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Pain in Shackles

"Breaking the Shackles: Anto’s Journey" Collection

By Anto Sg (Agus Sugianto) (with authorization).

Pasung Survivor, Tulungagung, East Java, Indonesia.

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The Effects of Lead and Selenium on Melanoma Induction

Isabel Sá,¹ Tânia Nogueira,¹ Elisabete Cunha.²

Abstract

Background: Melanoma is a malignant skin cancer and is one of the most aggressive malignancies in humans. Heavy metals, including lead, are known to cause cellular toxicity and have been studied for their potentials to induce apoptosis in tumor cells. Since selenium is considered to act protectively in cases of lead poisoning, this study focused on the effects of sodium selenite and lead chloride, both alone and combined, on melanoma cell apoptosis. Methods: This study was carried out by doing cell culture of melanoma cells (B16-F10 cell line) and using C57BL/6 mice. Melanoma cells suspended in lead (II) chloride, sodium selenite, or lead (II) chloride + sodium selenite solutions were injected subcutaneously to mice to induce tumor growth. After 12 days, tumors were excised and measured, followed by flow cytometry and a statistical analysis using a one-way ANOVA. Results: In the group of mice receiving a single injection of melanoma cells suspended in 10 µmol/l of lead (II) chloride, the growth of tumor was significantly slower than in the control group. In mice treated with lead (II) chloride 50 µmol/l and 100 µmol/l, no tumor was visible at the end of the experiment. With a single injection of lead (II) chloride and sodium selenite at concentrations ≥ 10 µmol/l, the weight and size of the tumor were substantially smaller than in the control group. Conclusion: The effect of lead (II) chloride on melanoma induction is dependent on the concentration of lead (II) chloride. Future applications may include the use of lead (II) chloride to increase apoptosis and necrosis in tumor cells and thus suppress tumor cells proliferation.

Keywords: Selenium; Lead; Melanoma; Apoptosis; Necrosis. (Source: MeSH-NLM).

Introduction

Modern life and industrialization bring comfort and convenience, but also entail the increase of exposure to harmful substances, including heavy metals. Different metals induce different conditions, depending on the concentration and the type of exposure.¹ Heavy metals are considered to be toxic due to their ability to induce a variety of deleterious effects. The toxicity caused by heavy metals, such as arsenic (As), mercury (Hg) and lead (Pb), has already been recognized by health authorities as occupational health hazards.

Heavy metals are chemically reactive and bioaccumulative, which means that the human body is not able to effectively eliminate them, differing them from other potential toxic agents. The consequences of exposures to lead, cadmium (Cd), and mercury and the consequent pathologica changes in the liver, kidney and bone are well documented.²⁻¹⁰ Moreover, thorium (Th), cadmium, lead, chromium (Cr), nickel (Ni), and beryllium (Be) are heavy metals with confirmed carcinogenic effects in animals and humans.¹¹⁻¹⁵ Thus, there is an increasing evidence that the exposure to heavy metals could be associated with the occurrence of lung, liver, bladder, kidney, colon and skin cancer.¹⁵

One of the most widely used heavy metals is lead. This metal can enter the body through inhalation, ingestion and dermal exposure. The induction of inflammatory processes is one of the various effects caused by lead. The toxicity of lead results from its interaction with the functional groups of enzymes.¹⁶ Unfortunately, human exposure to lead is an inevitable consequence of human life, since exposures occur mainly from two sources: occupational and environmental. Lead is a toxic heavy metal which is likely to lose electrons easily, forming positively charged ions that tend to be soluble in biological fluids. It has higher affinity for groups containing sulfur, such as sulphydryl (SH), than for ones containing oxygen.¹⁷ Lead forms covalent bonds, causing changes in the properties of sulphydryl-containing enzymes, such as solubility, dissociation, the relative affinity to receptors, distribution and excretion.¹⁷ Lead toxicity affects several organ systems, including nervous, hematopoietic, renal, endocrine and skeletal systems.¹⁷

Melanoma is a malignant tumor which originates from melanocytes, cells that produce the pigment melanin that gives color to skin, hair and eyes. The incidence of this skin cancer has been increasing more rapidly than any other cancer type. It is one of the most aggressive malignancies in humans and is responsible for 60% to 80% of skin cancer deaths.¹⁷ This is not only because of its incidence and propensity to affect young adults, but also because of its high metastatic potential, aggressive clinical behavior, and extraordinary resistance to the currently available chemotherapeutic and immunological treatments.¹⁸ During the development of malignant melanoma, there is a complex interaction of environmental and endogenous (genetic) factors, including the deregulation of cell proliferation, the programmed cell death (apoptosis),¹⁹ and cell-cell interactions.²⁰
Selenium and its compounds, both inorganic and organic, have recently attracted oncologists’ attention after several epidemiological studies revealed an inverse correlation between the intake of selenium and the incidence of cancer. Selenium has quite important biological and biochemical functions in organisms because of its antioxidant properties, preventing the formation of free radicals that cause DNA damage and promote tumor genesis. It also is a moderate antagonist for the toxic effect on the body of many heavy metals such as arsenic, cadmium, mercury, and lead. Selenium is used in methylated forms, which are less toxic and still have effects on carcinogenesis, and more than 90% of the experiments have used sodium selenite. Selenium confers protection, in part by inducing cellular free radical scavenging systems and by enhancing peroxide breakdown. Thus, selenium enhances the capacity of the cell to cope with oxidative stress. The selenoproteins (Se-P) may be useful in the prevention of cancers which are associated with persistent chronic inflammation and infection, since Se-P are presumed to be involved in alleviating the toxicity of heavy metals. Some Se-P have important enzymatic functions because they generally contain selenocysteine (SeC) in the active site, as well as cysteine (Cys) residues, indicating that it is capable of transporting selenium and binding to heavy metals. Thus, we believe that Se-P has three separate roles: (1) antioxidant defense; (2) a role in the transport of selenium; (3) a protective role as a natural chelator of heavy metals. In addition, the anti-tumor activity of selenium is directly related to its antioxidant activity, acting on the protection of Cys residues of reduced glutathione (GSH), which is considered to be the most important compound in the detoxification of carcinogens. Apoptosis and necrosis are two types of cell death that can occur due to in vivo or in vitro exposure to cadmium or lead, which caused an increase in lyses or necrosis. Selenium provides a significant protection against cadmium-induced apoptosis.

Given the facts that lead is toxic by causing mainly necrosis and that selenium is an antagonist to the toxic effects of many heavy metals, the aim of this study was to investigate the potential of lead for the treatment of melanoma and the potential protective role of selenium against the toxic effects of lead. We hypothesise that lead can be used to treat melanoma, along with selenium to work against the toxic effects of lead.

Methods
C57BL/6 mice were used in this study in view of the similarity between melanoma in mice and melanoma in human and the relative ease of melanoma induction in mice compared to other animal models. The investigators who performed the subcutaneous injection, tumor growth measurements, flow cytometry, and the statistical analysis were not blinded to group allocation.

Animals
Seventy eight female C57BL/6 mice (Charles River Laboratories España S.A., Barcelona, Spain) between 6-8 weeks of age and weighing about 19.5 ± 2.0 g were kept under standard housing conditions (29 x 34 x 16 cm autoclavable polystyrene boxes with a wire lid and built-in feeder and water drinker, 12-hour light cycles from 7 a.m. to 7 p.m., and controlled humidity and temperature) and with food and water ad libitum. The animals were assigned randomly into 10 treatment groups (six mice per group) and one control group (n = 18) (Table 1).

All animals were treated in accordance with the European Council Directive 2010/63/EU on the protection of animals used for scientific purposes. After the experiments, the animals were euthanized with a lethal injection of lead, since it was considered to be the way which implied the minimum pain, suffering and distress (Article 6 of the European Directive).

Reagents
Sodium selenite and lead (II) chloride were purchased from Sigma Chemical Co. (St. Louis, Missouri, USA) at four concentrations: 1, 10, 50, and 100 µmol/L. The suspensions were prepared in 500 µl of sterile phosphate-buffered saline (PBS) and resuspended with 5 x 10^6 melanoma cells. These suspensions were injected into the air pouch of the mice, which is described later in this section.

Cell Culture
Melanoma cells (B16-F10 cell line) were purchased from ATCC (Manassas, Virginia 20110-2209, USA). The cells were cultivated in Dulbecco’s modified Eagle’s medium (DMEM) (Life Technologies, Inc., Rockville, Maryland, USA), which was supplemented with 10% fetal bovine serum (FBS) (HyClone, Logan, Utah, USA) and contained 100 units/ml of penicillin, 100 µg/ml streptomycin, and a solution of nonessential amino acids (Life Technologies, Inc.). The cells were maintained at 37°C in a humidified atmosphere of 5% CO2 / 95% air. This was the first step of the entire experiment.

Subcutaneous Injection
In order to form a subcutaneous air pouch, 5 ml of sterile air was injected into the subcutaneous dorsal midline of the animals 10 days after the cell culture was started. After three days, 2.5 ml of sterile air were reinjected in order to maintain the open space. This method was adapted from previously published experiments. Four days after the first injection, the following suspensions were injected directly into the air pouch: Control group: 300 µl of PBS + 300 µl of melanoma cells (concentration 5 x 10^5); Group I: 300 µl of lead (II) chloride + 300 µl of melanoma cells (concentration 5 x 10^5); Group II: 300 µl of sodium selenite + 300 µl of melanoma cells (concentration 5 x 10^5); Group III: 300 µl of lead (II) chloride and sodium selenite + melanoma cells (concentration 5 x 10^5).

For Groups I and II, we used lead (II) chloride or sodium selenite of four different concentrations: 1, 10, 50, and 100 µmol/L. For Group III, the molar ratio between selenium and lead was 1:1, as referenced in some recent studies regarding the molar ratio of selenium in tissues.

Tumor Growth
Measurements of body weight as a surrogate measure for tumor weight were made 0, 2, 5, 7, 9, and 12 days after treatment. On the 12th day, we aseptically excised, weighed, and measured the size of the tumors. For calculation of tumor volume, the following formula was used:

\[ \text{Tumor volume (cm}^3\text{)} = 0.52 \times (\text{length} \times \text{width} \times \text{height}) \]

Flow Cytometry
For flow cytometric analysis, each subcutaneous exudate sample,
retrieved from the already excised tumor mass via a needle introduced in the edema, was stained with TACSTM Annexin V-FITC Apoptosis Detection Kit (ROD Systems, Minneapolis, Minnesota, USA) for 15 minutes. This product detects the externalization of phosphatidylserine in apoptotic cells using recombinant annexin V conjugated to green-fluorescent FITC dye and necrotic cells using red-fluorescent propidium iodide (PI). After treatment with both probes, apoptotic cells show green fluorescence, dead cells show red and green fluorescence, and live cells show little or no fluorescence. After staining, the tumor cells were washed twice and suspended for flow analysis by fluorescence activated cell sorting (FACS) in a medium containing propidium iodide (Sigma). Data were collected on cells selected by forward light scatter (FSC) and PI gating in a FACScan analyser (Becton Dickinson) with CellQuest software.

**Statistical Analysis**

The statistical comparison between the data collected from experimental and control groups was performed using a one-way ANOVA. The numerical data are presented as means ± standard deviations, unless otherwise specified. Statistical significance was considered for p<0.05. All statistical analyses were performed using SPSS 14.0® for Windows.

**Results**

Our observations showed that 2-3 days after the injection of melanoma cells into the air pouch of the mice, tumor started to develop and a protruding mass was clearly seen under the skin around five days after injection. Between 5-12 days after treatment with lead (II) chloride, the changes in the body weight of the mice treated with lead (II) chloride 1 µmol/l were similar to that of the control group. For groups that were treated with lead (II) chloride 10, 50 and 100 µmol/l, no significant changes in body weight were observed, and the mean body weight on day 12 was significantly smaller than the control group (p<0.05) as a result. In contrast, for groups that were treated with sodium selenite 1, 10, 50 and 100 µmol/l, no significant differences were observed between the body weight of the treated mice and the control group (Figure 1).

After 12 days of treatment, we excised, weighed and measured the size of the tumors (Table 2). After an injection of 1 µmol/l of lead (II) chloride, the tumor continued to develop. In contrast, mice treated with 10 µmol/l of lead (II) chloride had smaller tumor weight and tumor volume compared to the control group. For mice treated with lead (II) chloride at a concentration higher than 50 µmol/l, no tumor mass was recovered, and the differences with the control group were significant (p<0.05). The tumor weight and volume of mice treated with sodium selenite of all concentrations were similar to the control group (Figure 2).

The tumor weight and volume for mice which were administered a single injection of equimolar (1:1) lead (II) chloride and sodium selenite 10 µmol/l were smaller than those of control groups. No tumor mass could be recovered from mice injected with the combination suspension at a concentration of 100 µmol/l (Figure 3).

The percentage of apoptosis and necrosis in melanoma cells after 12 days of treatment with 1 µmol/l of lead (II) chloride and with 1, 10, 50 and 100 µmol/l of sodium selenite was around 10%, the same as in the control group. When the melanoma cells were treated with a concentration of 10 µmol/l of lead (II) chloride, the percentage of apoptosis was around 20% and the percentage of necrosis was nearly 80%. With a concentration of 50 µmol/l of lead (II) chloride, the percentage of apoptosis was lower at 10%, while the percentage of necrosis was higher at around 90%. Finally, with a concentration of 100 µmol/l of lead (II) chloride, there was almost 100% of necrosis (Figure 4).

