with diastolic pressure of >120mmHg. Within this category of acute presentations, two subcategories are defined – the hypertensive urgency and the hypertensive emergency. Flamboyant terminology aside, what distinguishes the latter ‘emergency’ from the former ‘urgency’ is evidence of acute end-organ damage. Emergencies therefore include various incipient pathologies of the cardiovascular, renal and central nervous systems. Fortunately these are less common encounters for receiving physicians, with a recent large multicentre study identifying acute pulmonary oedema (30.9%), myocardial infarction (17%), acute aortic dissection (7.9%), acute kidney injury (5.9%), cerebrovascular accident (22%) and hypertensive encephalopathy (4.9%) as features of hypertensive emergencies in 25.3% of hypertensive crises, with the remainder of the presenting population demonstrating a hypertensive urgency with inherent lack of evidence of end organ damage.

The Why
The pathophysiology of acute hypertension remains yet to be fully elucidated, however authors in the field of hypertensive crisis appear to converge on the point of two common proposed pathophysiological events. A sharp elevation in systemic vascular resistance is thought to be one precipitating factor, with an aberrance of cerebral autoregulation of blood flow being another.

For the purposes of an acute clinician faced with a bleeping blood pressure monitor, what is perhaps more applicable to everyday clinical practice is the potential role of non-adherence to regular antihypertensive medications as discussed below.

The Who
A longitudinal study carried out in Switzerland and led by Saguner identifies several potential risk factors for manifestation of a hypertensive crisis. Female gender, obesity and concurrent somatoform disorder accompany hypertensive and coronary artery related cardiac disease as potential red flags. Perhaps unsurprisingly, a history of multiple antihypertensive therapies was also associated with greater likelihood of presentation with hypertensive crises, as was non-adherence to the same therapeutic regimen. The latter compliance related issue was identified as the most significant by the study’s authors.
Elderly patients and also those of African American ethnicity have been shown to demonstrate higher rates of hypertensive crises in general\(^8\), while Caucasian patients are reported to have higher rates of emergencies as opposed to the more benign urgency equivalent\(^9\).

**The When**

The findings of a comparatively small Italian hospital-based study\(^10\) utilising 360 patients were recently supported by a larger United States-based analysis\(^11\) of over 400,000 patients, with a seasonal variation in presentation of hypertensive crises noted. A winter peak and summer trough was reported by both groups of authors, suggesting transcontinental extrapolation of a potential seasonal phenomenon.

**Evaluation**

Comprehensive disposition notwithstanding, acute physicians are urged to adopt a targeted approach when considering a presentation with alarming blood pressure readings.

**Present…**

By nature of definition, the presentation of a hypertensive crisis encompasses a wide variety of symptomatology depending on whether a hypertensive urgency or incipient emergency is manifested.

The symptomatology of a patient demonstrating hypertensive urgency can be fairly non-specific to acute blood pressure elevation. A 2014 study into clinical presentation of hypertensive crises reported headache as the most prevalent symptom (74.11% of patients), followed by chest discomfort and dyspnoea (62.35%), vertiginous dizziness (49.41%), nausea and emesis (41.47%) as demonstrated in Figure 1.

![Figure 1. Symptomatology in hypertensive crises (adapted from Salkic S, Batic-Mujanovic O, Ljuca F, et al.)](image)

While all of these common presenting complaints can bring a patient to a physician’s attention, what often alerts the attending physician to the particular possibility of an acute hypertensive condition is the blood pressure reading obtained on initial assessment of the patient (for instance for triage purposes) even in the absence of overt symptomatology as reported above. Indeed, patients with minimal symptomatology may be prompted to present themselves for acute medical care by no more than the sounding of an ominous alarm on a home blood pressure reader or the disconcerted look of a perturbed primary care physician, sphygmomanometer in hand!

…*and Past*

The history taking process of an acute physician faced with a hypertensive crisis should target several key areas which may prove essential in differentiating a case of urgency from an evolving emergency. With the potential for end organ heart, kidney and brain-related complications in mind, a physician should probe the possibility of chest discomfort, dyspnoea and signs of congestive cardiac failure (as indicators for incipient cardiovascular complications), headache, visual changes, dizziness and altered consciousness (potential harbingers of neurological complications) as well as recent history of oliguria as a marker of possible related renal insult.

Having conducted an interrogation for worrisome symptomatology, evaluation should proceed to a ‘hypertension history’. Prior diagnosis of hypertension and hypertensive crises in particular should be elaborated on, with this including a history of any prescribed regular antihypertensive therapy and both the adherence to and effect of the latter. Relevant to the notorious polypharmacy patients, any history of concurrent medication use must be clarified so as to give an indication of potential interactions.

Of historical note is the potential for hypertensive crisis following interaction of tyramine with mono-amine oxidase inhibitors (the so-called *cheese effect*), while a provoked hypertensive crisis more relevant to modern medicine is the potential effect of illicit substances including cocaine and amphetamine-based products\(^13\).

**Examination**

As with the evaluation of the hypertensive crisis patient’s history, examination should place particular emphasis on distinguishing urgency from emergency.

**Parameters**

Assessment of vital signs can provide valuable indicators. Whilst initial systolic pressure is not necessarily a predictor of the ability to achieve a prespecified target range pressure within thirty minutes\(^14\), the presence of tachycardia has been shown to be an ominous sign more prevalent in emergency than urgency, with a strong statistical association demonstrated with hypertension-related left ventricular failure\(^15\).

**Physical**

Cardiovascular examination should assess for the presence of signs of cardiac failure (including an elevated jugular venous pressure, added S3 heart sound or pulmonary rales) as well as the feared asymmetric pulses or new mid-diastolic murmur associated with aortic dissection. Auscultation for renal bruits should be performed, and a neurological assessment for possible stroke indicators undertaken.
Whilst chronic hypertension patients will often have subtle fundoscopic abnormalities, ophthalmological review for evidence of acute changes including new retinal haemorrhages or exudates together with papilloedema should be carried out.

**Investigation**

The unique circumstances of individual presentations aside, the prompt acute medical investigation of a hypertensive crisis should include a minimum number of bedside, laboratory and imaging investigations as suggested in Figure 2. Comparison of each of these to pre-existing baseline investigations may be invaluable in giving an indication of level of acute pathology and therefore care required.

**Figure 2. Investigations in hypertensive crises**

**Bedside**

Electrocardiography affords rapid exclusion of major acute ischaemic cardiac events, as well as providing an indication of chronic hypertrophic changes and a quantitative indicator of heart rate elevation. Simple dipstick urine testing can assist in exclusion of significant proteinuria pending formal urinalysis studies.

**Laboratory**

Full blood count analysis will give an indication of haemoglobin level where dissection is suspected, while serum markers of renal profile including creatinine level in particular may suggest varying degrees of acute kidney injury where present. Cardiac biomarkers may complement electrocardiography in exclusion of acute events.

As ever, a metabolic panel and blood gas analysis represent valuable tools in the acute physician’s arsenal where acute and evolving physiological disturbances are suspected.

**Imaging**

Presence of pulmonary congestion in keeping with left ventricular failure as well as the mediastinal widening of an aortic dissection may be assessed via simple chest radiography. More complex imaging such as computerised tomographic (CT) scanning may be indicated as dictated by clinical presentation, as in the event of neurological manifestations.

**Treatment**

Established guidelines suggest definitive management of a hypertensive emergency should involve lowering of blood pressure by 25% in the first hour and then to 160/100-110mmHg thereafter if stable, as indicated in Figure 3. Meticulous and continuous monitoring in an intensive care setting for parenteral administration of antihypertensive agents including labetalol, clevidipine and fenoldopam is beyond the scope of most practising acute physicians.

**Figure 3. Broad management of a hypertensive emergency**

Hypertensive urgency, however, need not require such invasive interventions, with oral therapy utilising labetalol, captopril or clonidine followed by a period of vigilant observation usually proving sufficient. A once popular practice of oral nifedipine is advised against, owing to the precipitous drop in pressure with inherent risk of tissue ischaemia observed on administration of this agent. Emergent pharmaceutical options including novel felodipine formulations may also be considered.

