A SYSTEMIC REVIEW OF VITAMIN B12 DEFICIENCY

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ABSTRACT

Background: **Vitamin B12 or cobalamin deficiency has a prevalence of 12-20% in the general population and its incidence is expected to increase as the elderly population grows. Clarity on its criteria for diagnosis, evaluation and management will be useful to family physicians. A review on vitamin B12 deficiency, its evaluation and management has been attempted in this paper.**

Methodology: **A PubMed search of papers published in the last five years was conducted in early September 2007 on vitamin B12 deficiency for available guidelines and relevant full-text reviews. Full-text articles were also accessed through UpToDate and World Wide Web. 85 papers were short listed of which 27 papers were used for this review.**

Results: **High risk patient groups may be identified and include elderly, pure vegans, relatives of patients with pernicious anemia and patients with gastrectomy or small intestinal disorders. Food-cobalamin malabsorption and pernicious anemia account for majority of causes of vitamin B12 deficiency. It is associated with potentially serious complications such as related to neuropsychiatric conditions and hemolytic anemia. Clinical manifestations are mainly noted in neuropsychiatric evaluation, gastrointestinal and hematological systems. Hematological indices with classical megaloblastic changes may not be always present. There is no consensus on the definition of vitamin B12 deficiency state and is dependent on plasma cobalamin and its metabolites. Different cutoff points are adopted in various assays of plasma cobalamin. A level of less than 200 pg/ml (<148 pmol/L) is consistent with clinical vitamin B12 deficiency. Measurement of metabolites, methylmalonic acid and homocysteine and in recent years, holo-transcobalamin II assays may be use to support diagnosis of vitamin B12 deficient state in the presence of equivocal plasma cobalamin level and obvious clinical manifestation of deficiency. Management of subclinical vitamin B12 deficient state is not well defined. Parenteral route is the traditional treatment for vitamin B12 replacement. Oral preparations appear to be a suitable alternative, but may need monitoring to ensure compliance. Early treatment is crucial for neurological manifestation.**

Conclusions. **Family physicians need to be aware of a growing burden of vitamin B12 deficient state in the population. The challenge is to correctly identify this condition and adequately managed it.**

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Keywords: vitamin B12 deficiency, manifestations, investigations and treatment

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INTRODUCTION

Vitamin B12 deficiency is not an uncommon condition and the incidence is expected to increase as the elderly population grows[1,2]. Since the early 19th century, observations of anemia associated with neurological and gastrointestinal abnormalities were noted. Since then, progress has been made on its pathophysiology, its diagnosis, investigations and management. Classical megaloblastic anemia may not always be present even in obvious vitamin B12 deficiency state[3,44]. There is no consensus though made on the definition of vitamin B12 deficiency, its evaluation and treatment. Traditional replacement treatment is by parenteral route. Daily oral vitamin B12 administration could be a suitable alternative but needs monitoring to ensure compliance[3]. This article attempts to review especially available guidelines and authoritative full-texted journals to guide family physicians in the understanding and management of vitamin B12 deficiency.

METHODOLOGY

A PubMed search was conducted between 1-6 September 2007 for articles published in the last 5 years on Vitamin B12 deficiency, its causes, clinical presentation, laboratory evaluations and replacement therapy. The search strategy involved:

1. Keywords and search strategy: (causes of cobalamin) OR (vitamin b12 deficiency)
   Limits: added to PubMed in the last 5 years, published in the last 5 years, only items with links to full text, only items with links to free full text, only items with abstracts, Humans, Clinical Trial, Meta-Analysis, Practice Guideline, Randomised Controlled Trial, Review, Consensus Development Conference, Consensus Development Conference, NIH, Guideline, Journal Article, English, Core clinical journals, Systematic Reviews, MEDLINE. A total of 213 articles were retrieved. Of these, 22 relevant articles were shorlisted and 3 full-text articles and 6 abstracts were reviewed.
2. Keywords and search strategy: (clinical presentation) AND (cobalamin) OR (vitamin B12 deficiency)
   Limits: added to PubMed in the last 5 years, published in the last 5 years, only items with links to full text, only items with links to free full text, only items with abstracts, Humans, Clinical Trial, Meta-Analysis,

Practice Guideline, Randomised Controlled Trial, Review, Consensus Development Conference, Consensus Development Conference, NIH, Guideline, Journal Article, English, Core clinical journals, Systematic Reviews, MEDLINE. A total of 98 articles were retrieved. Of these, 19 articles were selected and 7 full-text articles and 7 abstracts were reviewed.