### Table 1. Treatment Groups.

<table>
<thead>
<tr>
<th>Treatment Groups</th>
<th>PbCl2</th>
<th>PbCl2</th>
<th>PbCl2</th>
<th>PbCl2</th>
<th>PbCl2</th>
</tr>
</thead>
<tbody>
<tr>
<td>Na2SeO3</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>0 µmol/l</td>
<td>18′</td>
<td>6′</td>
<td>6′</td>
<td>6′</td>
<td>6′</td>
</tr>
<tr>
<td>1 µmol/l</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>10 µmol/l</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>50 µmol/l</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>100 µmol/l</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**Legend:** † Control group, ‡ Treatment group I: PbCl2, * Treatment group II: Na2SeO3, † Treatment group III: PbCl2 + Na2SeO3.

### Table 2. Tumor Weight and Volume after 12 Days of Treatment.

<table>
<thead>
<tr>
<th>Treatment groups</th>
<th>n</th>
<th>Tumor weight (g)</th>
<th>Tumor volume (cm³)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Control</td>
<td>18</td>
<td>5.43 (1.31)</td>
<td>4.98 (2.12)</td>
</tr>
<tr>
<td>PbCl2</td>
<td>1 µmol/l</td>
<td>6</td>
<td>3.17 (1.93)</td>
</tr>
<tr>
<td></td>
<td>10 µmol/l</td>
<td>6</td>
<td>0.32 (0.26)</td>
</tr>
<tr>
<td></td>
<td>50 µmol/l</td>
<td>6</td>
<td>0 (0)</td>
</tr>
<tr>
<td></td>
<td>100 µmol/l</td>
<td>6</td>
<td>0 (0)</td>
</tr>
<tr>
<td>Na2SeO3</td>
<td>1 µmol/l</td>
<td>6</td>
<td>3.95 (1.18)</td>
</tr>
<tr>
<td></td>
<td>10 µmol/l</td>
<td>6</td>
<td>3.16 (1.19)</td>
</tr>
<tr>
<td></td>
<td>50 µmol/l</td>
<td>6</td>
<td>2.69 (1.07)</td>
</tr>
<tr>
<td></td>
<td>100 µmol/l</td>
<td>6</td>
<td>2.65 (0.91)</td>
</tr>
</tbody>
</table>

**Legend:** † Data presented as mean ± Standard Deviation.

Figure 1. Changes in Body Weight of Mice Following Lead (II) Chloride or Sodium Selenite Injections.
The Effects of Lead and Selenium on Melanoma Induction

When melanoma cells were treated with 50 µmol/L of lead, a significant decrease in their viability was observed compared to the control group. Similar effects were observed in the present study: the development of melanoma appears to be negatively associated with lead (II) chloride concentration.

In contrast to findings of previous studies which suggested the potential of selenium as a cancer preventative agent and an anti-metastasis agent, our study did not find a significant effect of selenium on tumor development. When the tumor was treated with an equimolar injection of lead (II) chloride and sodium selenite, the weight and total volume of the tumor were smaller than the control group at a concentration of 10 µmol/l, and no tumor was recovered at a concentration of 100 µmol/l. The effects of lead (II) chloride or lead (II) chloride + sodium selenite on tumor growth were similar.

Selenium has a protective role against the development of tumors because it delays the oxidative damage in DNA and lipids as well as regulates cellular and molecular events that are essential for cell growth and carcinogenesis. Selenium is also considered to protect the organism in cases of poisoning with lead, mercury and cadmium. When melanoma cells were treated with lead (II) chloride ≥ 50 µmol/l, the percentage of cell with necrosis increased. However, when they were treated with the same concentrations of sodium selenite, no significant differences in the percentages of apoptosis and necrosis were observed between the treatment groups and the control group. Thus, our findings were in accordance with other experiments which showed that the cadmium and lead caused an increase of lyses or necrosis.

Given the facts that chemotherapy and radiotherapy eliminate tumor cells by inducing apoptosis and that melanocytes are resistant to apoptosis, it is important to study the possibility of eradicating malignant tumor cells via necrosis induced by lead in certain concentrations. Nonetheless, it is also important to keep in mind that necrosis triggers inflammatory processes and thus it is vital to use an antagonist (such as selenium) to reduce the toxic and inflammatory effects of lead. Hence, the main goal is to make a compromise between the lead concentration and tumor cell destruction without causing severe inflammation problems as well as lead intoxications. This can be counteracted by using selenium as a lead toxicity detoxifier.

Our study findings demonstrated the potential of lead as a possible therapy for melanoma via the induction of necrosis, the accompanying inflammatory reactions of which could be counteracted by administering lead in combination with selenium, a lead antagonist. Future studies conducted using other techniques as well as full pathological studies are necessary to explore further the effects of lead and selenium on melanoma induction.

Discussion

Our study found that both the weight and total volume of tumors in mice treated with lead (II) chloride tends to be smaller with the increasing concentration of lead (II) chloride, results that are in accordance with previous studies. Similar findings were not observed following treatment with sodium selenite.

Lead and several inorganic lead compounds appear to have deleterious effects on skin, muscles, and the immune system. Lead has already been used to induce cell death in human neuroblastoma cells in previous studies. When neuroblastoma cells were treated with lead alone, they exhibited a significant decrease in their viability. Similar effects were observed in the present study: the development of melanoma appears to be negatively associated with lead (II) chloride concentration.

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Creating and Completing Service-Learning within Medical School Curricula: From the Learner’s Perspective

Frini Makadia,1 Priya P. Mehta,1 Clayton E. Wisely,1 Juan E. Santiago-Torres,1 Katherine Hartmann,1 Mary J. Welker,1 Diane Habash.1

Abstract

Background: This article describes a service-learning project implemented at local free clinics by students at the Ohio State University College of Medicine and identifies key factors in their success. Methods: In response to a lack of longitudinal patient-physician relationships at free clinics, the students developed an initiative linking free clinic patients with diabetes to primary care homes for longitudinal care and counseled patients on the benefits of establishing a longitudinal relationship with a primary care physician. Results: All patients counseled were linked, compared to a historical 10% linkage rate, and 76% of patients scheduling initial appointments. Five factors were identified and listed by the students as key to the project’s process, success, and impact. Conclusion: Although all of these listed factors may prove difficult to replicate, this case-study serves as a model for other medical schools incorporating service-learning and exhibits that medical students can become integral portions of healthcare infrastructure.

Keywords: Community Health Services; Students, Medical; Physicians, Primary Care; Curriculum; Physician-Patient Relations. (Source: MeSH-NLM).

Introduction

In the United States as well as other countries, diabetes mellitus has become a chronic condition that has been best managed with continuous, quality care. It is estimated that by 2020, more than half of the American adult population will have diabetes or pre-diabetes, ultimately escalating healthcare costs to approximately $300 billion per year.1 The bulk of this financial burden arises from the prevalence of diabetes and the rate of complications due to poor glycemic control within notable patient populations including those of lower socioeconomic status and of minority races. Much work has been done in the US to provide an ideal model of how to best provide care for patients with chronic diabetes through primary care homes.2 This paper discusses the ability to incorporate different resources, such as medical student-driven initiatives, in aiding and alleviating the growing strain of poorly managed chronic conditions on national health resources through primary care home expansion and connection.

In 2013, the Ohio State University College of Medicine (OSUCOM) implemented the Lead, Serve, and Inspire (LSI) curriculum.3,4 The LSI curriculum emphasizes early student participation in patient care through community preceptorships and team-based projects that promote self-directed learning and development of healthcare resources and infrastructure.5,6 In LSI, first-year students complete a community project at local medical practices.7,8 Each student identifies a specific patient population and co-develops, with partnering agencies, a program addressing medical needs of this population. The following report describes the experience of a pilot version at the Physicians’ Free Clinic (PFC) directed at providing patients with diabetes and no current access to primary care physicians an opportunity for longitudinal patient-physician relationships and factors leading to this program’s success.

Methods

Students completed and analyzed a needs assessment of six PFC patients with diabetes, none of whom had a primary care physician (PCP). Inclusion criteria consisted of an existing diagnosis of Type 1 or Type 2 Diabetes Mellitus (DM), English or Spanish as primary language, and at least one prior established appointment at the PFC. Individuals less than 18 years of age were excluded. Consequently, students created a script for a counseling session with patients which described the importance of continuing care and addressed impediments to accessing care that were highlighted by these primary discussions. Students met with
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Original Article

Figure 2

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Each patient’s stage of change regarding attitudes towards seeking a PCP was assessed. During this initial encounter, subjects also completed a survey capturing information on demographics, financial and socioeconomic status, food security, social support, primary care provider use, as well as general and diabetic health.

Additionally, students expedited linkage of patients to local PCMHs by working directly with care coordinating staff at both facilities. During this time, the number of referrals, scheduled appointments, and attended appointments were noted for each patient with the aid of coordinators at each local PCMH. Students implemented this work for six weeks while tracking linkage rates and all PCP appointments (Figure 1).

Results

During the six weeks, 23 of 23 patients (100%) were referred to a PCMH, with 18 of 23 patients (78%) scheduling an appointment (Figure 2).

Based on the promising potential of this pilot project, the students independently continued beyond the required preceptorship and expanded their work to an additional local free clinic, an IRB approved research initiative referred to as the LINKED study, and an OSUCOM student interest group to continue counseling sessions for uninsured patients at local clinics.

Expansion allowed: (1) continued quantification of scheduling and linkage data, (2) evaluation of the impact of counseling and linkage on patients’ health and perceptions of health, and (3) generation of a 3 year-sustainable student group recognized as linkage counselors.

Discussion

The pilot student group identified factors enabling success that can allow other groups to implement similar initiatives in hopes of expanding access to primary care for patients with inadequate management and attention to their chronic conditions.

1. Teamwork and Diversity of Students

A key component for success within this pilot initiative lay within the group itself: students had diverse backgrounds, networks of resources, and willingness to develop meaningful concepts. While this variety was originally not pre-determined, it developed into a crucial aspect of the team’s productivity.

Students of various programs comprised the initial pilot group including independent study program, doctorate of medicine and philosophy (MD/PhD), master of business administration (MBA), and master of science (MS) candidates. The collaboration of all members enhanced problem solving in regards to scheduling, duties, group leadership, and communication with patients, partners, and stakeholders. Dual-degree students provided skills for evidence-based and hypothesis-driven designs that enriched approaches to clinical improvement; others maintained patient-centered focus insuring that emphasis was placed on improving patient-based aspects of patient-physician relationships.

2. Representative Needs Assessment

Initiating a successful service-learning project must begin with a detailed needs assessment. The group utilized three different resources in doing so: guidance from faculty with pertinent experience, patient insight on diabetes-centered healthcare, and input from various PFC stakeholders on how to incorporate into the clinic’s service to its patients. The group developed an adequate cultural understanding of the clinic and its patients’ needs. This effective assessment ensured that the student group contributed, while remaining faithful, to the clinic’s vision and future goals regarding chronic care management. These conversations yielded the ideas ultimately leading to the formation of the LINKED study and student group.

Figure 1. Linkage and Scheduling Process.

Legend: A typical clinic night begins with meeting patients and discussing the benefits of a PCP. Interested patients were put in touch with a representative that set up a primary meeting with a PCP. Patients attended an appointment, were provided information on diabetes management, and possibly scheduled follow-up appointments.
3. Autonomy and Sustainability

Once trained in patient interactions and triaging procedures at the PFC, the students were given autonomy to implement and carry through the project. Counseling was integrated within the usual clinic flow and projects targeted expedient linkages with PCMH partners. From years 1 to 2, students recruited and sustained the project with 6 students, later increasing to 15, and gained recognition and funding as a student organization through the OSU Student Union and within the medical school. The success of the pilot program and its ultimate growth hinged upon this autonomy and self-sufficiency.

4. Witnessing Linkage, Health Outcomes, and Impact on Patients

Sharing linkage rates with educators, physician leaders, clinic and PCMH staff yielded many positive responses. Outcomes showed a referral rate of 100% compared to 10% obtained by PFC in previous years; of those referred, 78% scheduled an initial appointment and 35% were linked to PMCHs with multiple, attended appointments (Figure 2). The influence of this positive feedback fueled efforts of subsequent students to expand this work along with the support of all stakeholders.

Due to this success, a research study was further drafted and approved to assess (1) linkage rates, (2) patient health before and after linkage, (3) emergency department and free clinic use before and after linkage, and (4) identification of barriers to linkage. The student’s ability to quantify their initial clinical and community impact substantiated continuing community collaborations for the LSI curriculum and further highlighted the contributions medical students can provide as a mode of community resources.

5. Right Place, Right Time

This final factor was critical to the success of the pilot group. During the time of needs-assessment implementation, the PFC was in early stages of a paradigm shift towards linking its patients to PCMHs, but exhibited a low referral rate (10%). The student team’s success gave PFC evidence to support hiring two full-time linkage coordinators for their staff, demonstrating a fortuitously timed service by students for a community partner. It is not by chance that the students decided to pursue this particular project. Close coordination with clinic staff yielded directly relevant work that provided beneficial contributions beyond the boundaries of student preceptorships; this relationship provided the insight and support necessary to positively enhance clinic flow to improve patient care, support, and, potentially, long-term health.