A pitfall of physicians, perhaps panicked by the jargon ‘hypertensive urgency’ has been observed, with inappropriate management in such cases reported in multiple independent studies in recent years, with a 42.6% appropriate treatment rate in one study. A chief consideration when faced with hypertensive crises therefore, may be to avoid rash intervention.

Worthy of mention is the potential for common co-prevalent secondary causes of hypertension including sleep apnoea, renal artery stenosis or a state of hyperaldosteronism; present in 15% of cases in one series, recommendations have been made for consideration of these prior to therapeutic intervention.

**Outcome**

Indicators of greater likelihood of admission in patients presenting with severe hypertension may include presence of age >75 years, dyspnoea, altered mental status or creatinine elevation.

**…And Back Again**

Following discharge after an admission for acute severe hypertension, a 90-day readmission rate of up to 35% has been reported; this includes a multiple readmission rate of 41% with similar re-presentation accounting for 29% of this data. Curiously, dyspnoic initial presentation is emphasised by the same data source as a risk factor for readmission, with
additional risk factors including ictal phenomena at initial presentation and history of both drug abuse and prior severe hypertensive admission.

**Key Points**

- **Definition**
  - A hypertensive crisis involves pressures of >180mmHg systolic and >120mmHg diastolic
  - A hypertensive emergency does not include end organ damage
  - A hypertensive emergency implies end organ damage

- **Symptomatology**
  - The commonest symptoms are headache (74.11%), chest discomfort & dyspnoea (62.35%), vertiginous dizziness (49.41%) and nausea & emesis (41.47%)

- **Investigations**
  - Bedside should include urinalysis and echocardiography
  - Laboratory should include creatinine level
  - Imaging should include plain chest radiography

- **Management**
  - Blood pressure should be lowered by 25% over the first hour
  - In hypertensive urgency, oral therapy is often sufficient
  - Consider co-prevalent secondary causes

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**Competing Interests**

None declared

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Medical Pain - A Forgotten Cousin, or Lost Cause?

Andrew Kristian Grech

Abstract
Poorly recognised over the years, medical pain - as opposed to its surgical cousin - continues to be associated with ineffective management and distasteful patient reports. Definitions and practice guidelines are conspicuous by their relative absence, with the disproportionate involvement of specialist pain physicians with non-medical cases and the consequent dependence on less experienced junior medical staff precipitating a rampantly inadequate medical pain experience for patients.

Several barriers to effective practices in the field of medical pain are proposed herein, with seedlings of potential solutions proffered in the interest of stimulating awareness and propagating interest in this neglected area of practice.

Keywords: medical; pain; anaesthesia; education; chronicity; fear

Introduction

What is medical pain? One answer would be a poorly defined concept which suffers the ignominy of poor management.

A quick internet search for the term brings up several hits to clinics offering the services of medical practitioners with pain specialty training. Definitions of ‘medical pain’ however, as opposed to those of its more easily construed post-surgical cousin, are both sparse and elusive in the learned literature. One potential candidate is provided by the International Association for the Study of Pain (IASP), whose professional presence on the web offers both a respectable description of pain syndromes of medical aetiologies as well as a taxonomical guide thereto.

With a struggle to even define the concept, is it any wonder that medical patients with pain complaints continue to score reprehensible figures on studies into pain incidence and effective relief? This is far from a new phenomenon, with the British Journal of Anaesthesia (BJA) reporting a staggering 52% of medical inpatients in one study (N=1594) of a UK district general hospital to be in pain on the medical ward, with 20% and 12% of those in pain rating this complaint as severe and unbearable respectively. What is particularly distressing about these statistics is the fact that data collection in the same study occurred over five days; more than ample time for complaints to be reported or recognised and appropriate relief strategies implemented. Barriers clearly exist to the provision of adequate medical pain relief, with practice shown to fall below standards recommended by the Royal College of Anaesthetists. A sketchy definition is perhaps one such barrier, but what other challenges exist to management of medical pain?

Predictability & On-Call Skills

In contrast to the anticipated pain following an elective surgical procedure, medical pain is less predictable in onset and consequently more the realm of an on-call physician than a specialist pain management team. One unambiguous fact when equating specialist pain rounds and the on-call services of a more junior recruit is that the former clearly benefit from greater levels of experience, even allowing for acquisition of specialist training. The latter inevitably rely more heavily on the knowledge base afforded them by theoretical education, which sadly tends to be rather scant in undergraduate medical programmes.

The lack of early teaching of junior staff on the subject represents one barrier to pain management in general, with formal teaching on the subject of medical pain management a particular shortcoming in several international medical curricula. This fact is supported by the findings of a cross-sectional study in one Sydney hospital utilising a multinational population of medical interns and residents, indicating some 56.2% of responders felt education on pain management to be inadequate. Up to 68.8% of responders were willing to receive additional lectures on opiate use to increase their knowledge base in this regard, suggesting a definite dearth of dedicated teaching.

In recognition of similar sentiments, a dedicated junior doctor-targeted postgraduate pain curriculum was suggested in 2011 by the Faculty of Pain Medicine (FPM) of the Australia & New Zealand College of Anaesthetists (ANZCA). This not only recognises the need for effective pain management skills at an early career stage, but also proposes a core set of competencies...
and assessments thereof for application to early postgraduate physicians’ skill sets.

A Surgical Predilection?

Skills of junior on-call medics aside, the provision of committed specialist pain services undoubtedly represents one of the major advancements in acute pain patient care. And yet, the needs of medical patients have often been overlooked in favour of acute surgical pain relief, and presumably continue to be so in the face of a lack of convincing evidence to the contrary. One study published in 2008 reporting data from over 220 United Kingdom National Health Service (NHS) hospitals revealed a paltry 16% incidence of routine acute pain service in medical wards6. The same study revealed that 82.2% of clinical leads in acute pain services actually recognise this problem of inadequate pain control on medical wards. With this stark admission from front line algologists in mind, why do elderly and general medical patients consistently appear to produce disconcertingly poor results in pain studies?

Perhaps the lack of adequate medical pain services in the light of a frank admission to a predilection for surgical patients reflects inadequate training, staffing or application of resources as a barrier to effective management of medical pain.

Community Confounders

Limitations of secondary care pain services aside, the primary care setting also exhibits a confounding factor for professional provision of medical pain management – the propensity for patients to easily self- medicate their complaints with non-prescription remedies. The inmemorial complaint of headache in the community provides a convenient example of the potential for patients to self-manage their pain symptom. In doing so however, they simultaneously skirt the legion of adverse drug reactions, drug interactions and other implications including paradoxical rebound pain which may complicate management later on in the professional setting. Data published following a recent review of literature sources indicate codeine-based compound analgesics to be the most popular over-the-counter medications dispensed across several international populations. This telling fact may be suggestive of a trend in non-professional pain management which impedes effective management according to professional standards. Assuming a relative deficit of surgical to medical pain patients in the community, this may represent a unique challenge to providers of medical pain services.

Chronicity

One further important consideration to be made in medical pain is its potential for chronicity, with prevalence of leading pain disorders including lower back pain and chronic migraine indicated at 10.2%9 and 1-3%7 respectively in recent studies. The former in particular has exhibited an explosive trend in prevalence over recent years, with a more than 2.5-fold increase since 1992 in relative prevalence observed in one 2006 American study of households state-wide (N=5357)8.

Implicit in the chronicity of pain complaints exist a number of secondary disorders which can prove troublesome for effective engagement of pain management services. The European Journal of Pain quotes a large transnational study of chronic pain patients (N=46,394)10 as finding 21% of patients to have been diagnosed with depression because of their pain. Interestingly while almost half of subjects were self-administering over-the-counter analgesics and only 2% were being seen by a pain specialist, an astonishing 40% reported inadequate pain relief – an almost anticipated outcome of the ‘do it yourself’ approach to pain management in chronic, refractory cases? This may be less relevant in surgical pain experiences which intuitively represent a more acute event in a more controlled environment, and therefore may be more amenable to effective management than a drawn out pain experience over several years!