3. Keywords and search strategy: ((laboratory evaluations) or (investigation)) AND ((cobalamin) OR (vitamin B12 deficiency))
   Limits: added to PubMed in the last 5 years, published in the last 5 years, only items with links to full text, only items with links to free full text, only items with abstracts, Humans, Clinical Trial, Meta-Analysis, Practice Guideline, Randomised Controlled Trial, Review, Consensus Development Conference, Consensus Development Conference, NIH, Guideline, Journal Article, English, Core clinical journals, Systematic Reviews, MEDLINE. A total of 104 articles were returned. Of these, 24 articles were selected and 7 full-text articles and 6 abstracts were reviewed.
4. Keywords and search strategy: (replacement strategy) AND ((cobalamin) OR (vitamin b12 deficiency))
   Limits: added to PubMed in the last 5 years, published in the last 5 years, only items with links to full text, only items with links to free full text, only items with abstracts, Humans, Clinical Trial, Meta-Analysis, Practice Guideline, Randomised Controlled Trial, Review, Consensus Development Conference, Consensus Development Conference, NIH, Guideline, Journal Article, English, Core clinical journals, Systematic Reviews, MEDLINE A total of 97 articles were retrieved. 17 articles were selected and 9 full-text articles and 2 abstracts were reviewed.

Full-text articles were also accessed through UpToDate and the World Wide Web for the same period of PubMed search. A total of 27 full-text articles were used for this review.

RESULTS

SOURCES OF COBALAMIN (VITAMIN B12)

The main natural source of vitamin B12 for human are animal products. B12 cannot be manufactured by plants or animals. Animal products derived its B12 content from bacterial sources[4,5]. It is thought that only bacteria manufacture B12. Animal products would include egg, meat, fish and dairy products. These dietary sources of Vitamin B12 are usually in the forms of methyl, deoxyadenosyl- and hydroxocobalamin[5].

The synthetic forms of B12 supplements (hydroxocobalamin and in particular cyanocobalamin)[5] available in fortified cereals or multivitamins are other possible sources[6]. Methylcobalamin is also available as nutritional supplements. Pseudovitamin B12 found in certain organisms such as Spirulina spp are B12-like substances that do not confer biological activity in human[7].

Daily requirement of vitamin B12

The Food and Nutrition Board of the Institute of Medicine of the National Academy of Sciences has recommended *the daily required amount to be 2.4 mcg/day for male and female 14 years or older. Higher intake is necessary with states of pregnancy, lactation, thyrotoxicsis, liver disease and other medical conditions. The requirements for children are also listed in its website*[6].

Synthetic B12 supplements could be recommended for the vegans and the especially the elderly, as it has been found that up to 30 per cent of 50 years old and older adults may have atrophic gastritis, increased intestinal bacterial growth and impaired B12 absorption[6]. Daily requirement of up to 5 mcg per day has been recommended by the American Society of Geriatrics, the US Food and Drug Administration and the Association Francaise de Sécurité Sanitaire des Aliments[1].

Total body stores of vitamin B12 are 2-5 mg, of which, half is stored in the liver[4]. With a efficient reabsorption of over 75% of biliary excreted vitamin B12 by the enterohepatic circulation and low urinary loss of the vitamin there may be a delay of 5-10 years before onset of clinical illness if due to insufficient intake and much earlier if due to malabsorption[2].

Cobalamin Absorption

Cobalamin absorption[1,8,9] is dependent on multiple processes. Acid and pepsin in stomach liberate cobalamin bound to protein with subsequent binding of cobalamin to R factors present in saliva and gastric juices. Within the duodenum, pancreatic proteases free cobalamin from binding to R factors. Subsequent rapid binding of free cobalamin to intrinsic factor(IF) secreted by the gastric parietal cells. Uptake of cobalamin-IF complex is through specific cobalamin-IF receptors across ileal mucosal brush border. Within the enterocytes, cobalamin is removed from IF and transported across the enterocytes into the portal circulation bound to a transport molecule, transcobalamin II. Cobalamin-transcobalamin II complex is absorbed into target cells by endocytosis. Intracellular lysosomal enzymes degrade transcobalamin II freeing cobalamin. While 99% of ingested cobalamin required IF for absorption, about 1% of free cobalamin could be passively absorbed in the terminal ileum[2,4].

Within cells, cobalamin is enzymatically converted into its two active coenzyme forms, methylcobalamin and adenosylcobalamin[1]. With vitamin B12 deficiency, serum methlymalonyl-CoA and its metabolite methylmalonic acid (MMA) increase as a result of reduced adenosylcobalamin production. Homocysteine level accumulates as a result of failed methionine synthesis that uses cobalamin as a cofactor (cobalamin converts to methylcobalamin in the process)[2].

EPIDEMIOLOGY

The true prevalence of vitamin B12 deficiency is unknown and a figure of 20% of general population had been quoted[1]. The incidence increases with age[9]. A prevalence of 12% among community dwelling elderly had vitamin B12 deficiency in the Framingham study. The prevalence is even higher among

the institutionalised or who are sick[1]. In Britain, community dwellers (included those in nursing home) who were 60 years or older were diagnosed to have vitamin B12 deficiency that affects about 5% people in the 64-74 years age group and more than 10% in the group older than 75 years or older[10].

Small studies in Asia setting had reported high incidence of vitamin B12 deficiency. Asian Indians referred to two cardiology clinics[11] in India reported 75% of their 204 subjects with metabolic signs of vitamin B12 deficiency. In another Indian study, a hospital population radioassay study with a cutoff of 200 pg/mL found a vitamin B12 deficiency in 0.88% of patients, with borderline values in 3.8%[4]. Pernicious anemia was the main cause of megaloblastic anemia among 52 Chinese patients attending a regional Hong Kong hospital (mean age 73.5 years old)[12]. Local prevalence of vitamin B12 deficiency is not known.