Service-learning involves integrating academic curricula with meaningful service to enhance both aspects through formal and informal reflection. Based on the students’ success and experiences in linkage, the PFC has further developed their efforts to link patients by expanding their staff to ensure adequate patient linkage – a move that relieves the financial burdens of unmanaged diabetes as well as expands the presence of the clinic in the Ohio community. The linkage process has also been an effort that health care providers and PCMHs have considered to ensure continuity of care with the same physician and improve long-term healthcare outcomes. Thus, the goals of the preliminary LINKED study align with the current reform in healthcare seen in the United States.

While this initiative has provided fruitful implementation of counseling and linkage at local free clinics, its impact is limited by sample size; the subsequent study inspired by this pilot group further addresses these concerns. Additionally, due to the nature of the patients’ social infrastructure, timely and reliable communication for follow-up proved to be difficult; this was managed with strong relationships with local PMCHs which allowed for collection of linkage data.

The initiative described is one example of successful service-learning. The combination of motivated students, autonomy and flexibility, quantification of impact, and location at a facility ready for change led to successful implementation and continued expansion of the LINKED initiative. The LINKED project can be used as a model of service-learning within a medical school curriculum that aligns with current changes in national healthcare infrastructure while enhancing the local healthcare infrastructure in helpful and practical manners.

Figure 2. Initial Scheduling and Linkage Results.

Legend: Of the original 23 patients interviewed at the PFC, 23 (100%) were referred to PMCHs compared to the historical 10% rate at the PFC. Eighteen patients of the original 23 (78%) made an initial appointment with a primary care home and 12 (52%) attended those meetings. Overall, 35% of all patients met and counseled were longitudinally linked with multiple, attended appointments with their PCP.
References

Acknowledgments
The authors sincerely thank Daniel Clinchot, MD for his dedication to teaching and his guidance throughout the pilot project; the CAPS curriculum committee for the opportunity to undertake this project; Jennifer Lehman, of the Ohio State University Department of Family Medicine, for her tireless assistance with the project; and all clinics for their dedicated partnership throughout this process – including Isi Ikharebha, Executive Director of the Physicians Free Clinic (PFC); Dr. Nathan Yost, physician-volunteer at the PFC, the OSU Medical Student Steering Committee of the Columbus Free Clinic, Buhari Mohammed, MD of the Columbus Neighborhood Health Center, and Dana Vallangeon, MD of the Lower Lights Christian Health Center. The students involved in this work would also like to thank Diane Habash for her enthusiasm and dedication to both this project and our development as inquisitive, patient-focused physicians.

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Author Contributions
Conception and design the work/idea, Collect data/obtaining results, Analysis and interpretation of data, Write the manuscript: FM, PPM, CEW, JEST, KH, MJW. Critical revision of the manuscript, Approval of the final version, Administrative or technical advice: FM, PPM, CEN, JEST, KH, MJW, DH.

Cite as:
Mutation in Genes FBN1, AKT1, and LMNA: Marfan Syndrome, Proteus Syndrome, and Progeria Share Common Systemic Involvement

Tonmoy Biswas.¹

Abstract

Genetic mutations are becoming more deleterious day by day. Mutations of Genes named FBN1, AKT1, LMNA result specific protein malfunction that in turn commonly cause Marfan syndrome, Proteus syndrome, and Progeria, respectively. Articles about these conditions have been reviewed in PubMed and Google scholar with a view to finding relevant clinical features. Precise keywords have been used in search for systemic involvement of FBN1, AKT1, and LMNA gene mutations. It has been found that Marfan syndrome, Proteus syndrome, and Progeria commonly affected musculo-skeletal system, cardiovascular system, eye, and nervous system. Not only all of them shared identical systemic involvement, but also caused several very specific anomalies in various parts of the body. In spite of having some individual signs and symptoms, the mutual manifestations were worth mentioning. Moreover, all the features of the mutations of all three responsible genes had been co-related and systemically mentioned in this review. There can be some mutual properties of the genes FBN1, AKT1, and LMNA or in their corresponding proteins that result in the same presentations. This study may progress vision of knowledge regarding risk factors, patho-physiology, and management of these conditions, and relation to other mutations.

Keywords: Genetic mutation; Marfan syndrome; Proteus syndrome; Progeria; Gene FBN1; Gene AKT1; Gene LMNA; Musculo-skeletal system; Cardiovascular system; Eye; Nervous system (Source: MeSH, NLM).

Introduction

The haploid human genome consists of 3 billion nucleotides but changes in one single base pair can result in dramatic physiological malfunctions.¹ Mutations are changes in the genetic sequence at different levels that cause diversity among organisms.² This can be happened by way of a number of factors.

Mutation is common in all types of organisms which is chiefly classified in three types; deleterious mutation with harmful effect upon host, neutral mutation with no effect, and advantageous mutation for welfare of the organism. But, most of the non-neutral mutations are deleterious.³ ⁴

If a deoxyribonucleic acid (DNA) repair mechanism fails, the physiological consequences of a mutation are quite inconstant, ranging from single cell death or cell carcinoma to hereditary genetic outcomes. Mutations in germline cells of human generally produce inheritable consequences, while mutation in somatic cells of human ordinarily only have outcomes affecting the individual in which the mutation occurs (National Council for Science and the Environment, Washington, DC. Available from:  http://www.eoearth.org/view/article/159530/, updated 2014 April 10, cited 2014 April 18).

Every cell, in order to function properly, depends on thousands of proteins to function in the right places at the right times. Changes in DNA caused by mutation can cause errors in protein synthesis, creating partially or completely non-functional proteins which in combination ultimately could result in genetic disorders.⁴

Records in human mutation databases are increasing day by day.⁵ Even about one hundred thousand diseases showed association with mutation of only 3,700 genes.⁶ Around 300 new “inherited disease genes” (and about 10,000 new mutations) are added to the record book in a year.⁷ The Human Gene Mutation Database (HGMD) is a complete assortment of germline modifications in nuclear genes containing over 141,000 mutations identified in more than 5,700 different genes up to June 2013.⁸ The first genetic mutation was reported in the year 1977 in HGMD Professional database with a maximum entry of 13,490 in 2013. Among the entries Missense/Non-sense mutations are more than 82,000 (Human Gene Mutation Database. Available from:  http://www.hgmd.cf.ac.uk/ac/index.php, updated 2014 April 12, cited 2014 April 18).

Besides some common disorders, mutations sometimes report some rare diseases like progeria, Marfan syndrome (MFS), Mandibuloacral dysplasia (MAD), Loeys-Dietz syndrome, Wolff-Parkinson-White syndrome, Ehlers-Danlos syndrome, Proteus syndrome, Cantu syndrome, etc. Some of them shows same prevalence pattern, some shows nearly same clinical features and presentations. But, in spite of knowing about affected proteins of mutation, the actual pathogenesis and course of the disease is not clear. Over a decade have passed after the completion of human genome project but the gene mutation diseases’ treatment is still in a labyrinth. For a better treatment, pathogenesis should be discovered and to look through it, it is needed to track the effects of affected proteins which is reflects by common manifestations in different systems of the body.

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The reason for selecting these three genes is to study their little known pathophysiology. The documented similarities between them were wanted to compile in a review.

Search Strategy and Selection Criteria
A literature search was conducted using Google Scholar, PubMed (Medline), The Human Gene mutation Database, and Genetic Home of US national Library. Key word combinations included “Marfan syndrome clinical features”, “Proteus syndrome features”, “Progeria syndrome features”, “Gene FBN1 mutation”, “Gene AKT1 mutation”, “Gene LMNA mutation”. One hundred thirty five articles were chosen for review. The inclusion criteria incorporated the articles on disease case reports, databases, review papers and original papers. The exclusion criteria were unavailability of any full article, unclear presentation, non-relevant study and reports of different languages other than English. The common features were assembled into this narrative review. This review follows the Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) Statement.

Gene FBN1, AKT1, LMNA and associated proteins
FBN1 gene is located on chromosome 15q15-21.3. This gene is 200kb and divided into 65 exons. It encodes fibrillin-1, a large extracellular matrix glycoprotein which assembles in extracellular matrix. In this matrix, fibrillin-1 binds to other molecules of it and other proteins to form 10-12 nm threadlike filaments called microfibrils. Microfibrils are main constituent of elastic fibers responsible for stretching and supporting many tissues of the body. It also store a protein called transforming growth factor beta (TGF-ß), a critical growth factor which helps in proliferation, differentiation, motility, and apoptosis of cells. Microfibrils help to regulate the availability of TGF-ß, which is inactivated when stored in microfibrils and activated when released (National Library of Medicine, NLM - FBN1. Available from: http://ghr.nlm.nih.gov/gene/FBN1, updated 2014 April 12, cited 2014 April 18).

AKT1 is located on chromosome 14q32.32. It is also known as PKB, RAC-PI. This gene initiates for a protein called AKT1 kinase which is responsible for signaling in the cells for its growth, multiplication, stability and apoptosis (NLM, Genetic - AKT1. Available from: http://ghr.nlm.nih.gov/gene/AKT1, updated 2014 April 12, cited 2014 April 18).

In mouse, it is found that, during apoptosis, Akt is cleaved by caspases and mediates survival signals for protection against apoptosis. Signaling involving AKT1 kinase also appears to be vital for the usual growth and function of the nervous system. It has a role in cell-to-cell communication among neurons, neuronal survival, and the formation of memories. The AKT1 gene belongs to a class of genes known as oncogenes.

The LMNA gene, also known as lamin A/C is located on the long (q) arm of chromosome 1 at position 22. More precisely, the LMNA gene is located from base pair 156,082,545 to base pair 156,140,088 on chromosome 1. This gene translates some slightly diverse proteins called lamins; among them lamin A and lamin C are common in the most body cells. These proteins have an almost duplicate sequence of amino acids. The small difference in the sequence makes lamin A longer than lamin C due to encoded by an extra exon. Lamins A and C are structural proteins called intermediate filament proteins that provide stability and strength to cells. Lamins A and C are scaffolding (supporting) components of the nuclear envelope. Specifically, these proteins are located in the nuclear lamina where it regulates the movement of molecules into and out of the nucleus. Between lamin A and C, only the lamina protein must be processed from prelamin A before becoming part of the lamina (NLM, Genetic - LMNA. Available from: http://ghr.nlm.nih.gov/gene/LMNA, updated 2014 April 12, cited 2014 April 18).

Mutation of the Gene and diseases
Mutation in the Gene FBN1 causes MFS, Ectopia lentis, Shprintzen-Goldberg syndrome, and Hereditary aortic aneurysm. A mutation in the FBN1 gene has also been identified with Weli-Marchesani syndrome, stiff skin syndrome, neonatal MFS, juvenile idiopathic arthritis, and acromicric or geleophysic dysplasias.

When mutation occurs in AKT1 gene, it causes Proteus syndrome. AKT1 gene is an oncogene which can create breast, ovarian and colorectal cancer after mutation and may have some association with schizophrenia (NLM, Genetic - AKT1. Available from: http://ghr.nlm.nih.gov/gene/AKT1, updated 2014 April 12, cited 2014 April 18). Mutation in gene AKT1 may also causes endometrial carcinoma, bladder tumors, squamous cell carcinoma of lung, metastatic thyroid cancer, hepatocellular carcinoma, and acute leukemia, and many other tumors of the body.

Mutations in the LMNA gene are related to a number of diseases, including Hutchinson-Gilford progeria syndrome (HGPS), limb girdle muscular dystrophy, familial partial lipodystrophy, Emery-Dreifuss muscular dystrophy, dilated cardiomyopathy, Charcot-Marie-Tooth disease. The mutated gene of lamin A that causes HGPS commonly known as progerin. Loss of lipid level, type-2 Diabetes mellitus, Dispersed Leukomelanodermic Papules, mandibulocaudal dysplasia, lethal restrictive dermopathy, and atypical progeroid syndrome (APS) are also result of mutation in LMNA gene.

In latter sections, MFS due to FBN1 mutation, Proteus syndrome due to AKT1 mutation and Progeria syndrome due to LMNA mutation is going to be discussed for common systemic involvement.

Common systemic involvement of these gene mutations
Musculo-Skeletal system
The phenotypes of MFS caused by FBN1 mutation, Proteus syndrome caused by AKT1 mutation and Progeria caused by LMNA mutation commonly results musculo-skeletal system abnormality.