Fear of Pain

Chronicity of pain in turn evokes a largely self-explanatory phenomenon known as fear of pain, which can present a potentially sizeable obstacle to management of patients. High levels of fear of pain and also movement as a provocative agent thereof have been described in 38.6% of fibromyalgia syndrome patients (N=233)11, with this heightened fear of a painful experience linked to increased disability, depressed mood and most importantly pain severity. This latter component alludes to one of the more insurmountable barriers to management of chronic medical pain – the impasse resulting from a vicious circle of pain, fear and infinite vice versas.

The fear of pain may in turn be compounded by a fear of narcotic analgesic therapy on both the part of the patient and the prescribing physician, with this being an issue in non-cancer pain as well as malignant disease. The fear of commencing and continuing long term opioids is traditionally said to be particularly prevalent in the primary care setting12. Fear can arise in view of a number of reasons, including the potential for addiction and major side effects as well as the notion that opiates represent a terminal stage in a disease process. Mention of opiates has been linked to accusations of ‘hidden diagnoses’ on the part of the physician, where patients suspect malignant pathology has been concealed from them by their care provider out of a deep-rooted belief that opiate analgesia is merited solely by cancerous conditions13. Whether this signifies an already fragile patient-doctor relationship or a contribution to the deterioration thereof, the connotation for effective management of medical pain remains a significant one. Repeated careful review of patients on long term opiate therapy for chronic non-cancer pain must be emphasised however, with up to 19% of chronic pain patients found to have some form of addictive disorder in a 2001 paper on the subject14 courtesy of the BJA.
Conclusion

In summary, patients requiring relief of medical pain issues are clearly disadvantaged by the presence of numerous hurdles to effective management of their complaints. The literature base in this regard is conspicuous by its absence, with practices in medical pain management being poorly evidence-based as a result. This represents a major potential target for investigative studies and research into potential trends and best practices. Exploration of effective methods for implementation of improved education for newer staff and also resource allocation for more experienced practitioners would also be of benefit to the standard of care in medical pain.

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Acute Oesophageal Necrosis: A Case Report and Review Of The Literature

Sabina Beg and David Rowlands

Abstract
Here we present a case of Acute Oesophageal Necrosis, a rare but increasingly recognised endoscopic finding. At gastroscopy distal necrosis of the oesophagus is observed. This condition is associated with a poor prognosis and therefore diagnosis should prompt aggressive correction of abnormal physiology.

Abbreviations: AON - Acute Oesophageal Necrosis

CASE
A 79 year old lady presented to the accident and emergency department with severe abdominal pain. On admission she was hypotensive and hypothermic. Blood tests demonstrated raised inflammatory markers and white count, but were otherwise unremarkable. A CT scan revealed no abnormalities. She was treated with intravenous fluids and empirical antibiotics.

She had multiple co-morbidities, including ischaemic heart disease, hypertension and chronic kidney disease.

Three days into her admission she had a single episode of hematemesis and a gastroscopy was arranged. Endoscopic features were as per figures 1-5. Histology taken at the time showed necrotic tissue with evidence of candidiasis. Her treatment was optimised with a two-week course of fluconazole with the dose adjusted for her renal function and parenteral nutrition, with good clinical response. She was discharged after a two week hospital admission. A repeat gastroscopy 10 weeks later showed complete resolution of endoscopic features with no evidence of perforation or stricture formation.

DISCUSSION
The images seen at endoscopy demonstrate a region of oesophageal ulceration progressing to a diffuse, circumferential, black discoloration of the distal oesophageal mucosa, with an abrupt transition to normal mucosa at the gastro-oesophageal junction (Figs. 1-3). These endoscopic features, in the absence of a history of ingestion of caustic substances, are diagnostic of Acute Oesophageal Necrosis (AON), also known as 'Black Oesophagus'. Whilst histology confirming necrosis is not necessary to make the diagnosis, it is confirmatory.

AON was first described in 1990 by Goldberg et al, since which over one hundred cases have been reported in the literature. Population studies have suggested the incidence of this condition to be between 0.08% and 0.2%, although interestingly one post-mortem series of 1000 patients failed to reveal any cases. There is a male preponderance, with an incidence four times greater than that for women and a peak incidence during the sixth decade of life.

The aetiology of this condition is not entirely clear; however case reports to date suggest that this is almost exclusively observed in those who are systemically unwell, usually in the context of multi-organ dysfunction. It has been postulated that necrosis most commonly occurs as a consequence of hypoperfusion caused by a low flow state in those with underlying vascular disease. This is likely to account for the predilection for the distal third of the esophagus, which is relatively less vascular. Individual cases have occurred in association with bacterial, viral and fungal infections, whilst malnutrition, malignancy and immune-compromise appear to be important factors.

The most common indication for the gastroscopy that makes the diagnosis of AON is hematemesis and melena, accounting for over 75% of cases. It is therefore likely that AON is significantly under reported as endoscopy is often precluded in those who are clinically unstable. Further it is not clear whether hematemesis is a universal symptom of this condition; it is conceivable that AON may go undiagnosed in those in whom this is not a feature.

Whilst AON has no specific treatment, its presence is indicative of significant systemic compromise and predicts a poor prognosis. This diagnosis should alert physicians that close monitoring and aggressive treatment is required to optimise patient outcomes. There is no clear role for the use of anti-acid therapy, however this is commonly used in management due to patient symptoms, which usually includes hematemesis. Similarly, candidiasis may occur in conjunction with AON, whilst it is not thought to be causative, treatment is considered prudent given the poor prognosis associated with this condition.
For those that recover from their acute systemic insult the prognosis appears to be good. The long-term sequale of this condition includes oesophageal stenosis due to structuring. Evaluation with a repeat gastroscopy if therefore indicated if dysphagia develops.

CONCLUSION

The clinical course of AEN is variable, with an associated mortality of 32%. The severity of the underlying clinical condition appears to be the most important factor in determining prognosis. There is no specific treatment for AON. The current body of experience suggests aggressive management of abnormal physiology optimises outcomes. Antibiotics, antifungals and nutritional support should be considered on an individual basis.
Competing Interests
None declared

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Generalized Lymphadenopathy: an unusual presentation of syphilis

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Abstract
This report describes a case of secondary syphilis represented by generalized lymphadenopathy. Histopathological analysis of biopsy specimen revealed the presence of a well-developed epithelioid granuloma including central areas of caseous necrosis. As granuloma formation can be seen in numerous diseases, additional clinical and laboratory diagnoses are necessary aids in the diagnosis of the granuloma aetiology. In this case, granulomatous lesion with caseous necrosis was highly suggestive of tuberculosis, but the identification by Ziehl-Neelsen staining was negative. However, the serologic tests of syphilis (VDRL and TPHA) confirmed the diagnosis of syphilis. As illustrated by this case, syphilis should also be considered as a possible cause of generalized lymphadenopathy. Awareness by the clinician of such a presentation would make it easy to diagnose syphilis at an earlier stage.

Keywords: Syphilis; Granuloma; Diagnosis; Lymphadenopathy; Caseous necrosis.

Introduction
As syphilis is a notable clinical and pathological imitator, its diagnosis remains challenging. Physicians should be vigilant to suspect syphilis in cases of non-specific signs, such as lymphadenopathies, even in patients with no apparent risk for sexually transmitted infections or a history of primary syphilis.

Case Report
We report the case of a seventy-year old woman with a medical history of arterial hypertension. She had neither smoked cigarettes nor drunk alcohol and she had no significant medical family history. The patient presented with a history of swelling in the left axilla of one year duration. The swelling gradually increased in size and was painless. There was a history of occasional low-grade fever and weight loss, but no cough or night sweats.

On initial examination, the patient was thin with generalised lymphadenopathy: she had an axillary adenopathy that measured 4 cm in diameter in the right axilla and one measuring 3 cm in the left axilla. She also had two cervical lymph nodes that were less significant, and one enlarged right inguinal lymph node of about 3 cm in diameter. The existing lymph nodes were painless, mobile, mildly tender and smooth. Otherwise, breasts, limbs and other regions were essentially normal. No skin rash or suspect lesions were noticed. All her family members were well, with no contributory medical history, and none of them had similar symptoms.

A complete blood count revealed a white blood cell count of 5300/l (neutrophils 40%, eosinophils 19%, lymphocytes 30%, monocytes 10%), and a C-reactive protein of 14 mg/l. The remaining results of her full blood count, electrolytes, liver enzymes, lactate dehydrogenase and urine analysis were within normal limits. Calcium and phosphate levels were normal in both blood and urine analyses. Both human immunodeficiency virus screening and the serological tests for hepatitis B and C were negative. Mantoux test did not show any indurations. Smear and culture of the sputum were negative. Her chest x-ray and abdominal ultrasound were normal.

A CT scan of the patient’s neck and chest showed a marked anterior mediastinal mass of about 50 mm diameter with multiple calcifications. Several small lymph nodes were also noticed in the cervical and axillary areas. An axillary lymph node biopsy was performed. Histopathological examination of the biopsy specimen revealed a granulomatous lesion with epithelioid and multinucleated giant cells (Fig.1) associated with calcifications and central areas of caseous necrosis (Fig.2), which were highly suggestive of tuberculosis.

According to these clinical and pathological findings, the most common granulomatous diseases are mycobacterial diseases such as tuberculosis, hence why the diagnosis of tuberculous lymphadenitis was highly suspected, and the patient was given anti-TB drugs. However, other differential diagnoses were considered, including bacterial infections like syphilis or actinomycosis, protozoal infections such as toxoplasmosis, and miscellaneous diseases such as sarcoidosis, Crohn’s disease and Wegener’s granulomatosis. To distinguish disease processes and make a definitive diagnosis, further investigations, such as special stains, culture methods and serologic tests, were indicated.
Additional histological stains, including Ziehl-Nielsen, were performed and returned negative, excluding the diagnosis of tuberculosis. In the meantime, the serological tests showed a positive venereal disease research laboratory test (VDRL: 1/8) and Treponema Pallidum haemagglutination assay (TPHA: 1/350). As a result, the diagnosis of secondary syphilis was confirmed and tuberculosis treatment was ceased.

Fig 1: Epithelioid granuloma with giant cell

Fig 2: Eosinophilic granuloma with acellular caseous necrosis

The patient received intramuscular injections of 2.4 million units of benzathine penicillin every three weeks. Additional clinical and laboratory examinations were performed for both the patient and her family. She did not present with any manifestations of cardiovascular or neurological syphilis. Her husband’s VDRL and TPHA tests were negative. After a nine-month follow-up, the patient had no clinical or laboratory evidence of syphilis.

Discussion

Syphilis is predominantly a sexually-transmitted disease with both local and systemic manifestations. The causative organism is the spirochete Treponema Pallidum (TP) which was first demonstrated on the 17th of May 1905.

Syphilis has many non-specific signs and symptoms that may be overlooked by the physician, because in some cases it may simply be indistinguishable from other more common diseases. In fact, syphilis can share clinical manifestations with other treponemal and non-treponemal diseases, and it may be asymptomatic in some stages. Unfortunately, undiagnosed and untreated syphilis may lead to life-threatening complications such as hepatitis, stroke and neurological damage. Therefore its clinical diagnosis must be supported by laboratory tests.

Several older methods can be used to confirm syphilis diagnosis such as direct identification of TP by dark-field microscopy or direct fluorescent antibody tests, but such tests are not practical in a routine clinical setting and these methods can only be performed on lesion exudate or tissue.

As a consequence, the diagnosis in most patients is based on serological tests. Guidelines from the United States of America (USA) and Europe recommend a combination of two tests: the first one is a non treponemal (cardiolipin, reaginic) test, essentially Venereal Disease Research Laboratory (VDRL) or rapid plasma reagin (RPR); and the second is a treponemal test, essentially TP haemagglutination assay (TPHA), TP particle agglutination, or the fluorescent treponemal antibody absorption (FTA-abs) test.

In our patient, the most significant clinical finding was lymphadenopathy. This case presented diagnostic difficulties because of its clinical and histopathological resemblance to other pathological conditions. In fact, the presence of generalised lymphadenopathy and the finding of granulomatous lesions with epithelioid cells in the biopsy were highly suggestive of tuberculosis. As a matter of fact, tuberculosis tops the list of aetiological causes of granulomatous infections.

Worldwide it is considered the leading cause of contagious disease leading to approximately 1.4 million deaths per year. Its prevalence is still extremely high in certain populations especially in low-and middle-income countries such as Tunisia where the disease is endemic.

Tuberculosis is caused by Mycobacterium tuberculosis (M. tuberculosis) and M. bovis, an acid and alcohol fast organism. Histopathology is characterized by the presence of epitheloid granuloma with Langerhans giant cells and central caseous necrosis.

Lymphadenitis is the most common extra-pulmonary manifestation of tuberculosis but its diagnosis is difficult, often requiring biopsy. In such granulomatous disease, and in cases of persisting doubts, it is necessary to identify the specific etiological agent by further investigations such as special stains, culture methods and molecular techniques like polymerase chain reaction (PCR) and serological tests, as in the case of syphilis.

In the case of tuberculosis infection, demonstration of the mycobacteria can be done with Ziehl-Neelsen staining or by immunofluorescence using auramine-rhodamine. Mycobacterial culture and detection of mycobacterial DNA using PCR are also used. Since the growth of mycobacterium in culture requires a long time, additional histological stain with Ziehl-Nielsen was performed, but returned negative in the case of our
As a consequence, the diagnosis of tuberculosis was excluded and syphilis was considered as a definitive diagnosis.

Conclusion

Granulomatous lesions can be seen in numerous diseases. A definitive diagnosis cannot be made on the basis of the history and physical examination alone, confirmatory testing should be performed in order to identify the specific etiologic agent correctly. Diagnosis of the disease in the initial stages would be beneficial not only to allow the patients to receive early treatment, but also to prevent the spread of the disease to others.

Competing Interests
None declared

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Intractable Yawning and Fluoxetine

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Abstract
Yawning is found in almost all animals including reptiles. Various theories have tried to describe yawning as a reflex to increase arousal & alertness in an exhausted and tired state. Several Medications are known to give rise to excessive yawning. This unusual, under recognised and usually ignored side effect can cause the sufferers to have severe problems. SSRI’s which are a well-established first line treatment for depression can lead to intractable yawning. We hereby present a case of intractable yawning in an individual on an SSRI namely fluoxetine. There was a clear temporal relationship i.e. starting Fluoxetine led to intractable Yawning and its discontinuation relieved it.

Keywords: Depression, Fluoxetine, Intractable yawning

Abbreviations: SSRI-Selective Serotonin Re-uptake Inhibitor

Background
SSRIs (Selective Serotonin Uptake Inhibitors) are very commonly used in Depression and Anxiety. Though considered as safest antidepressants, they have some common side effects which include gastrointestinal side effects, headache and at times sexual dysfunction. Yawning is one of the rare side effects of SSRIs. SSRIs were found to be the commonest cause of not so common drug induced yawning in a meta-analysis\(^1\). Isolated cases of intractable yawning have been reported with citalopram\(^2\), fluoxetine, citalopram and sertraline\(^3\) in the literature. Excessive yawning can cause injury to Temporo-Mandibular Joint (TMJ)\(^4\). Paroxetine has also been shown to cause intractable yawning\(^5\). Yawning possibly helps in thermoregulation and is an unconscious effort by the body to cool the brain\(^6,7\). It is known that yawning can be contagious. Reading, talking, seeing someone yawn or even thinking about yawning can induce yawning in the subjects\(^8\). Susceptibility to contagious yawning is different for different individuals depending upon their ability to process information about self\(^9\).