In MFS, most of the visible signs are related to the skeletal system. Persons may have dolichostenomelia, arachnodactyly, abnormal indentation or protrusion of the sternum, stooped shoulders, malocclusions, abnormalities of the spine, presence of osteopenia (mainly in Marfan children), inadequate bone acquisition. The diagnosis of MFS relies on defined clinical criteria (Ghent nosology), outlined by international expert. MFS causes the femoral head protruding into abnormally deep hip sockets (protrusio acetabuli). Protrusio acetabuli is a criterion for the diagnosis of MFS. If acetabuli is protruded for long time, the femoral head protruding into abnormally deep hip sockets (protrusio acetabuli). Protrusio acetabuli is a criterion for the diagnosis of MFS. If acetabuli is protruded for long time, the femoral head protruding into abnormally deep hip sockets (protrusio acetabuli). Protrusio acetabuli is a criterion for the diagnosis of MFS. If acetabuli is protruded for long time, the femoral head protruding into abnormally deep hip sockets (protrusio acetabuli). Protrusio acetabuli is a criterion for the diagnosis of MFS. If acetabuli is protruded for long time, the femoral head protruding into abnormally deep hip sockets (protrusio acetabuli). Protrusio acetabuli is a criterion for the diagnosis of MFS. If acetabuli is protruded for long time, the femoral head protruding into abnormally deep hip sockets (protrusio acetabuli). Protrusio acetabuli is a criterion for the diagnosis of MFS. If acetabuli is protruded for long time, the femoral head protruding into abnormally deep hip sockets (protrusio acetabuli). Protrusio acetabuli is a criterion for the diagnosis of MFS. If acetabuli is protruded for long time, the femoral head protruding into abnormally deep hip sockets (protrusio acetabuli).
time, it can cause anomaly in the hip joint and acetabular line.\(^9\)

MFS also shows vascular smooth muscle cell apoptosis.\(^{35,37}\)

In Proteus syndrome, skeletal abnormalities are the most frequent findings.\(^{35}\) Proteus syndrome shows megaspondylo dysplasia,\(^{36}\) and crano-facial abnormalities.\(^{35,9}\) Abnormal bony edges, bony invasions, joint immobility, and loss of overlying soft tissues have been reported in cases of it.\(^{35,36}\) Manifestations of Proteus syndrome include large sized finger in association with permanent medial or lateral deflection of one or more fingers, fusion of the bones in fingers or toes, or webbing of the soft tissues between the digits.\(^35\)

In this condition, overgrowth of muscle and abnormally large muscle group with asymmetric muscle development are found.\(^{36}\) Some smooth Muscle shows hyperplasia.\(^{32,38}\)

In Progeria caused by LMNA mutation, skeletal defects include severe osteolysis,\(^{39}\) hypoplasia, dysplasia, and pathological fractures. It can cause severe alterations in osteogenesis, including craniofacial disproportion with a “plucked bird” appearance,\(^{40-42}\) short dystrophic clavicles, and thin and high pitched voice that may also occur.\(^{40-43}\) It also cause resorption of the clavicle,\(^{42,43}\) microvascular inadequacy, matrix abnormalities, bony maldevelopment, abnormally broad metaphyses and epiphyses, avascular necrosis of the femoral head.\(^{44}\) The patients also have an extremely aged appearance and the limbs are usually thin and may be associated with stiff joints, and coxa valga. They also demonstrate “horse riding” stance and wide based shuffling gait.\(^{45}\) The ranges of motion for wrist, ankle, and hip rotation may decrease than normal.\(^{45}\) There is chance of stooped shoulders, calcaneovalgus, genu valgum, kyphosis, or calcaneo varus.\(^{46,47}\) The muscle strength is preserved.\(^{46,47}\)

More specifically, MFS and Progeria both cause abnormal chest cavity where MFS can cause pectus excavatum or pectus carinatum,\(^{35}\) and Progeria may cause pyriform thorax with tapering of ribs.\(^{35,36}\) Osteopenia occurs in both of the cases which is axial or peripheral in MFS,\(^{36}\) and generalized in progeria.\(^{48-49}\) MFS also share pathological fracture and vascular smooth muscle cell defect with progeria.\(^{46,47,48-49}\) On the other hand, Proteus syndrome and progeria both have dental abnormalities where Proteus syndrome may cause alveolar dental ridges,\(^{50}\) and Progeria cause dental crowding with delayed teeth eruption.\(^{51,52}\)

Some other regular features of musculo-skeletal system which are common in all these three mutations are discussed in the Table 1.

### Cardio-vascular system

The MFS, Proteus syndrome and Progeria commonly cause cardio-vascular system abnormalities.

In MFS, cardio-vascular systems, usually diagnosed in young age is associated with poor prognosis.\(^{46}\) Cardiac arrhythmias, sudden cardiac death, endocarditis,\(^{46,47}\) are also cardiovascular manifestations of the MFS. Mitral Valve Prolapse is indicated as a useful diagnostic tool.\(^{47,51,53}\) The cardiovascular manifestations are the leading cause of death in MFS.\(^{35}\) MFS can also cause dilatation of the main pulmonary artery (MPA), dysfunction of the myocardium due to microfibrillar defect,\(^{47}\) abnormal reading on an electrocardiogram (ECG) but aortic wave reflection is not elevated in MFS.\(^{31,54}\) Infantile MS presents high morbidity with mitral regurgitation and heart failure.\(^3\) Clinical presentations of these manifestations comprise short breath, cardiac palpitations, abnormal heartbeats or angina pectoris with pain radiating to the back, shoulder, or arm.\(^{15}\) Myocardial infarction and bacterial endocarditis are some cardiac causes of death.\(^{14}\) In vascular system, there can be many types of defects in arterial wall including calcification. Rarely it shows axillary artery aneurysm.\(^{35,55}\)

Proteus syndrome affects cardiac system less but sometimes it reports complex congenital heart disease and some myocardial abnormalities.\(^{27,56}\) Multiple superficial, visceral and vascular abnormalities are present in Proteus syndrome.\(^{30}\) Vascular malformations have also been reported in this case with variety of types. They grow proportionately with the patient; they never regress, but they can expand.\(^3\) It can also cause cerebral vascular malformations,\(^{31}\) vascular tumors, portwine stains (PWS), and venous anomalies (varicosities, prominent veins).\(^42\)

<table>
<thead>
<tr>
<th>Involvement of</th>
<th>Marfan syndrome</th>
<th>Proteus syndrome</th>
<th>Progeria</th>
</tr>
</thead>
<tbody>
<tr>
<td>Spine</td>
<td>Abnormal curvature of spine (scoliosis), kyphoscoliosis and other abnormalities.</td>
<td>Vertebral dysplasia, asymmetry and enlargement.</td>
<td>Severe scoliosis and decreased spinal flexion.</td>
</tr>
<tr>
<td>Skull and facial</td>
<td>High palate, small jaw</td>
<td>Calvarial thickening, frontal bony prominence, macrocephaly, hyperostoses of the skull. Nasal bridge deformity, external auditory canal overgrowth.</td>
<td>Persistent open fontanelles, cranio-facial disproportion, short and sculptured nose, large bala head, small jaw.</td>
</tr>
<tr>
<td>Joint</td>
<td>Abnormal flexion, pain, early osteoarthrosis.</td>
<td>Abnormal flexion</td>
<td>Avascular necrosis of joint bones, Hip dislocation</td>
</tr>
<tr>
<td>Motion</td>
<td>Limited.</td>
<td>Limited.</td>
<td>Limited.</td>
</tr>
<tr>
<td>Muscle</td>
<td>Atrophy and hypoplasia.</td>
<td>Rarely. Atrophy may present in quadriceps femoris.</td>
<td>Sometimes atrophy.</td>
</tr>
</tbody>
</table>
In HGPS, the principal factor affecting mortality in individuals is cardiovascular disease. The description of the cardiovascular features of HGPS has proven to be quite consistent,\(^{66}\) that include prominent atherosclerosis and calcification of coronary arteries and others. The coronary artery disease leads to ischemic changes in the myocardium, including well-defined infarcts. In addition, it may also cause narrowing of the small intramural arteries, which may contribute to myocardial fibrosis.\(^{66}\) Chest x-rays shows cardiac enlargement and the electrocardiogram (ECC) shows right atrial hypertrophy sometimes.\(^{63,67}\) Sonographic and ECC evidence of myocardial ischemia is not common initially, but after a few years, echocardiograms and carotid Doppler sonography may show hypertrophy of the intimal layer of the internal carotid artery. Atherosclerotic changes, tricuspidus with increased echo texture, left and right atrial dilatation, calcific aortic stenosis, cardiomegaly, and hypercholesterolemia are also seen in progeria.\(^{64,66}\) Death from cardiac complications at an average age of 14 years is usually preceded by angina pectoris and myocardial infarction,\(^{64}\) caused by progressive atherosclerotic disease.\(^{66}\) Children may die of myocardial infarction when they are found with diffuse loss of vascular smooth muscle and endothelial cells throughout their coronary arteries and replacement by fibrosis and adventitial thickening.\(^{67}\) If an old man has typical HGPS, he shows refractory congestive heart failure due to arteriosclerotic heart disease and hypertension, and also has arteriosclerosis obliterans.\(^{68}\) Sometimes loss of vascular smooth muscle cells (VSMCs) in the great vessels, veins, smaller arteries, and arterioles is seen in a case of progeria. There is spontaneous breaks in elastic structures,\(^{59,60}\) and prominent adventitial fibrosis too.\(^{69}\) Vascular atherosclerotic changes may cause subdural hemorrhage leading to death in some cases. Small collagen fibrils in the atherosclerotic intima and media with extensive loss of mural smooth muscle cells in the aorta are also reported.\(^{66}\) Progeria can cause cerebral infarction and renal infarction.\(^{66}\)

More specifically, MFS and Progeria both cause mitral valve calcification and increased echo texture.\(^{56,60,64}\) MFS also cause mitral valve prolapse, regurgitation, fluttering of mitral leaflet,\(^{70}\) and severe rheumatic mitral stenosis.\(^{49}\) MFS and Proteus syndrome also share ventricular hypertrophy and dysfunction,\(^{71,72}\) systolic and diastolic abnormality,\(^{64,66}\) cardiac murmur, angina pectoris, congestive cardiac failure and myocardial infarction in common.\(^{53,54,66}\) On the other hand, Proteus syndrome and Progeria both can cause thickening of myocardial septum,\(^{66}\) cardiomyopathy, myocardial fibrosis and mass,\(^{59,66}\) and abnormality in vascular endothelium.\(^{59,64,67}\)

Some other regular features of cardio-vascular system which are common in all these three mutations are discussed in the Table 2.

### Eye

The MFS, Proteus syndrome and HGPS commonly affect eye.

In MFS, eye complications such as lens dislocation or ectopia lentis occur in more than half the people who have MFS, earlier in women,\(^{71}\) and in some cases it is progressive (Mayo Clinic - MFS. Available from: http://www.mayoclinic.org/diseases-conditions/marfan-syndrome/basics/complications/con-20025944, updated 2014 April 07, cited 2014 April 18).\(^{72,73}\) Glaucoma is also common at a younger age which can damage the optic nerve.\(^{74,75}\) Sometimes MFS reports phthisis bulbi, bilateral or unilateral blindness.\(^{29,30}\) The another ocular abnormality is enlargement of the globe, presumably caused by stretching of the tunica scleralis, and the zonular fibers.\(^{76,77}\) Some studies suggest prevalence of retinal detachment and some suggest prevalence of ectopia lentis. This variation recommend other genotype-phenotype relationships exist which may account for differences in ocular manifestations of MFS.\(^{71}\)

The ocular manifestations of a Proteus syndrome are due to severe maldevelopment and malfunction of the neuroretina. Epibulbar tumors are recorded most commonly,\(^{71}\) while periorbital exostoses are infrequent,\(^{78,79}\) extraocular tendons and posterior segment involvement can be seen in a case of Proteus syndrome presenting with vertical strabismus secondary to a fibrous tumor within the superior oblique tendon.\(^{77,80}\) Sometimes myopia associates with mild calcific band, abnormal vitreous structure, vitreous hemorrhage, and a resolved serous retinal detachment in a patient of Proteus syndrome.\(^{81}\) The oncogene of Proteus syndrome may show some overgrowth syndromes in eyes.\(^{71}\) Sometimes epibulbar cystic lesions with nodular gliosis are also reported in this condition.\(^{81}\)

In Progeria, loss of eye brows and eye lashes with prominent eyes is common in the early childhood.\(^{82,83}\) Eyelid retraction, lagophthalmos, superior sulcus deformity, upper lid lag in down gaze, and poor pupillary dilation are also reported. In the HGPS, eyes look prominent (pseudoprostosis) probably due to lid retraction, although there is no true protrusion. Superior sulcus deformity may also occur due to lipodystrophy of the orbital fat. Patients with HGPS do not develop other ocular features associated with aging, such as presbyopia, arcus senilis or age-related macular degeneration. Other rare ocular

### Table 2. Common Features Found in Marfan Syndrome, Proteus Syndrome, and Progeria Involving Cardio-vascular System.

<table>
<thead>
<tr>
<th>Traits</th>
<th>Marfan syndrome</th>
<th>Proteus syndrome</th>
<th>Progeria</th>
</tr>
</thead>
<tbody>
<tr>
<td>Heart conduction</td>
<td>Arrhythmia</td>
<td>Thickening of myocardial septum may affect conduction.</td>
<td>ECG shows giant P waves</td>
</tr>
<tr>
<td>Contractile dysfunction</td>
<td>Present</td>
<td>Thickening of myocardial septum may affect contraction.</td>
<td>Present</td>
</tr>
<tr>
<td>Hyperplasia of arterial wall</td>
<td>Seen</td>
<td>Seen</td>
<td>Seen</td>
</tr>
</tbody>
</table>
manifestations of the HGP syndrome are bands of skin running from the upper lid to the cornea, senile ectropion, ptosis with Marcus-jaw-winking phenomenon, dry-eye syndrome, and iridocorneal adhesions.\textsuperscript{96,97}

More specifically, MFS and Proteus syndrome both cause optic nerve damage;\textsuperscript{84,93} and the former can also cause hypoplasia and papilledema of optic nerve.\textsuperscript{84,93} Proteus syndrome and Progeria both have features of nystagmus or nystagmoid movements.\textsuperscript{84,93}

Some other regular features of eye which are common in all these three mutations are discussed in the Table 3.