Case
A 60 year old postman presented with his first episode of depression. He attended the GP who started him on sertraline (an SSRI). He developed serious headaches and did not notice any therapeutic benefit. He was then referred to the psychiatric services for further management. He was assessed, Sertraline was stopped and Cipramil 20mg was introduced. He was reviewed after 2 months and the dose was increased to 40 mg to which he responded partially but relapsed within 4 months. There were no changes in his psycho- social circumstances. Cipramil was stopped and he was started on fluoxetine 20 mg. Once again the response was partial and was overshadowed by midnight insomnia and increased sleepiness in the daytime. Fluoxetine was increased to 40 mg and he was reviewed after 4 months when he reported clear and significant improvement in his depression but complained of “excessive yawning spells” causing him problems at his work place. The psychiatrist was surprised at the number of times he yawned at the Out Patient Clinic review. On further discussion it became clear that this side effect had become highly troublesome. He complained that his jaw was in severe pain. He was unable to do his delivery rounds and was having clear episodes of attention lapses leading to letters being put to wrong addresses. He was transferred to “sorting” the post at sorting counters and was taken off delivery rounds. Even here the intractable yawning continued and he was committing sorting errors. By now it was affecting his colleagues too and they also started yawning (it is known to be contagious). It was affecting his self-confidence and was extremely embarrassing in all social situations to an extent that he started avoiding social interactions. He was drowsy all the time. He was clearly suffering more due to excessive yawning than due to depression. He was unable to perform his employment duties and was signed off sick. At that point the dose of fluoxetine was reduced to 20 mg. After a couple of weeks his yawning reduced significantly but was still disruptive to his routines. He was advised to slowly taper off fluoxetine over next 4 weeks. Unfortunately his depression relapsed and his GP restarted him on Fluoxetine 20 mg. He was reviewed by the psychiatrist after a couple of weeks. Once again he reported return of intractable yawning.

Fluoxetine was stopped once again and he was started on Mirtazapine 15 mg. There was very little response. The dose was increased to 30 mg after around two weeks. This led to him...
to experience nausea and vomiting. Unfortunately Mirtazapine too had to be stopped. He was then tried on amitriptyline 50 mg which improved his sleep and symptoms of Depression. He was reviewed in the outpatient clinic after a couple of months. He did not develop any side effects and responded quite well. He then started his job starting from part time to full time within 6 weeks. After 6 months on the same dose of amitriptyline, did not have any symptoms of depression and was finally discharged from the mental health services.

Discussion

SSRI is the first line antidepressants used in the treatment of depression and Anxiety disorders. They are known to have least side effects and safest when it comes to overdosing. Intractable Yawning is quite an unusual and uncommon side effect. One has to be conscious of the fact that it may cause yawning that can be pathological and can cause severe disruption of patient’s life. It can contribute to poor compliance. It is quite easy to overlook and ignore this side effect as yawning usually seems to represent sleep problems which is also a significant feature of the associated depression itself.

Excessive yawning can cause Jaw/facial pain. It can even cause dislocation of temporo-mandibular-joint. It can cause severe problems with one’s work and self-esteem. The sufferer might be misunderstood for being inattentive, indolent and sluggish. It might affect relationships with spouse/friend/relatives and especially at place of work. It can be misunderstood by doctors and lead to unnecessary tests and investigations. One has to be aware when prescribing SSRIs in patients who are driving or are involved in handling heavy machinery, athletes, airline pilots, surgeons, life guards, air traffic controllers and many other professionals. Due to its contagious nature, it’s not only the patient who is affected but also others around him. Excessive yawning can adversely affect the level of arousal, the level of concentration and work efficiency leading to poor performances in tasks requiring undiverted attention.

Hence excessive or intractable yawning has to be kept in mind while prescribing the so called most safe anti-depressant class of medication, the SSRIs, in this case fluoxetine.

Competing Interests

None declared

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Physical health of people with severe mental illness: Don’t just screen… intervene!

Javed Latoo, Oladipupo Omodunbi, David Hindley, Amanda Derbyshire and Rachael Kane

Abstract

Introduction: A growing number of studies suggest a causal relationship between antipsychotic treatment and metabolic disturbances. The most frequent problems linked to antipsychotic drugs have been abnormalities of glucose metabolism such as insulin resistance, hyperglycaemia or new onset diabetes mellitus and dyslipidemia, including increased levels of total cholesterol, LDL-cholesterol and triglycerides. The study was aimed at reviewing the practice regarding the routine monitoring of physical health of service users on antipsychotic treatment. The study set out to reduce the cardio-metabolic effect of antipsychotic medication in service users. The study was also aimed at contributing to a reduction in the mortality rates in people with severe mental illness as well as testing out approaches to improve the physical health of people with serious mental illness who are receiving care from the Early Intervention in Psychosis Teams. The promotion of a more integrated approach to the physical health care of people with a SMI was also targeted.

Methods: In November 2012, the Warrington and Halton Early Intervention in Psychosis service (EIP) conducted the initial audit, designed by AQuA as a baseline measure of the current standard of physical health screening amongst the Early Intervention patients in the two boroughs. The recommendations from the National Institute for Health and Care Excellence (NICE) and Maudsley prescribing guidelines were the frameworks for the AQuA design. The Research and Audit Governance Group in the 5 Boroughs Partnership NHS Foundation Trust approved the audit. A retrospective review of the clinical records of all patients opens to the EIP, who were prescribed antipsychotics, was undertaken. Six physical health parameters were examined and these include; serum lipid profile and blood glucose levels. Others measures were body weight, height, Body Mass Index (BMI) and blood pressure. These parameters were entered into the survey monkey audit tool developed by AQuA. Recommendations were made following the initial audit. A re-audit was carried out in May 2013.

Results: The re-audit in May 2013 showed an increase in the number of service users being screened and monitoring for the six identified parameters A robust and comprehensive recording system has been developed, resulting in more service users receiving appropriate screening and physical health monitoring. Better links and working relationships have been established with primary care services and there is increased awareness of the need for physical health monitoring in professionals and service users. Regular and well-equipped physical health clinics with well-trained staff have been established across both localities. Other secondary care agencies within the Trust are now more aware of the requirements for physical health screenings.
A greater inherent predisposition to develop metabolic abnormalities coupled with metabolic adverse effects of antipsychotic drug treatments may negatively influence physical health.8 Many of these problems can be avoided if close attention is paid to the physical health of patients on antipsychotic treatment. A longstanding debate persists concerning who is responsible for the physical care of patients with serious mental illness. Psychiatrists and physicians are advised to play an active role in ensuring that patients with mental illness are not disadvantaged.9

The Warrington and Halton Early Intervention in Psychosis Team is based in the 5 Boroughs Partnership (5BP) NHS Foundation Trust in the North West region of the United Kingdom, and in collaboration with Advancing Quality Alliance (AQuA), they embarked on a joint audit between November 2012 and May 2013 with the aim of reviewing the practice regarding the routine monitoring of physical health of service users on antipsychotic treatment. The study set out to reduce the cardio-metabolic effect of antipsychotic medication in service users. The study was also aimed at contributing to a reduction in the mortality rates in people with severe mental illness as well as testing our approaches to improve the physical health of people with serious mental illness who are receiving care from the Early Intervention in Psychosis Teams. The promotion of a more integrated approach to the physical health care of people with a SMI was also targeted.

Method

In November 2012, the Warrington and Halton Early Intervention in Psychosis service (EIP) conducted the initial audit, designed by AQuA as a baseline measure of the current standard of physical health screening amongst the Early Intervention patients in the two boroughs. The recommendations from the National Institute for Health and Care Excellence (NICE) and Maudsley prescribing guidelines were the frameworks for the AQuA design. The Research and Audit Governance Group in the 5 Boroughs Partnership NHS Foundation Trust approved the audit.

A retrospective review of the clinical records of all patients opens to the EIP, who were prescribed antipsychotics, was undertaken. Six physical health parameters were examined and these include: serum lipid profile and blood glucose levels. Others measures were body weight, height, Body Mass Index (BMI) and blood pressure. These parameters were entered into the survey monkey audit tool developed by AQuA.

Other items audited were the frequency of screening, the number of physical health parameters evaluated at each period of recording and the smoking status of the service users. Clinical records were checked for documented history of physical illness in all patients. The number of service users receiving physical health interventions as a result of the screening and the number of service users who were offered physical health interventions at the screening but either refused treatment or did not respond to the referral was also recorded. The results were presented at a Trust-wide forum and recommendations were made, and disseminated shortly afterwards. A re-audit was done in May 2013.

Results

Table 1, summarises the demographic details of patients at baseline and re-audit. 55 patients were involved in the baseline audit and 52 patients were involved in the re-audit. No significant differences were observed in both audits in terms of gender distribution and age. Majority of the patients involved in both audits were of white British ethnicity.

Table 1: Demographic details of patients at baseline audit and re-audit

<table>
<thead>
<tr>
<th></th>
<th>Nov 2012</th>
<th>May 2013</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total number of patients</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male: female</td>
<td>35:20</td>
<td>22:30</td>
</tr>
<tr>
<td>Age</td>
<td>14-36</td>
<td>15-36</td>
</tr>
<tr>
<td>White British Ethnicity</td>
<td>52</td>
<td>48</td>
</tr>
</tbody>
</table>

Baseline audit: November 2012

Screening and monitoring

The table below indicates the number of service users receiving a screening for weight, height, BMI, glucose blood levels, lipid blood levels and blood pressure at the 4 week, 3 month, 12 month and 24 month assessments.

Table 2: Physical health screening of service users at baseline

<table>
<thead>
<tr>
<th></th>
<th>4 weeks recorded screening</th>
<th>3 months recorded screening</th>
<th>12 months recorded screening</th>
<th>24 months recorded screening</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 type of screening</td>
<td>5 (9.1%)</td>
<td>12 (21.8%)</td>
<td>18 (32.7%)</td>
<td>18 (32.7%)</td>
</tr>
<tr>
<td>2 types of screening</td>
<td>14 (25.5%)</td>
<td>17 (30.9%)</td>
<td>5 (9.1%)</td>
<td>5 (9.1%)</td>
</tr>
<tr>
<td>3 types of screening</td>
<td>4 (7.3%)</td>
<td>4 (7.3%)</td>
<td>3 (5.5%)</td>
<td>6 (10.9%)</td>
</tr>
<tr>
<td>4 types of screening</td>
<td>5 (9.1%)</td>
<td>3 (5.5%)</td>
<td>5 (9.1%)</td>
<td>3 (5.5%)</td>
</tr>
<tr>
<td>5 types of screening</td>
<td>4 (7.3%)</td>
<td>0</td>
<td>1 (1.8%)</td>
<td>4 (7.5%)</td>
</tr>
<tr>
<td>6 types of screening</td>
<td>4 (7.3%)</td>
<td>3 (5.5%)</td>
<td>4 (7.3%)</td>
<td>2 (3.6%)</td>
</tr>
</tbody>
</table>

There was no screening recorded for 19 (34.5%) patients at 4 weeks, 16 (29%) patients at 3 months, 19 (34.5%) patients at 12 months and 17 (30.9%) patients at 24 months.

Smoking status of service users

Based on the analysis of those referred to the smoking cessation service, it was concluded that around 35% of service users within the EIP Service smoke. The findings from this data also indicate high refusal rates to smoking cessation programmes (at over 80% of those service users who confirmed that they smoke).

Documented history of physical illness
The presence or absence of physical illness was documented in the records of 35 patients. Where physical health problems were identified, patients were offered a number of interventions. These include referral to the dietician/exercise programmes, smoking cessation and referral to primary care services for illnesses such as, hypertension, diabetes and hyperlipidemia.

Table 3, summarises the types of interventions available for patients when physical health issues were identified. A number of patients (N/A) required no interventions, as physical problems were not identified.

Number of service users receiving physical health interventions

Table 3: Physical health interventions

<table>
<thead>
<tr>
<th></th>
<th>Yes</th>
<th>No</th>
<th>N/A</th>
</tr>
</thead>
<tbody>
<tr>
<td>Referral to dietician/exercise programme</td>
<td>15 (28.8%)</td>
<td>26 (50%)</td>
<td>14 (25.5%)</td>
</tr>
<tr>
<td>Treatment for Diabetes</td>
<td>0</td>
<td>22 (45.8%)</td>
<td>35 (60%)</td>
</tr>
<tr>
<td>Treatment for Hyperlipidemia</td>
<td>2 (4.2%)</td>
<td>23 (47.9%)</td>
<td>20 (54.5%)</td>
</tr>
<tr>
<td>Treatment for Hypertension</td>
<td>0</td>
<td>22 (45.8%)</td>
<td>33 (60%)</td>
</tr>
<tr>
<td>Help with smoking cessation</td>
<td>12 (24.5%)</td>
<td>19 (38.8%)</td>
<td>24 (43.6%)</td>
</tr>
</tbody>
</table>

Re-audit: May 2013

Screening and monitoring

The table below indicates the number of service users receiving a screening for weight, height, BMI, glucose blood levels, lipid blood levels and blood pressure at the 4 week, 3 month, 12 month and 24 month assessments. The table shows that 29 patients had their screening recorded at 4 weeks, 19 (66%) of which had 6 types of screening. At 24 months, out of the 16 patients who had their screening recorded, 15 (95%) had 6 types of screening. Patients with no screening parameters were omitted.

Table 4: Physical health screening of service users at re-audit

<table>
<thead>
<tr>
<th></th>
<th>4 weeks recorded screening</th>
<th>3 months recorded screening</th>
<th>12 months recorded screening</th>
<th>24 months recorded screening</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 type of screening</td>
<td>2 (7%)</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>2 types of screening</td>
<td>2 (7%)</td>
<td>2 (8%)</td>
<td>1 (4%)</td>
<td>1 (5%)</td>
</tr>
<tr>
<td>3 types of screening</td>
<td>1 (3%)</td>
<td>1 (4%)</td>
<td>3 (11%)</td>
<td>0</td>
</tr>
<tr>
<td>4 types of screening</td>
<td>3 (10%)</td>
<td>3 (12%)</td>
<td>1 (4%)</td>
<td>0</td>
</tr>
<tr>
<td>5 types of screening</td>
<td>2 (7%)</td>
<td>1 (4%)</td>
<td>1 (4%)</td>
<td>0</td>
</tr>
<tr>
<td>6 types of screening</td>
<td>19 (66%)</td>
<td>18 (72%)</td>
<td>21 (77%)</td>
<td>15 (95%)</td>
</tr>
</tbody>
</table>

Smoking status of service users

The overall data confirms that 25 patients, who were identified as smokers, were offered smoking cessation, 19 of which refused, thus giving an overall refusal rate of 76%.
To tackle the identified issues a local project group was constituted. This group was made up of a consultant psychiatrist, business manager, nurse consultant, team manager, an occupational therapist (OT), a support worker (STR), a pharmacist, social services, public health leads, wellbeing nurses, a service user representative, and a locally based General Practitioner. The group had monthly meetings.

Patients in the Warrington and Halton Early Intervention in Psychosis Service were screened using the 5 Boroughs Partnership (5BP) Comprehensive Physical Health Assessment tool. This tool covered the 6 parameters targeted in the audit and other relevant health information such as, smoking, diet, exercise, sexual health, sleep, dental and optical health, ECGs, and other routine bloods checks. An in-house database in which results could be recorded was devised and implemented. A notification list which alerted on computer when a screening is due was developed; a GP DVD and information leaflet for the GP website and the Clinical Commissioning Group (CCG) Newsletter were produced. Wellbeing Nurse-led clinics were held in Halton and a STR-led physical health clinic was initiated in Warrington. Access into the path labs for both localities was established to help facilitate prompt access to blood results. Regular AQuA meetings took place in Salford, Manchester, and links were established with the Medical Director and the Clinical Commissioning Group, who were regularly, provided progress reports.

The re-audit in May 2013 showed an increase in the number of service users being screened and monitoring for the six identified parameters (see Table 8). A robust and comprehensive recording system has been developed, resulting in more service users receiving appropriate screening and physical health monitoring. Better links and working relationships have been established with primary care services and there is increased awareness of the need for physical health monitoring in professionals and service users. Regular and well-equipped physical health clinics with well-trained staff have been established across both localities. Other secondary care agencies within the Trust are now more aware of the requirements for physical health screenings.

Why should we be doing regular physical health monitoring? The benefits of monitoring the physical health of individuals with serious mental illness cannot be overemphasised; it allows early identification and subsequent management of cardiovascular and other risk factors in a timely manner. The Maudsley Guidelines recommend monitoring of blood lipids at baseline, at 3 months and yearly. Similar recommendations are made for the weight, which includes BMI and waist size when possible. Plasma glucose measurements are recommended at baseline, at 4 to 6 months and yearly. Blood pressure measurements are recommended at baseline and frequently during dose titration. Full blood count and electrolyte measurements are recommended at baseline and yearly. In the last few years, agencies worldwide have also developed clinical guidelines. In the United States, the American Diabetes Association, American Psychiatric Association, American Association of Clinical Endocrinologist and the North American Association for the Study of Obesity have released joint guidelines.