**Nervous system**

The MFS, Proteus syndrome and Progeria commonly cause nervous system abnormalities.

In MFS, the most common and classic neurological manifestations are cerebrovascular.\textsuperscript{83-85} Patients with MFS may have a subarachnoid hemorrhage or intracranial aneurysm,\textsuperscript{86} and near total erosion of a pedicle. Dural ectasia can be added to the list of pleiotropic manifestations of the MFS.\textsuperscript{86} There is probability of heterogeneous involvement of other components of Extra Cellular Matrix microfibrils at the basis of this cerebrospinal manifestation.\textsuperscript{86,90} Dural ectasia with bone erosion which are often reported in this condition can be associated with severe postural headache secondary to spontaneous intracranial hypotension resulting from cerebrospinal fluid leaks caused by underlying fibrillinopathy.\textsuperscript{87-95} It is recognized as a potential complication in children with MFS,\textsuperscript{96} and also reported with severe back pain in adults.\textsuperscript{96,97} When neural symptoms or findings do occur they may be related to stretching and traction mechanisms.\textsuperscript{97}

Proteus syndrome often presents hemimegalencephaly with high incidence of other brain anomalies.\textsuperscript{86,87} This includes hypoplasia of the corpus callosum and crus cerebri, grey and white matter damage and cortical migration/organizational disorders.\textsuperscript{86} Neurologic sequelae caused by vertebral anomalies are reported too.\textsuperscript{84,93} Proteus syndrome has evidence to develop pinealoblastoma, Dandy-Walker malformation, corpus callosal abnormalities, periventricular calcification, hypo dense periventricular white matter, and mental deficiency. Hemimegalencephaly is not a finding in this entity; reported abnormalities include hydrocephalus, porencephaly, cerebral calcifications, and polymicrogyria. Additional Central Nervous System (CNS) findings are thought to be the sequelae of vascular dysplasia, and include infarcts, atrophy, porencephaly, and calcifications.\textsuperscript{88} Some neurological defects like hydrocephaly, lissencephaly, partial agenesis of the corpus callosum are also reported with the Proteus syndrome.\textsuperscript{97} It may cause paraspinal hamartoma.\textsuperscript{98} Protuberance of the skull,\textsuperscript{99} structural and functional asymmetry of the central nervous system,\textsuperscript{99} hydrocephalus and mental retardation are also some features of proteus syndrome.\textsuperscript{89} Epilepsy and ohtahara syndrome is diagnosed in children affected by Proteus syndrome associated with infantile spasms, myoclonia, and partial epilepsy in newborn infants.\textsuperscript{97}

In HGPS, diffuse encephalopathy, and Pseudotumor cerebri has been reported.\textsuperscript{89} Even a mild head injury can cause intracranial pathology in a progeria patient. Progressive atherosclerosis of intracranial vessels is responsible for formation of the hematomas in this condition.\textsuperscript{98,99} In progeria, motor and mental development is normal, as are intelligence.\textsuperscript{100} But there may be a low-frequency conductive hearing loss.\textsuperscript{101}

There is chance of Peripheral neuropathy,\textsuperscript{102} cerebrovascular disease of aging in this age related disease, progeria.\textsuperscript{102}

More specifically, MFS and Progeria both may cause headache,\textsuperscript{103-106} and do not have any mental retardation.\textsuperscript{105,106} MFS and Proteus syndrome both have spinal cord involvement whereas MFS may cause spinal Cerebro-spinal Fluid (CSF) leaks, spinal arachnoid diverticula, trauma, and congenital enlargement of spinal canal,\textsuperscript{86,90,104} and Proteus syndrome may cause spinal stenosis, paraspinal tumor, and spinal cord compression.\textsuperscript{86,90} On the other hand, seizures in seen in both Proteus syndrome and Progeria.\textsuperscript{106,108,104}

Some other regular features of nervous system which are common in all these three mutations are discussed in the Table 4.

**Not shared systemic phenotypes**

MFS often presents spontaneous recurrent or bilateral pneumothorax,\textsuperscript{107} congenital malformations,\textsuperscript{108} pneumonia, bronchiectasis, emphysematous bullae, upper lobe fibrosis, aspergillosis and other lung related disorders.\textsuperscript{109,110} Patients may have lower values of Forced Vital Capacity and Total Lung Capacity and other spirometric values,\textsuperscript{111,112} with a decrease in carbon monoxide transfer factor, and lung elastic recoil.\textsuperscript{112} Other Lesser known areas of involvement are renal and dermatologic.\textsuperscript{111,117}

Table 3. Common Features Found in Marfan Syndrome, Proteus Syndrome, and Progeria Involving Eye.

<table>
<thead>
<tr>
<th>Traits</th>
<th>Marfan syndrome</th>
<th>Proteus syndrome</th>
<th>Progeria</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ophthalmic anthropometric measures</td>
<td>Increased axial length</td>
<td>Overgrowth syndromes can cause length or distance abnormality</td>
<td>Reduced horizontal palpebral fissure length, inter pupillary distance, inner canthal distance and outer canthal distance.</td>
</tr>
<tr>
<td>Refractive errors</td>
<td>Myopia and astigmatism</td>
<td>High myopia</td>
<td>Myopia or hyperopia</td>
</tr>
<tr>
<td>Cornea</td>
<td>Unilateral corneal opacities, flat cornea</td>
<td>Keratopathy</td>
<td>Corneal dryness, opacities, clouding and keratopathy.</td>
</tr>
<tr>
<td>Retina</td>
<td>Detachment or tear in the retina</td>
<td>Abnormal retinal pigment, dysgene sia. Diffuse retinal disorganization and choriotelial mass</td>
<td>Retinal arteriolar narrowing, tortuosity, Retinal angiosclerosis and retinopathies.</td>
</tr>
<tr>
<td>Cataract</td>
<td>Seen</td>
<td>Seen</td>
<td>Seen</td>
</tr>
<tr>
<td>Strabismus</td>
<td>Present</td>
<td>Present</td>
<td>Present</td>
</tr>
</tbody>
</table>
In Proteus syndrome, patients most commonly show bilateral ovarian serous cystadenomas, mesothelioma, and papillary carcinoma of the thyroid. Rare connective tissue nevus and brownish epidermal nevus in various regions, benign and malignant tumors and hamartomas are also seen in proteus syndrome. Commonly encountered tumors include hemangiomas, lymphangiomas, lipomas, epithelial tumor of the female genital tract, testicular and paratesticular tumors. Four types of abnormal fat may occur in Proteus syndrome: lipomas, lipohypoplasia, fatty overgrowth, and partial lipohyperplasia. There may be fatty matter infiltration, subependymal nodules, and parenchymal distortion. Other rare tumors include meningioma, Parotid monomorphic adenoma, astrocytoma, optic nerve tumor, pinealoma, breast intraductal papilloma, leiomyoma, endometrial carcinoma, and giant kidney cysts. Multiple tumors in the same patient are often seen in proteus syndrome, with distal renal tubular acidosis and nephrocalcinosis, dilated and tortuous renal veins with possible calcifications.

Progeria can cause low blood pressure, vertical midline groove, the chin, sclerodermatous skin, reduced subcutaneous fat, prominent superficial veins, dyspigmentation, and alopecia of skin.

A progeria case may present some biochemical abnormalities like hypoaminoacidemia, hyperaminoaciduria, increased radioactive iodine uptake in thyroid, and other abnormalities in blood.

Progeria patients may be seen to sleep with open eyes, labial weakness, and nasal speech affecting speech fluency. Localized glomerulosclerosis, tubular atrophy, mesengial matrix growth, papillary adenoma are shown in older cases.

**Vision of future research**

The genes responsible for the three diseases are not known to interact, so the possibility of mutation in any of them affecting functions of the other two is quite unlikely. However, recent studies suggest that mutations in the penultimate exon of FBN1 (in the 3’ terminus) give rise to a neomorphic phenotype leading to a condition known as Wiedemann-Rautenstrauch syndrome, a rare disorder characterized by overlapping of the clinical manifestations of both marfan’s syndrome and progeroid syndrome. It has been suggested that this rare subgroup of MFS, comprising of congenital lipodystrophy, a neonatal progeroid appearance, and a progressive clinical course with early lethality, should be referred to as marfanoid-progeroid syndrome. Evidence of involvement of any mutation in the LMNA gene, the one associated classical progeria has not been unveiled till now. Any association of mutation in the AKT1 gene with the aforementioned circumstances is yet to be explored.

**Conclusion**

Genetic mutation is day by day increasing entries in the disease directory and started threatening the mankind like never before. MFS, Proteus syndrome, and Progeria are one of the most recognized mutation related diseases caused by mutation of FBN1, AKT1, and LMNA genes correspondingly. If we go through the clinical features and systemic involvements of these mutations, we can find common involvement of musculo-skeletal system, cardiovascular system, eye, and nervous system. In musculo-skeletal system, deviations of spinal curvature, abnormalities in the extremities, skull, and facial bones are reported in all the three mutations. All cause abnormal flexion and limited range of motion of joints. In cardiovascular system, all the three mutations have reported abnormality of the aorta and cardiac conductive system. Contractile dysfunction of heart and hyperplasia of arterial wall have been seen in common too. In case of eye, MFS, Proteus syndrome, and progeria share many clinical features. All cause cataract, strabismus, and refractive errors along with same kind of retinal and corneal abnormalities. These mutations also have described some common nervous system features where all cause meningeal abnormalities, neurovascular abnormalities, congenital and developmental abnormalities. Stroke has been seen in all the three cases too. Though the mentioned mutations have certain individual unique characteristics too, the outcomes indicate that there can be some relation among the proteins related to these mutations, or among the genes of which modification occurs. The results of this review will enrich the field of genetic research and medicine. Furthermore, this study can help to acknowledge the reported sign & symptoms of three diseases and inter-relation among them. Additionally, it is recommended to have more attention in this field.

**Table 4.** Common Features Found in Marfan Syndrome, Proteus Syndrome, and Progeria Involving Nervous System.

<table>
<thead>
<tr>
<th>Traits</th>
<th>Marfan syndrome</th>
<th>Proteus syndrome</th>
<th>Progeria</th>
</tr>
</thead>
<tbody>
<tr>
<td>Neurovascular</td>
<td></td>
<td></td>
<td>Transient ischemia, stenosis of cerebral, vertebral and basilar arteries, arteriosclerosis, atherosclerosis, Epidural hematoma</td>
</tr>
<tr>
<td>Stroke</td>
<td>Seen</td>
<td>Seen</td>
<td>Seen</td>
</tr>
<tr>
<td>Meninges</td>
<td>Dural ectasia, hernia of meninges or meningioma</td>
<td>Meningioma</td>
<td>Meningeal hematoma.</td>
</tr>
<tr>
<td>Congenital CNS abnormality</td>
<td>Present</td>
<td>Present</td>
<td>Present</td>
</tr>
<tr>
<td>Developmental CNS abnormality</td>
<td>Present</td>
<td>Present</td>
<td>Present</td>
</tr>
</tbody>
</table>
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Author Contributions

Conception and design the work/idea, Collect data/obtaining results, Critical revision of the manuscript, Approval of the final version: TB

Cite as:

Ocular Auscultation: A Review
Daniel Fernando Gallego,1 Ana Maria Rivas-Grajales,2 Carlos Jose Gallego,1

Abstract
Ocular auscultation is a commonly neglected step of routine physical examination. An adequate ocular auscultation can be helpful in discovering an ocular bruit, which is an important diagnostic finding for a broad spectrum of pathologic conditions, some of which are potentially fatal. In this article, we present a literature review on the physical exam maneuver of ocular auscultation, as well as the pathophysiology and differential diagnosis of ocular bruits. We also included a description of the adequate auscultation technique and a discussion about the applicability of ocular auscultation in clinical practice.

Keywords: Auscultation; Physical Examination; Carotid Stenosis; Carotid-Cavernous Sinus Fistula; Neurological Examination (Source: MeSH, NLM).

Introduction
Ocular auscultation is the physical exam maneuver that consists of listening to the vascular sounds of the head and neck by placing the stethoscope on the surface of the eyelids and surrounding structures. The development of an ocular murmur is secondary to the turbulent flow inside the vessels around the orbit, which can arise from localized pathologies (e.g., stenosis of the carotid artery) or systemic conditions (e.g., anemia). Moreover, ocular bruits have been identified in patients suffering from life-threatening conditions, such as subarachnoid hemorrhage, stroke, and carotid-cavernous fistulas. Ocular bruit has also been reported as the only auscultatory finding in cases of symptomatic atherothrombotic vascular disease.

Despite its clinical relevance, the auscultation of the orbit is often neglected in the routine neurological examination, especially now that better diagnostic tools are replacing clinical examination, including the use of Doppler ultrasound technology in evaluating orbital lesions. Anyhow, physical exam maneuvers and radiological tools are not mutually exclusive and, in other scenarios, have been proven to have additive diagnostic efficacy. For example, the use of cardiac auscultation complemented by echocardiography has shown improved accuracy in murmur identification compared to echocardiography or physical exam alone.