Even though the side effects of antipsychotics are well established, many mental health services today have yet to adopt a practice of regular blood monitoring as recommended by international guidelines. The issue of responsibility for monitoring metabolic abnormalities remains a much debated topic today. The primary responsibility for managing the physical health of individuals with severe mental illness has been said to lie with primary care. Another side of the debate, however, exists, and two consensus conferences have called on mental health care providers to take responsibility for the physical health of their patients. It is widely recognized that mental health teams have a role to play in the monitoring of the physical health of their service users; however, many psychiatrists still consider psychiatric symptom control as their primary responsibility. Studies have also shown that Individuals with Serious Mental Illness do not readily access primary care. Despite the availability of Clinical Guidelines, screening for and monitoring of metabolic problems in patients with serious mental illness remains suboptimal.

The usual practice in most centers for monitoring physical health parameters and guidelines used vary and are rarely regulated. Local resource availability is likely to play a significant role in guideline selection. Physical equipment, staffing levels and other resource issues may need to be taken into consideration prior to devising a local guideline. Development of a specialised phlebotomy service, for example, to the outpatient clinics will be a welcome addition, introduction of a key worker system as seen in the Warrington and Halton Early Intervention in Psychosis Team and consideration of the physical health needs of patients as part of the key worker’s duties, a simple one-page monitoring prompt attached to the patient’s medical file, educational intervention and oversight by the senior clinicians may all increase the adherence to routine blood testing guidelines. Regular liaison with General Practitioners regarding a joint approach to physical health monitoring would also help improve adherence to the guidelines.
References

Do thalidomides have a role in the treatment of multiple sclerosis?

G.V. Sherbet

Abstract

Angiogenesis is pivotal component of many normal biological programmes as well as of pathogenetic processes involved in tumour growth and progression and of inflammatory and autoimmune diseases such as multiple sclerosis (MS), a demyelinating disease of the CNS. Many angiogenic factors are expressed in MS and in the animal model of MS known as experimental autoimmune encephalomyelitis. Inhibition of angiogenesis by suppressing these angiogenic effectors or inhibiting the elements of angiogenic signalling might provide a viable way to target therapy to manage MS. The focus of this article is on the ability of thalidomide and its analogues to inhibit angiogenic signalling systems. Thalidomide is a highly toxic drug but its analogues, lenalidomide and pomalidomide, show reduced toxicity and greater efficacy of growth suppression and inhibition of angiogenesis. The thalidomides are highly efficient suppressors of canonical and non-canonical angiogenic signalling by PI3K (phosphoinositide-3 kinase)/Akt, NF (nuclear factor)-κB and mTOR (mammalian target of rapamycin). Here a postulate is presented that the perceived potential synergy between the thalidomides and modulators of angiogenic signalling might deliver benefits of thalidomides more effectively and at lower dosages compatible with greater safety of administration.

Keywords: Multiple sclerosis; angiogenesis signalling; thalidomides

Angiogenesis is an integral process in biological programmes of embryonic development, tissue damage and regeneration, tumour growth and progression and pathogenesis of inflammatory and autoimmune diseases. MS (multiple sclerosis) is a demyelinating disease of the CNS (central nervous system). Angiogenesis has been a consistent feature of demyelinating plaques of MS. Many inducers of angiogenesis are expressed in these plaques. They are also closely associated with the animal model of MS viz. EAE (experimental autoimmune encephalomyelitis) (Table 1). This has led to the suggestion that inhibition of angiogenesis by suppressing these effectors or inhibiting the elements of angiogenic signalling pathways might provide a viable way to target therapy to manage MS.

Table 1. Angiogenic mediators of MS

<table>
<thead>
<tr>
<th>Angiogenic agent/mediator</th>
</tr>
</thead>
<tbody>
<tr>
<td>Vascular endothelial growth factor (VEGF)/VEGF receptor 2</td>
</tr>
<tr>
<td>(VEGFR2)</td>
</tr>
<tr>
<td>Nitric oxide (NO) and NOS (NO synthase)</td>
</tr>
<tr>
<td>Transforming growth factor-β (TGF-β)</td>
</tr>
<tr>
<td>Basic fibroblast growth factor (bFGF)</td>
</tr>
<tr>
<td>Matrix metalloproteinases (MMP)</td>
</tr>
<tr>
<td>Hepatocyte growth factor (HGF)</td>
</tr>
</tbody>
</table>

[Note: Inhibitory effects of thalidomides were described by Sherbet; D’Amato et al.; Kenyon et al.; Lu et al.]

Multiple sclerosis is an autoimmune inflammatory condition and so immunomodulators have been used in treatment. It is recognised that aberrant activation of the immune system and the associated network of its regulation are important events in the pathogenesis of the disease. This is the rationale for using immunomodulatory agents in disease control. Among immunomodulators of note are Fingolimod which prevents infiltration of auto-destructive lymphocytes into the CSF, Teriflunomide which reduces lymphocyte infiltration of the CNS, axonal loss and inflammatory demyelination, and dimethyl fumarate, which modulates the immune system by many mechanisms. Furthermore, much attention has been devoted to the immunomodulatory properties of MSCs (mesenchymal stem cells). Thalidomides are also capable of modulating the function of key element of the immune system related to the pathogenesis of MS, but this brief article is intended to emphasise the potential of thalidomide and its analogues as potent inhibitors of angiogenesis and the latent possibility of their use as a therapeutic agent in the control of MS.

Thalidomide was introduced over four decades ago to treat respiratory infections and to combat morning sickness in pregnant women. It was withdrawn when it was found to be highly teratogenic. The teratogenic effects are a result of the binding of thalidomide to cereblon, a protein found in both embryonic and adult tissues. Cereblon is required for normal morphogenesis. It is inactivated by binding to thalidomide and this leads to teratogenesis. Thalidomide possesses immunomodulatory, anti-inflammatory, anti-angiogenesis and cell proliferation inhibitory properties and this has suggested its use in the treatment of cancer. Analogues of thalidomide, viz. lenalidomide and pomalidomide, have been synthesised and
these possess reduced toxicity and greater efficacy\textsuperscript{10, 11}. Recently, many studies have elucidated the signalling pathways which thalidomides inhibit and thereby suppress cell proliferation, promote apoptosis and inhibit angiogenesis. These have led to the suggestion of combining the modulators of these signalling pathways to synergise with thalidomides to deliver the suppressor effects with enhanced efficacy and at lower concentrations thus reducing the side effects\textsuperscript{5} (Figure 1).

Most of the work on the efficacy of thalidomide and the analogues has been carried out in preclinical models. Quite understandably, in the clinical setting very little effort is seen to check whether thalidomide or the analogues provide any beneficial effects in MS or neuro-inflammatory disease. Clinically orientated investigations so far relate mainly to multiple myeloma and some other forms of haematological malignancies but not solid tumours\textsuperscript{5}. Any perceived beneficial effects are probably outweighed by the side effects. We need to expend more effort and design and develop new analogues with reduced toxicity. In this context one should emphasise that pre-clinical exploration of the potential synergy between the thalidomides and the acknowledged modulators of the signalling pathways would be worthwhile. This might enable the delivery of benefits more effectively and at lower dosages. It is needless to say that safety of drug administration is of paramount importance.

### References


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Retinitis Pigmentosa

M Suresh Babu, C R Venkatesh, P K Kiran, S Sunil Kumar and K Prabhath Kiran Reddy

Keywords: Retinitis pigmentosa
Abbreviations: RP- Retinitis pigmentosa

A 19 year old male presented with a history of recurrent respiratory tract infections and progressive diminution of vision. Fundoscopy was performed and showed the changes in image below.