The non-use of ocular auscultation in clinical practice could be due to the lack of knowledge of the technique and the lack of awareness of the clinical implications of an orbital bruit. In this article, we present the pathophysiology and differential diagnosis of orbital bruits, as well as a brief description of the ocular auscultation technique. We also included an Evidence Based Medicine section with a literature review on ocular auscultation and the prevalence of ocular bruits in selected populations.

Pathophysiology of Ocular Bruits
An understanding of vascular hemodynamics is useful for the interpretation of vascular sounds in any anatomical site. An arterial bruit indicates the presence of stenosis at or proximal to the area of auscultation. As the stenosis increases, the potential energy (pressure) proximal to the stenosis is transformed into kinetic energy (velocity) within the stenosis, resulting in a turbulent flow and an audible sound. Cranial and orbital bruits represent vibrations arising from vascular structures within the cranium, neck and, occasionally, from cardiac lesions. The orbits serve as a “window” for sound transmission and minimize dissipation through bony structures. There are four factors that may alter the intensity and duration of arterial bruits: high inflow resulting from a high cardiac output, diminished side-branch flow, poor or absence of collateral vessels, and augmented outflow.

Regarding ocular bruits, three underlying pathophysiological processes related with the aforementioned factors should be suspected. First, the confluence of blood vessels with high blood flow resulting in a high arteriovenous pressure difference in the proximities of the ocular cavity; this is characteristic of vascular malformations and carotid-cavernous fistulas, in which a considerable blood volume is diverted from vessels with high hydrostatic pressure (arteries) to those with low hydrostatic pressure (veins). Second, the occlusion in the internal carotid artery with subsequent ipsilateral and contralateral arteriolar vasodilation; this is the case of stenotic lesions and a flow deviation to contralateral vessels. Finally, an ocular bruit could be a sign of increased cardiac output, as seen in anemia and hyperthyroidism.

Differential Diagnosis of Ocular Bruits
An ocular bruit can be associated with a wide range of patho-
The main conditions that have been associated with this finding are presented in Table 1.

Carotid-cavernous fistula is the main condition that should be suspected when an ocular bruit is found in clinical examination. This finding is part of a diagnostic triad consisting of proptosis, chemosis and ocular bruit and has been reported in 50% of cases. In patients with vascular malformations, which can be silent despite their size, an ocular bruit could be the only physical finding. The confluence of high-flow vessels is the underlying pathophysiology in this condition.

One other disease that is associated with ocular bruits is the presence of an ischemic cerebrovascular accident or a transient ischemic attack due to stenosis in the internal carotid artery. Two cohorts of patients with cerebrovascular disease reported a prevalence of ocular bruits of 28% and 0.6%, respectively, while another cohort of symptomatic stroke patients reported a prevalence of 72%. In cerebral ischemia, the collateralization process determines the infarcted area. When the internal carotid artery is occluded, a retrograde flow deviation occurs through the external carotid artery via the ophthalmic artery towards the intra-cerebral system, producing the vascular murmur. Vasodilation of the episcleral arteries has been described as an additional useful physical finding. A cautious palpation of the facial artery branches may reveal a hyperdynamic high-grade lesion in the internal carotid artery.

The vasculitides can also present with an ocular bruit as a consequence of vessel incompliance due to systemic inflammation and possibly due to narrowing of the vessel lumen. For example, patients with giant cell arteritis, which is characterized by an inflammation in the lining of the temporal artery, can be associated with an ocular bruit. This finding has also been reported in a patient with Churg-Strauss syndrome.

Conditions that increase the systemic blood flow (e.g. anemia) should be considered in the differential diagnosis. The presence of an ocular bruit has been reported in two case series with chronic kidney injury. Ocular bruits have also been described in Paget’s disease, in which the increased cardiac output results from an increased rate of angiogenesis. Finally, an ocular bruit can radiate from distant vascular structures, such as thoracic and abdominal aneurysms, aortic stenosis, and hypertension in pediatric patients.

**Ocular Auscultation Technique**

Auscultation should take place in a quiet room with both the patient and the examiner relaxed and in a comfortable position. Historically, a large and narrow bell has been used in ocular auscultation, like the one included in the Ford-Bowles stethoscope (Figure 1). However, for practical reasons, the bell found in modern stethoscopes is considered appropriate. Cranial bruits should be listened over the skull, and examination should include the frontal, temporal and mastoid regions and the eyeball, with the latter being more favorable for fainter sounds.

The auscultation of the orbit should be done by gently placing the bell of the stethoscope over patient’s closed eye (Figure 2). To minimize the sound produced by eyelid tremor, the patient should be asked to stare at a fixed point while the examiner gently closes one of the eyes and firmly places the stethoscope over the closed eye. If the patient is unable to keep his sight fixed, the examiner can help by placing a finger as a reference point in front of the patient’s eyes. Finally, the patient should be asked to hold his breath. Orbital bruits are usually faint and high-pitched, and the examiner should focus on the systolic phase of the cardiovascular cycle. Placing a thumb over the carotid artery should help in identifying the first heartbeat.

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### Table 1. Differential Diagnosis of Ocular Bruit.

<table>
<thead>
<tr>
<th>Category</th>
<th>Conditions</th>
</tr>
</thead>
</table>
| **1. Vascular conditions** | - Carotid-cavernous fistula  
- Arteriovenous malformations  
- Cerebrovascular accidents  
- Severe atherosclerosis  
- Internal carotid artery stenosis  
- Vasculitides  
  - Churg-Strauss disease  
  - Temporal artery vasculitis |
| **2. Systemic conditions** | - Anemia  
- Thyrotoxicosis  
- Paget’s disease |
| **3. Irradiation from distant structures** | - Aortic aneurysms  
- Aortic stenosis  
- Hypertension (in infants) |

Legend: From Retonthenet Copyright©2008-2014 All rights reserved. Reprinted with permission from David Skinner.
Auscultation of the frontal, zygomatic, temporal, and mastoid regions should be performed using the diaphragm of the stethoscope and always be preceded by an adequate inspection and palpation. Forced expiratory maneuvers, such as Valsalva maneuver, can be used to intensify the bruit.

Prevalence and Clinical Significance of Ocular Bruits: An Evidence Based Medicine Section

A literature review was performed using PubMed/Medline, Embase and SciElo databases, searching for the terms 'ocular auscultation', 'ocular bruit', and 'ocular murmur'. Additional relevant papers were retrieved from the articles' references. All reviewed abstracts and articles were in English. The amount of literature found was scarce as we expected; the majority of articles were case series and case reports. No recent reviews on ocular auscultation were found. This limitation restricts drawing conclusions on two important issues: the prevalence of ocular bruits in health and disease and the clinical importance of ocular auscultation in medical practice.

In relation to prevalence, to date there are no specific studies published with this purpose, and the current epidemiological data is derived from case series and prospective cohort studies. The only reported data for ocular murmurs in healthy population is as an innocent finding in 30%-60% of normal infants and children under six years of age. The reported prevalence in pathological conditions varies widely across studies, with cerebrovascular disease being the most studied. For example, Hirose et al. reported seven ocular bruits in 250 patients, and Gautier et al., found only one ocular bruit in 150 patients with cerebrovascular disease. In contrast, Hu et al., found 72 ocular bruits in 50 patients with symptoms of stroke or transient ischemic attack. While a definitive deduction is not possible with all of the studies being prospective cohort studies, we believe that the differences in the prevalence could be accounted for by demographic variables, such as age, race and clinical factors. For instance, Hirose et al. studied a sample of patients with cerebrovascular diseases of variable severity. On the other hand, Hu et al., included only patients with symptomatic atherothrombotic ischemic carotid disease, which suggests the presence of a more severe underlying condition. Further studies with standardized inclusion criteria aimed at evaluating the prevalence of ocular bruit in cerebrovascular disease and non-cardiovascular conditions are needed.

Concerning clinical importance, there are contradictory views about the utility of ocular auscultation as a routine practice. A report by the National Institute of Health in 1975 concluded that ocular auscultation was of limited use due to its poor predictive value in lesion localization and the severity estimation.

However, in favor of ocular auscultation in specific clinical settings, Purcell reported a patient who underwent enucleation after an ocular trauma. Ocular auscultation was not performed during physical examination, and the patient suffered a near fatal bleeding during the procedure due to a ruptured arteriovenous fistula. The author concluded that this event could have been prevented by a complete ocular examination.

Ocular bruits have been shown to be a crucial finding in guiding diagnostic evaluation. Hu et al., conducted a prospective study in patients with symptoms of cerebrovascular disease. They found that an ocular bruit was the only auscultatory finding in 28% of the patients. In addition, ocular bruits were 57% more common than neck bruits in patients with intracranial carotid artery occlusion. Smith et al., reported a patient with severe carotid stenosis, which manifested clinically as limb-shaking transient ischemic attack. The finding of an ocular bruit in the neurovascular examination shifted the diagnostic evaluation towards a vascular condition rather than a focal motor seizure. These two studies illustrate how the presence of an ocular bruit could inform the clinician about the existence of vascular conditions and

Figure 2: Adequate Technique for Ocular Auscultation. The bell of the stethoscope should be placed over the patient’s closed eye. The examiner’s finger can be used to keep the patient’s sight fixed and avoid eyelid tremor (A). Auscultation should include the zygomatic (B) and temporal regions (C).
provide guidance towards a successful diagnosis.

Finally, Atta et al., compared the clinical characteristics of a retrospective cohort of patients with venous stasis orbitopathy. The study findings revealed that 30% of patients with carotid-cavernous fistula had an ocular bruit, compared to 0% in the non-vascular group. Ocular bruit was found to be the only significant physical finding useful in differentiating carotid-cavernous fistula from other etiologies, mainly compressive mass lesions.

Based on the previous studies, we propose that ocular auscultation should be performed in all patients with clinical suspicion of cerebrovascular disease and carotid cavernous fistulas. Despite the limited evidence supporting the predictive value of ocular auscultation, we believe that awareness of the clinical relevance of ocular bruits is an important step towards encouraging research efforts in this field.

**Conclusion**

We presented the clinical relevant points of ocular auscultation, including ocular auscultation technique, pathophysiology, and differential diagnosis of ocular bruits. In spite of the improvement of diagnostic tools, clinical examination remains an important aspect of clinical practice due to its low cost and wide accessibility. Ocular auscultation is required in the detection of ocular bruits, a physical finding that can lead to the diagnosis of a wide range of diseases, some of which are life-threatening.

Although the literature on this subject is scarce, we believe there is enough evidence to suggest that it is important for physicians to acknowledge the role of ocular auscultation in patients with suspicion of cardiovascular and neurological conditions, especially atherothrombotic diseases and carotid-cavernous fistula. Further studies are needed to document the prevalence of ocular bruits in the general population and selected populations (e.g. patients with cerebrovascular disease).
References


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Author Contributions

Conception and design the work/idea, Collect data/obtaining results, Critical revision of the manuscript, Approval of the final version, Contribution of patients or study material: DG, AMRG, CJG

Cite as:

**Abstract**

**Background:** Kissing aneurysms are two independent but adjacent aneurysms protruding from two contralateral arterial locations. This report describes a successfully treated case of kissing aneurysms at the Department of Neurosurgery, Medical University of Gdańsk. **Case:** A 45-year-old asymptomatic woman was diagnosed with unruptured bilateral aneurysms located in the pericallosal-callosomarginal division. Her medical history included a previous intracranial aneurysm and arterial hypertension. The patient underwent a successful treatment by surgical clipping and was discharged in good condition; neither disability nor neurologic deficit was noticed upon discharge. Surgical wound healing was complicated by an infection and resulted in a reoperation for the patient. **Conclusion:** The etiology of kissing aneurysms is still unknown and the best treatment method stills remains unclear. Thus, every case has to be carefully and individually assessed by an interdisciplinary team. As a result, patient transfer to an experienced neurosurgical center could be beneficial.

**Keywords:** Intracranial Aneurysm, Anterior Cerebral Artery, Microsurgery, Angiography, Kissing aneurysms (Source: MeSH, NLM).

**Introduction**

The prevalence of intracranial aneurysm is estimated at approximately 3.2%. The major characteristics of aneurysms include type (saccular, fusiform, dissecting, mycotic, blood-blisters-like, distal, etc.), size (micro, small, medium, large, giant etc.) and location (branching sites of anterior, medial or posterior cerebral artery etc.). Unruptured aneurysms are asymptomatic in most cases. When ruptured, they cause subarachnoid hemorrhage (SAH), also known as hemorrhagic stroke. Main SAH symptoms include sudden onset of severe headache, seizures, and neurologic deficits with rapid deterioration leading to loss of consciousness. Basic diagnosis involves computed tomography (CT) imaging or lumbar puncture. SAH represents a state of medical emergency; even when treated early, SAH is associated with mortality up to 50% (including neurologic deficits in many of the survivors). The main treatment options include open surgery with direct microsurgical clipping of the aneurysm neck or an endovascular procedure that occludes the aneurysmal lumen. The risk of an aneurysm rupture depends on various risk factors such as the aneurysms’ characteristics (localization, type and size) and the patients’ characteristics and co-morbidities (hypertension, gender, cigarette smoking, alcohol intake, and prior history of aneurysm).

Kissing aneurysms (KAs) are unusual locational phenomena of multiple aneurysms. Although the prevalence of multiple aneurysms can be up to 20% of all intracranial aneurysms, the KAs – adjacent bilateral aneurysms arising from the same artery – are quite unique with an incidence as low as 0.2%. Kissing aneurysms can be classified into two categories: type 1 represents aneurysmal necks that are located on the same parent artery and type 2 exists where each aneurysmal neck is located on different parent arteries. The most common location for KAs is the internal carotid artery (ICA), but other sites such as the distal part of the anterior cerebral artery have also been reported. However, KAs associated with the posterior arterial supply of the brain are mainly type 1. Kissing aneurysms are more common among women, especially middle-aged (40-59 years old). An interesting, but separate phenomenon is mirror-like (or twin) aneurysms that are located bilaterally on analogs of arteries (eg. left and right middle cerebral artery, MCA).

Diagnosing KAs can be difficult in terms of determining the number or structure of aneurysms based on radiologic examination. It has been suggested that more than half of KAs are not been recognized preoperatively. Thus, the decision-making process can be particularly challenging. There is no recommended screening for intracranial aneurysms, so in most of the cases they are revealed only when they have ruptured. In a minority of the patients, the presence of an aneurysm is known beforehand. In these special cases, it is highly important to make a prompt diagnosis of unruptured aneurysms, evaluate the risk of bleeding, and consider its eventual prophylactic treatment.
We present a case of unruptured KAs successfully treated surgically at the Neurosurgery Department of the Medical University of Gdansk. Informed consent was obtained from the patient for this study.

The Case
A 45-year-old asymptomatic woman was admitted to the Department of Neurosurgery for the planned surgical clipping of unruptured bilateral aneurysms located in the division of the anterior cerebral artery into the pericallosal and callosomarginal arteries (A2/3 kissing aneurysms, Figure 1 A, B). Kissing aneurysms were radiographically diagnosed, after the patient’s previous aneurysm surgery.

The patient’s medical history included hypertension, epilepsy, and 14 pack-years of smoking. According to the patient’s family, in 2012 she had an extreme case of alcohol intoxication resulting in tonic seizures. Her surgical history included a previous surgical clipping of an unruptured aneurysm in 2012 performed on the division of the right middle cerebral artery (MCA) segments M1/M2. A computed tomography angiography (CTA) scan was performed and revealed bilateral (kissing) aneurysms (4 x 4.5 mm in size) occurring at the bifurcation of the anterior cerebral artery into the pericallosal and callosomarginal arteries (A2/3 division). This aneurysm was classified as type 1 as each aneurysmal neck was located on the same parent artery (Figure 1).

The patient’s neurological status upon admission was normal and her general physical examination was unremarkable. Cerebral angiography was performed and the diagnosis of KAs was confirmed (Figure 1 C, D).

The patient underwent surgical clipping via a right frontal craniotomy approach under general anesthesia. The skull was opened with a free bone flap. Opening of the interhemispheric fissure was performed and the aneurysms were reached from the right and left side (Figure 2). Clips on the necks of the aneurysms were deployed during surgery.

Figure 1. Radiologic images of the Patient’s Aneurysms.
The procedure should secure the presence of the aneurysm in the surgical field, allowing for proper clipping and control of the aneurysm necks. Vascular patency was confirmed using ICG Pulsion (active ingredient: indocyanine green dye; Pulsion Medical Systems SE); temporary clipping was not applied. No electrophysiological monitoring was used during the surgical clipping. In addition, the surgery was prolonged (5 hours).

The early postoperative course was uneventful. Magnetic resonance imaging (MRI) performed on third post-operative day revealed no perfusion disturbances in the area of the surgery.

The patient was discharged from the hospital on the 10th post-operative day in good general condition; neither disability nor neurologic deficit was noticed (o score on the modified Rankin scale). No pre- or post-operative neuropsychological testing was performed. The patient was referred for a follow-up appointment after 10-12 days from the discharge date and a neurosurgical follow-up appointment after 8-10 weeks. The surgical wound healing was complicated by an infection. As a result, the patient received empirical clindamycin treatment. Given the wound infection, a reoperation combined with cranioplasty was performed to evade the epidural pus and antibiotic therapy was continued. This post-operative period was uneventful and the patient was scheduled for a subsequent cranial allograft procedure.

Discussion

Kissing aneurysms derive their name from the specific spatial arrangement of two separate but adjacent malformations. Besides certain congenital predispositions (e.g. Marfan syndrome, Ehlers-Danlos syndrome, autosomal dominant polycystic kidney disease etc.), the causes and risk factors of KAs have not been fully defined. It can be assumed, however, that the risk factors are multifactorial and similar to those of other types of multiple aneurysms. The described patient’s gender, history of smoking, hypertension, and an unclear episode of alcohol abuse should all be considered as risk factors for aneurysm formation as well as contribute to the potential for aneurysmal rupture in the future.

Studies have suggested that 57% of KAs are not recognized preoperatively. Digital subtraction angiography (DSA) is the gold standard for detecting small and large aneurysms. In non-emergency situations, DSA is essential to establish whether acute treatment is needed or not, and if so, to select a proper treatment option. Angiograms can, however, be misleading or even negative as described in a similar report. Computed tomography angiography could also be a helpful tool to visualize such malformations because it provides an option for the non-invasive imaging of KAS. Importantly, it should be emphasized that CTA can miss aneurysms smaller than 3mm or give false positive results. Recently, more and more unruptured intracranial aneurysms are detected incidentally using MRA but treatment decisions are rarely made based on MRA alone.

Management of unruptured aneurysm remains controversial. Generally, aneurysms smaller than 7mm are at a low rupture risk. However, lesions located in the anterior circulation are at an intermediate risk of rupture. In this case, taking into consideration the patient’s risk factors, the surgical protection of KAs seems desirable. According to Rinkel et al., the relative risks (RR) for aneurysm rupture and their corresponding risk factor in our patient included hypertension (RR 2.0), heavy alcohol intake (RR 2.1), female gender (RR 2.1), smoking (RR 3.4), and the presence of multiple aneurysms (RR 1.7). The multidisciplinary team decided upon the microsurgical clipping of the aneurysm necks. According to guidelines, 45-year-old patients can benefit from surgical treatment. Endovascular treatment seems to be more challenging in circumstances involving KAs given the two vascular origins without a direct communication and the aneurysms at the distal parts of intracranial vessels (such as A2/A3) being more difficult to treat by coiling.

The preferred treatment method for a single unruptured aneurysm remains controversial; thus, an unruptured KA makes the decision process even more complicated. Endovascular treatment has lower overall unfavorable outcomes but the patient’s age seems to be a crucial factor. Surgery-related morbidity and mortality are quite low among patients under 60 years of age. However, endovascular procedures can lead to an increased risk of recurrence or retreatment in this patient group. It is noteworthy that the surgical procedure provides the neurosurgeon with access and space for more maneuvers within the surroundings of the bilateral lesion. Surgery is difficult due to the dual arterial supply of KAs. The procedure should secure both aneurysms simultaneously; however, this maneuver can lead to a higher risk of intraoperative bleeding.

The patient had regular (every 6 months) follow-up care at the Neurosurgery Outpatient Clinic. Computed tomography angiography examination was performed after 12 months, showing complete aneurysm occlusion with no new pathologies. Althou-
Kissing aneurysms are a treatment challenge because of their unknown etiology, difficult imaging diagnosis, and no officially stated treatment method. In our opinion, every case has to be considered individually by an interdisciplinary medical team. In order to assure positive outcomes, patients with this malformation should be referred to an experienced neurosurgical center. Further studies are needed to allow for a better understanding of this condition and the therapeutic options available to patients with KAs.
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Down Syndrome and Quality of Life: A Case Report

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Abstract

Background: Quality of life is considered a crucial component to the well-being of patients with Down syndrome. The strength of quality care through stable social and psychological interactions has built a framework for a positive well-being for patients with Down syndrome, improving their quality of life. Case: A 55-year-old African American female with a history of Down syndrome, congenital heart disease, and newly-diagnosed early onset Alzheimer’s disease presented with an arm contusion resulting from regular caretaking. The patient’s history was reviewed, and the complexity of her condition was discovered. While a subset of Down syndrome patients have cardiac complications and others have early-onset Alzheimer’s, our patient had both. We believe this complicated her condition. After the diagnosis of Alzheimer’s was made, the caregivers noticed a significant decline in her ability to communicate and continue day-to-day activities. Despite the decline in functions, a positive mood was apparent. Conclusion: Multiple medical interventions, along with strong family support, positively contributed to the patient’s quality of life. Therapies targeting cognition could result in the maintenance of quality of life and, ultimately, lower health care costs.

Keywords: Down Syndrome; Alzheimer Disease, Early Onset; Heart Defects, Congenital; Quality of Life (Source: MeSH, NLM).

Introduction

Quality of life is considered a crucial component to the well-being of patients with Down syndrome. Down syndrome treatment should include quality of life improvement measures because although an increase in longevity may not be observed, maintained communication and social interactions can. The strength of quality care through stable social and psychological interactions has built a framework for a positive well-being for people living with disabilities. Quality of life is increasingly being recognized as a measuring tool to assess the progression of disease. Within the definition, quality of life encompasses the overall environment and includes the families and friends of Down syndrome patients who provide the highest degree of care. Through lifestyle modifications, medical interventions and strong support networks, patients with Down syndrome can increase their life expectancy.

In this paper, we demonstrate how quality of life is important to Down syndrome patients and why quality of life is an important measurement in treating these patients.

The Case

Our patient was a 55-year-old African American female brought into the Emergency Room by her father (primary caregiver who gave informed consent for this report) in September 2012 with concerns about a large contusion on her arm from routine caregiving. Her past medical history included Down syndrome (1961), mitral valve dysfunction (family could not recall time of diagnosis), and cerebrovascular accident (2010). Patient had no known allergies. Medications included: miconazole (M尼斯 Tat), warfarin (Coumadin), pantoprazole (Protonix), zinc oxide, phenytoin (Dilantin), protamine sulfate, digoxin (Digox), and acetaminophen (Tylenol). Surgical history included two pros-thetic valve placements (family could not recall time of surgery, but associated it with mitral valve dysfunction diagnosis), Medtronic AT500 series cardiac pacemaker implantation (2005), supraventricular ablation (2009), and G-tube placement (2012).

The patient’s father was alive and well at 79 years old, while her mother was 24 years old when birthing her and died at 43 years old from metastatic breast cancer. The patient’s paternal grandmother had Alzheimer’s disease. The patient lived with her father and sister (another caregiver giving informed consent). She was born overseas, had never been employed, but did attend sheltered workshops. She thoroughly enjoyed regularly attending church. Her family denied any alcohol, tobacco, or illicit drug use.

During a home visit in October 2012, we observed our patient, who was bed-bound and unable to communicate her needs effectively, receive exceptional family care. The patient had 24-hour care by her father and daily visits by her sister and a nurse supplied by the hospital. They constantly integrated her into conversations and daily tasks, thereby improving her...
independence; this was beneficial through her noticeable positive mood. During our time with her, we observed her gain the skills to feed herself and very minimally converse. Her father and sister were vigilant about tending to her and ensuring that she try and at least maintain her new skills. They ensured prompt organization of appointments for her cardiac surgeries and follow-up appointments at the hospital and with our team.

Discussion

**Family Care and Deinstitutionalization**

Quality of life can be deemed as subjective; however, it is increasingly being recognized as an asset in the monitoring of disease progression. Strong family support, solid communication, and long-lasting friendships have all contributed to increasing the quality of care for patients with Down syndrome. Continuous support and attentiveness by the patient’s father and sister allowed the patient to be interactive and learn new tasks. They carefully monitored her, yet allowed her to practice independence by interacting with the people in her community and attending church. This added to her quality of life.

Time spent with her family provided us insights on her ability to properly communicate with caregivers and their ability to appropriately interpret her requests. A positive environment empowers Down syndrome patients to continue to learn and teach themselves small tasks in their daily lives. External factors such as socioeconomic factors, strong community support, and proper daily resources all influence the overall well-being of patients with Down syndrome and increase their ability to function to their maximum capacity.

**Strengths and Limitations to Our Approach**

For six months, our group made multiple home visits and interacted with the caregivers to better understand her changing medical status. Over time, it was clear her condition was becoming more complex. As her cognition declined, we relied more on the caregiver’s interpretation of her feelings. Throughout the six-month follow-up period, we maintained constant communication, tracked patient’s progression, and witnessed the importance of a positive environment and family support. Historical data gathering was limited by incomplete hospital charts, lack of verbal communication by the patient, and difficulties with data recall by the family.

**Conclusion**

It is our belief that a combination of advanced medical interventions and support greatly improve the quality of life in Down syndrome patients. Treatment of comorbidities, therapies targeting cognition, and added support for patients with Down syndrome help increase their involvement in daily activities, social bonding, and quality of life.
Case Report

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The International Journal of Medical Students
Elective Undergraduate Medical Research: A Medical Student Experience

Zhi X. Chong. 1

The Experience

Research brings many benefits for undergraduate medical students, and evidence-based medicine (EBM) has been recognized as the most effective paradigm in making clinical decisions. 1 Regrettably, EBM teaching is often missing from the curriculum at most medical schools in developing countries. 1 Therefore, I would like to share my first research experience to emphasize the importance of research to one’s future career.