What is the finding suggestive of?
1. Retinitis pigmentosa
2. Drug toxicity
3. Congenital rubella
4. Syphilis

Answer: Retinitis Pigmentosa

Retinitis pigmentosa (RP) is a bilateral inherited progressive retinal degeneration presenting in the first to second decades of life. The inheritance can be autosomal dominant, autosomal recessive or X-linked recessive. Hallmark symptoms of RP are nightblindness and visual field constriction. Fundus changes in retinitis pigmentosa include waxy pallor of optic disc (black arrow), arteriolar attenuation (white arrow head) and bony spicule pigmentation (white arrow) in the mid-peripheral fundus, which is predominantly populated by rods. Vessel attenuation is the earliest feature seen clinically. Although intraretinal pigmentary migration is relatively easy to observe, it requires years to develop, so early RP may only exhibit vessel attenuation without pigmentation (previously known as RP sine pigmento). Prognosis is variable and tends to be associated with the mode of inheritance.

Drug toxicity with chloroquine can result in visual disturbances. History of drug usage prior to vision disturbance can be present. Fundus examination shows a subtle bulls eye macular lesion characterized by a central foveolar island of pigment surrounded by a depigmented zone of RPE atrophy, which is itself encircled by a hyperpigmented ring. In congenital rubella, a history of maternal infection will be present. Fundus findings include salt and pepper pigmentary disturbance involving the periphery and posterior pole with normal vessels, RPE mottling and no intraretinal pigmentary migration. Syphilitic retinopathy may have sectorial or generalised pigmentation. The onset can be from adulthood to old age. History of genital ulcer may be present.

Acknowledgements
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Competing Interests
None declared
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A stroll down memory lane - All sciences end as poetry!

James Paul Pandarakalam

Poetry is a way of expressing the subjective experiences that spill over the rational mind and it permits spontaneous overflow of subjective feelings. The ability to express oneself through poetry, and share that experience, is one of the unique human experiences that distinguish us from lower biological forms. The strife and struggle of modern men have made them miserable wretches on the face of this beautiful cosmos, and the technological revolution has taken the poetic sense from them; a time old coping mechanism. Those not capable of expressing their own sorrows and joys of everyday life in poetic words could find a surrogate writer in The Gushing Fountain.

In his collection of poetry, Dr Latoo (who is currently working as a Consultant Psychiatrist in United Kingdom) has catered poems for every mood and occasion: love, parting and sorrow, inspiration, rapture, memory, nature, solitude, and contemplation. Some of them are deeply personal and the author is trying to unearth a time capsule he had left in his native country of Kashmir. Dr Latoo appears to be searching for inner truths and making a self exploratory pilgrimage in his collection of poetry. Poetry has the power to describe and dramatize one’s own life, and Dr Latoo has done it well. The themes generally move from childhood to old age, love to grief, sorrow to joyfulness, aggressive nationalism to corrupted politicians, and depression to psychosis. There are pearls of mystical wisdom embedded in the poetry:

“Oh be choreographed by a great master for our sustenance
Rather than just be a part of random unplanned accident.”

There are wise statements in “Divine Justice”:

“Anything like fatalism shall be a contradiction
Of the Divine justice, free will and Lord’s will.”

All poetries have some hidden messages, and the book as a whole stands for immense moral values. “Woman” stands for women’s rights and dignity. The thoughts about the forgotten orphans are heart touching. “Behold a Man - Judging others” points towards the fallacy of judging other people without correcting oneself. Mental health professionals are particularly prone to this error because they are often professionally bound to assess their clients; we are only supposed to assess others and not judge others. We should not even judge ourselves, but only do self-assessment – God is the only Judge. The author writes about very ordinary humble human beings like the barber, Rupa, Ayesh, Ahmed, Puja etc. “Marriage” highlights the sanctity of wedlock. These poetries reflect the world view of the author. “Hold fast to thy dreams” may be inspired by Langston Hughes (1902 - 1967) and reminded me of my father who liked the verses of Hughes on dreams. “A raven who wants to be a dove” refers to people who pretend to be what they are not - wearing borrowed garments.

There are also poems about the author’s travelling experiences. A century ago, if a poet wrote about airport, he would have been frowned upon by the peer group, but in the 21st century it is appropriate to write such poetry. “Noisy airport and my mind” illustrates the hustle and bustle of contemporary life and gives the book a modern flavour. “By the Dal Lake” is nostalgic and the author is trying to recapture and share his lost Kashmiri literary Empire with the readers. Born in Kashmir, there is no surprise that the author renders beautiful nature in his poems. One wonders, if William Wordsworth were born in Kashmir, what would have been the content of his writings. Dr Latoo’s dual identity is evident when he writes about Kashmir and London.

In these days of global union through mere technology, poetry may have a serious role in the “international soul-union.” The days of regional poetry are over. Poets like Dr Latoo may be able to contribute to the formation of a healthier global village; poetry penetrates beyond the psychic realm into the spiritual dimension. There is a mission of peace and love in the Gushing Fountain, and the author is not enforcing any strong
convictions on the readers. There is a poet-philosopher in the author of the Gushing Fountain.

The author has used rhyming and free verse styles of poetry. Metaphors and similes are appropriately embedded in various situations:

"A smile on our face blooms the gardens of her innocent soul
A tear in our eyes arises from the blood of her bruised heart"

(From the poem, "Mother")

Lyrical poetries are ravishingly harmonious and there are no repetitions. The thoughts are clear and there is an exotic element in all the poetry. On the whole, all the poems are cerebral and riveting. The works are relevant to the present century and can be appreciated by scholar and casual readers alike. Every poem is an experience to be savoured and memorised. Let these pieces of poetry echo and reverberate not only in the conflict-ridden valleys of Kashmir, but all around the world until they find rest in the minds of the waiting millions.

Psychiatry is going through an identity crisis because the newer medications are not as effective as expected to be and clinicians are turning to different forms of psychotherapy. Poetry/lyric therapy could be another form of psychotherapy that needs attention in the field of soft psychiatry. Dr Latoo’s book could be an inspiration and encouragement in this line of treatment. Hypnothearists readily recognize that words are like loaded bullets and are highly potent. To an extent, poetry therapy involves the principles of both hetero- and self- hypnotherapy. Primitive and modern religions take advantage of the potentials of different forms of poetry in religious rituals for healing and promoting health.

A study of the mechanism of poetry writing is helpful in developing better conceptual models of creativity and deeper understanding of mental process. Sudden flashes of creative insight and other intuitive leaps, which arise from states of mind through intermediate steps that remain hidden beneath consciousness, and such ultrafast processing involving a concealed intermediate step, is consistent with quantum computations. A poet who enjoys superior mental health is capable of swinging from the unconscious quantum logic to the classical logic of consensus consciousness with an ultrafast speed. In psychotic states, “the quantum gates” do not shut swiftly as in normal mental states and the sufferers get trapped in the quantum logic. The usefulness of poetry therapy in psychotic patients, who get stuck in the quantum logic of the unconscious mind back to the classical logic of ordinary consciousness, needs further analytical studies. The primary aetiology of psychotic disorders may be biological, but secondary symptoms are quantum-linked and the new generation of psychotherapists have to learn the quantum metalinguages to communicate with psychotic and depressed patients. Poetry is such a source of quantum meta-language.

Poetry therapy promotes abstract thinking and develops imaginative powers. It is also a means of relieving and revealing innermost sentiments; it helps to ventilate overpowering emotions and hidden tensions. It is a form of self-expression and aids to build greater self-esteem; useful in strengthening interpersonal skills and communication skills. It would be valuable in repairing the assault of psychosis on the personalities of the sufferers. Quoting from my own memory lane, I became interested in poetry therapy when I comprehended the core problem of a patient who wrote:

“Moon, you shine at the centre of the sky,
Catching attention from all over the world,
Don’t you know that I am lonely?”

Poetry is of the heart and imagination whereas science is about reason and logic and may be grounded on contradictory principles. If science is about objectivity, poetry is essentially about subjectivity and to blend those human experiences harmoniously is a hard task; Dr Latoo has successfully achieved this goal. A man of science, when he writes poetry, has to liberate himself from the shackles of rationalism so that he can be a wholly free human: to be a poet one has to be a natural human being. To quote from Jean-Jacques Rousseau: “Man is born free and everywhere he is in chains.” Let us hope that the Gushing Fountain will have a part two and even more!

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None declared

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