I was first involved in research while I was in my third year of medical school. At my school, research is optional. I conducted research during that time because I wanted to participate in a scientific poster competition at the East Asian Medical Student Conference (EAMSC) in Japan in 2013. I formed a research team with several of my friends, and that is where our journey began.

For a first-time researcher, the experience can be very challenging and requires a lot of preparation. 2 3 With little knowledge of how research is conducted, we started to read up on the latest research articles and consulted with several lecturers on research during that time because I wanted to participate in a scientific poster competition at the East Asian Medical Student Conference (EAMSC) in Japan in 2013. I formed a research team with several of my friends, and that is where our journey began.

The experience was not an easy one. We faced several difficulties during the data collection process. Firstly, we did not manage to obtain financial support for our study. As a result, we had to use our own pocket money to prepare the questionnaires and pay for the transportation fees. Secondly, we faced difficulties during the recruitment of study participants. The subjects were recruited on a voluntary basis, and some of the flood victims we approached asked to be paid to participate in the study. As a result, we faced some problems in recruiting enough participants during the initial stage. As time passed, with effort and determination, we managed to obtain a sample with adequate sample size and completed the data collection.

The next challenge was the data analysis. Statistical Package for the Social Sciences (SPSS) is the commonest statistical analytical tool for data interpretation in the medical field. 4 SPSS allows for a systematic and objective means of analysing the data collected. 4 However, a study has shown that most medical students are not familiar with SPSS, and the reasons could be the lack of interest and the lack of tutorials. 5 Most of us were inexperienced in performing statistical analysis, so we had to search online for SPSS tutorials and articles to learn how to analyse data using SPSS. With the help of the statistician at our school, we successfully completed the analysis and managed to proceed to the discussion of the study.

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The International Journal of Medical Students

Elective Undergraduate Medical Research: A Medical Student Experience

Chong ZX.

The discussion came easily to us because it mainly involved using our literature review and comparing our study results with those of previous studies. In the end, it took us three months to complete our research. Our project was represented at the national level selection competition and won the only place allocated to Malaysia to represent the country at the final competition in EAMSC in Japan.

In January 2013, the study was presented during the scientific poster competition at EAMSC Japan and was announced as the winning poster. However, that did not mark the end of our journey. After the conference, we wrote a research manuscript and submitted it to an international journal for publication. The manuscript was accepted and is expected to be published in 2015.

Medical students are future doctors. With the advances in science and technology in the field of medicine, EBM and research are becoming more important in disease management. Including scientific research training into medical school curriculum can train junior doctors to make clinical decisions which are based on the latest evidence. This reduces medico-legal errors and improves diagnostic accuracy. Additionally, exposing students to research early in their undergraduate study can nurture their interest in research and encourage them to become tomorrow’s scientists. At the same time, undergraduate medical research improves the curriculum vitae of a student, but this should not be the primary aim for a medical student to get involved in medical research.

To encourage more medical schools to introduce research into their undergraduate medical curriculum, several strategies can be considered. Firstly, introducing research elective programmes whereby pre-clinical students will do research in a group during a semester break as part of the elective programme may prove advantageous. Secondly, encouraging medical students to participate in scientific research competitions at the national or international level indirectly encourages them to do research. Students who have done research before can share their experiences with their friends and juniors to improve their understandings on research. More funds should be allocated to medical schools, so that they could employ experienced lecturers to teach the students on research. On top of that, financial support is also needed to help students gain access to the latest articles and guidelines. This allows them to have the opportunities to read the latest evidence and further increase their interest in research.

In conclusion, my first research gave me a very memorable experience. From the original idea to participation in an international medical student conference and the publication of the research report in an international journal, the journey was not easy but nonetheless enjoyable. I learned how to conduct research and meet new friends. My communication, leadership, and writing skills were improved after the research experience. Even though the process was tough, I would still recommend all medical students worldwide to try to conduct research at some stage of their student life to broaden their view of life and gain new experiences.

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Chronic Fatigue Syndrome: Where Do Your Views Lie? An Experience from a UK Medical Student

Rebecca L. Lambson.

The Experience

Chronic fatigue syndrome (CFS), also known as myalgic encephalomyelitis (ME), affects 0.2-2% of the United Kingdom (UK) population.1-3 Consequently, as junior doctors, we are likely to encounter someone with CFS/ME on a regular basis. Why, then, is this condition frequently shrugged off as fictitious among us, the medical profession? There are even disputes between our profession and patient groups regarding changing its name with the hopes of ridding the stigma associated with it.4 How striking is it that some patients feel that altering its name will change how they are treated? This article describes the attitudes I have witnessed towards CFS/ME within my four years as a UK medical student and reasoning as to why attitudes appear to be as they are.

CFS/ME is a debilitating condition characterised by at least six months of extreme and persistent fatigue, which is unrelieved by rest and is not attributable to a known cause (for example hypothyroidism).5-6 CFS/ME is said to be a diagnosis of exclusion, a default diagnosis made when no other cause of the fatigue can be found, despite thorough investigation. Clinical inclusion and exclusion criteria are used to aid the diagnostic process, such as the Fuduka criteria;6 however, a diagnosis of CFS/ME can still be seen as an unresolved problem by both the clinician and patient involved. This attitude that CFS/ME is a “last resort diagnosis” may be one reason why CFS/ME tends not to be highlighted in the medical world.

One of the great privileges of being a medical student is the variety of medical teams we get to encounter throughout our training. Much of what we see makes us strive to be as good as the doctors we have seen. It is these moments where we are filled with a sense of pride about the career we will be entering. Regretfully, there have been a few instances where doctors have felt ashamed of how situations surrounding CFS/ME were handled. I had been on a ward round whereby a raised eyebrow from a consultant portrayed the view of “it’s just yuppie flu” to colleagues. Could this be perpetuating the situation?

Another reason for the attitudes I have witnessed might relate to the lack of CFS/ME teaching at medical school. Whilst acknowledging how stretched medical curriculums are, for a condition with a similar prevalence to Parkinson’s Disease, we receive minimal teaching on CFS/ME. I argue that the addition of CFS/ME teaching would not be at the expense of other topics due to the large margin of overlap within teaching of core diseases. Furthermore, studies confirm that the number of pages within medical textbooks representing CFS/ME are far lower than for rarer conditions,7 despite us as junior doctors being much more likely to encounter CFS/ME. Does this lack of teaching portray CFS/ME as an unimportant condition?

A report on Scottish medical schools demonstrated that only two of the five (40%) schools mention CFS/ME within their curriculums (Available from: http://www.25megroup.org/Campaigning/ME%20in%20Parliament/scottish/ME%20Education%20in%20Scotland37.doc, updated 2014; cited 2015 Mar 17). Similarly, a survey on US medical schools found only 28.2% of schools included CFS/ME teaching in their curriculum.8 There is no available or published information regarding English medical schools on this matter. Therefore, despite being a common condition that profoundly affects quality of life, CFS/ME is massively underrepresented in medical school curriculums across the world.

Finally, doctors often thrash off of solving medical problems. For some, receiving test results which provide concrete answers underpins job satisfaction. Conditions such as CFS/ME have from patients attending a fatigue clinic, who described negative experiences. Furthermore, a discussion with some of my peers illustrated their views that patients with CFS/ME are not really ill. The sum of both patients’ and my own experiences suggests the problem is ingrained in many of our profession even at medical school. The health service within the UK is free at the point of access. This means that doctors are not paid according to the particular patients they see, suggesting there is no financial motive for these attitudes. Due to the hierarchical nature of medicine, a doctor’s views can influence the attitudes of junior team members. Could this be perpetuating the situation?

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diagnostic uncertainty; they are “medically unexplained” and do not fit into our neat box of diagnostics. Perhaps this is why CFS/ME is often not appropriately regarded within our profession. Could our own job satisfaction hinder patient care?

Having explored why CFS/ME appears to be disregarded generally, I propose it is due to a combination of factors. Firstly, social attitudes are passed among teams due to the hierarchical structure; secondly, there is little coverage at medical school; and finally, doctors are inbred problem solvers.

Where next for tomorrow’s doctors? Within the UK, the GMC take responsibility for “enhancing the quality of medical education programmes”,9 perhaps they need to re-examine this underachieved area. We need to stand up for CFS/ME by encouraging our universities to teach us about conditions with diagnostic uncertainty. Effective teaching has been demonstrated to improve attitudes towards CFS/ME.10 Has your training in CFS/ME been sufficient? In my education to date, I have witnessed significant examples of doctors lacking empathy for their CFS/ME patients. Personally, I feel adopting this viewpoint is counterproductive, and I am reluctant to be associated with doctors who do. We, as a profession, should not have discriminatory views on our patients, enabling them to be treated with the respect they deserve.

References
Ultrasonography as a Modern Teaching Support to the Anatomy Course: Is It Beneficial for Medical Students?

To the Editor,

The approach to evaluating anatomy teaching effectiveness has changed over time (from ancient Egypt through Baroque to modern times). In the 20th century, medical schools started to use first radiological images, such as roentgen images, during anatomy classes. Nowadays, computed tomographs, magnetic resonance images and ultrasonography are also widely used. At Mount Sinai School of Medicine in New York, new didactic methods, which included minimally invasive approaches, radiological imaging and plastinated prosections, are incorporated into anatomy courses for medical students. However, we should keep in mind that undergraduate medical curriculum, especially during the first year, is already overcrowded. Thus, every new supportive teaching method must have its efficacy carefully analyzed and scientifically proven before being introduced into medical schools.

Ultrasonography (US) is a cheap, easy-to-reach and safe supplement to the anatomy course. US practical classes can facilitate understanding of topographic anatomy. Students need to know the exact location of each anatomical structure in order to retrieve a proper US image.

In 2006, Rao and colleagues conducted a pilot study of integrating US curriculum into the first-year medical programme at the Wayne State University School of Medicine. They reported many advantages of their US courses, which pay special heed to the importance of knowing the basic US rules during the first year of studies. Subsequently, in 2014, Dreher and colleagues, in their research conducted on 269 first year medical students, proved that ultrasonography can be a valuable supplement to the musculoskeletal, thoracic, abdominal and neck anatomy lessons. They showed, on the basis of pre- and post-lesson surveys, that students significantly improved self-confidence with regard to their anatomical knowledge. Additionally, students were able to perform a basic US examination on their own following course completion.

Many works concerning the usefulness of US in teaching anatomy were conducted on the basis of questionnaires. All of them reported positive evaluations of the US classes by the students, although none of them compared the results of their studies with a control group. The only study trying to examine the positive influence of US on anatomy classes using a comparison group was performed by Knobe and colleagues in 2012. They proved that ultrasonography has a better effect on the understanding of anatomy compared to arthroscopy.

Based on the aforementioned studies, it seems that anatomy learning should be based not only on dissections, but also on complementary methods, such as US. It should be emphasized that works which have been published thus far concern only subjective opinions of the students. To reach definitive conclusions, long-term randomized controlled studies are needed in order to objectively compare US education with other learning modalities and obtain unambiguous results.

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Is Hepatorenal Syndrome a Diagnosis for the Emergency Physician?

Acute kidney injury (AKI) in the patient with decompensated liver disease is common and signifies a poor prognosis. Hepatorenal syndrome (HRS) is a potential cause of AKI in patients with acute or chronic liver disease. In the International Journal of Medical Students, Tan et al reported a case of HRS diagnosed in the emergency department in a patient who presented with fluid overload and AKI on a background of cryptogenic liver cirrhosis. The accompanying review on the topic was an excellent aspect of the article.

The diagnostic possibilities in a cirrhotic patient are broad and several are deserving of prompt treatment, including hypovolemia (such as from gastrointestinal bleeding), sepsis, and nephrotoxic drugs. A prognostic study of 562 patients with AKI and cirrhosis implicated HRS in only 13%, while infection was responsible for 46%. Indeed, it has been suggested that the diagnosis of HRS is one of exclusion. The initial management requires adequate intravascular volume expansion with albumin infusion for 2 days. HRS is then suspected when there is no response, and treatment for such should be considered then. This consists of the administration of vasoconstrictors, such as terlipressin (a vasopressin analogue) or alpha-adrenergic agents (e.g. noradrenaline and midodrine), combined with albumin. Ischemia may result from the use of vasoconstrictors and thus caution must be exercised, especially in patients with or at risk for coronary artery disease, peripheral vascular disease, or cerebrovascular disease. In addition, the use of vasoconstrictors in acute tubular necrosis, pre-renal azotemia or obstructive AKI could further aggravate renal function in this group of patients. In this regard, the role of the emergency physician (EP) in diagnosing and managing HRS is traditionally limited.

A survey of bibliography databases including Pubmed with MeSH terms “Hepatorenal syndrome” and “Emergency Medicine” yielded few studies supporting the diagnosis of HRS in the emergency department. However, this may change in the future as novel biomarkers such as neutrophil gelatinase-associated lipocalin (NGAL) allow early differentiation of different causes of AKI in the cirrhosis patient.

The authors should be commended on providing an interesting perspective. The EP must have a working knowledge of HRS and its prognostic significance given the appropriate clinical context, but in most systems of care would not have sufficient clinical information to establish a diagnostic certainty beyond the treatment threshold. We put forth the idea that EPs have a more important role in such cases to exclude or treat precipitating or co-existing emergencies including gastrointestinal bleeding and spontaneous bacterial peritonitis, and to initiate intravascular volume expansion.

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