CAUSES OF VITAMIN B12 DEFICIENCY

Pernicious anemia and food-cobalamin malabsorption (especially from atrophic gastritis) are common causes in especially elderly patients and reported in 15-20% and > 60% of the latter patient group respectively[1].

1. **Pernicious anemia(PA)**

   This is an autoimmune condition with genetic predisposition. Autoantibodies against gastric intrinsic factor(IF) are present in up to 70% patients with PA. Autoantibodies are present against gastric parietal cells with consequent chronic atrophic gastritis and state of achlorhydria [3].

   Chronic atrophic gastritis in PA has a 3 times increased risk of intestinal-type gastric ulcer and 13 times of gastric carcinoid tumors[4,13]. Pernicious anemia has also been associated with hyper/hypo-thyroidism and other polyglandular failure[14] .

   Pernicious anemia may be suspected in patients with macrocytic anaemia and low B12 levels[14] in the following circumstances:
   - Whites of northern European ancestry though it has been found to occur in other races.
   - Adult patients in 40-70 year old age group; congenital pernicious anemia occurs in children less than 2 years old.
   - Association with other autoimmune diseases – thyroid disease, vitiligo, type 1 diabetes mellitus, Addison disease and ulcerative colitis.
   - Macrocytic anemia is present with autoantibodies against intrinsic factors and gastric parietal cells.

2. **Gastrointestinal conditions**

   Food-cobalamin malabsorption arises as a result of inability to release cobalamin bound to dietary proteins or from intestinal transport proteins and occurs especially in the presence of reduced gastric acid secretion[1,8,13]. Food-cobalamin malsbsorption accounts for the bulk of vitamin B12 deficiency and the causes include:
   - *Gastric – atrophic gastritis with reduced acid production, H Pylori infection[15], gastrectomy, bariatric procedures[16]*
   - *Intestinal – bacterial overgrowth (may be related to antibiotic treatment or in blind loop syndrome)*
   - *Pancreatic exocrine failure*
   - *Long term ingestion of biguanides, antacids, H2 receptor blockers, proton pump inhibitors*
   - *Chronic alcoholism*

   Cobalamin malabsorption arises from impaired absorption or altered intestinal utilisation[1]. *Malabsorption conditions have been associated with gastrectomy, Crohn's disease, TB ileal disease, small bowel resection, fish tapeworm infestation and severe pancreatic disease.*

3. **Impaired dietary intake**

   Contributing factors are:
   - Strict vegans[17]
   - Women who are only moderate vegans and are entering into high cobalamin requirement states such as pregnancy and lactation[18]
   - Impaired intake or ingestion because of psychosocial reasons, edentulous state, or functional disability

4. **Hereditary causes**

   Rare causes[8,19] include:
   - Production of qualitative abnormal IF
   - Decreased uptake of IF-cobalamin complex in *juvenile megaloblastic anemia*
   - Congenital deficiency of transcobalamin (carrier protein)
   - Congenital enzyme deficiencies in homocystinuria and abnormality of methionone synthesis

MANIFESTATIONS OF VITAMIN B12 DEFICIENCY

Symptoms and signs of vitamin deficiency exhibit in multi-organ systems[20]. These are attributed mainly to hematologic, gastrointestinal and neuropsychiatric and changes.

1. **Hematologic manifestations**

   A macrocytic anemia is typically present. However, there are patients who may only have low B12 levels without changes in the hematological indices. The details are described in the next section.

2. **Gastrointestinal manifestations**

   Manifestations include glossitis(beefy, smooth due to loss of papillae and painful tongue), stomatitis, diarrhea, constipation, anorexia, weight loss[14]

3. **Neuropsychiatric manifestations**[4,21]

   Manifestations include
   - Myelopathy with presentation of subacute combined

degeneration of dorsal (posterior) and lateral spinal columns due to myelin defect
  - Neuropathy is symmetrical, affects legs early
  - Begins with parathesia and ataxia associated with vibration and position sense loss
  - Progress to severe weakness, spasticity, clonus, paraplegia, incontinence
- Peripheral neuropathy
  - Motor-sensory polyneuropathy (parathesia, numbness, weakness)
  - Mononeuropathy (olfactory, and optic)
  - Autonomic neuropathy (incontinence, impotence)
- Central nervous system symptoms:
  Memory loss, irritability, dementia, personality changes and psychiatric conditions (depression, confusion)
- Neural tube defects are associated with low folate and vitamin B12[4]

These manifestations may not be associated with abnormal hematologic indices indicative of cobalamin deficiency and this dissociation reported in up to 28% patients with neuropsychiatric signs[4].

4. Other manifestations

- Cardiovascular system – Tachycardia, congestive heart failure[4]
- Skeletal system – an increase in osteoporosis, hip and spine fractures due to suppression of osteoblastic activity has been reported[8]
- General – Lemon-yellow waxy pallor, premature whitening of hair, flabby bulky frame, mild icterus, and blotchy skin pigmentation in dark-skinned patients[4]
- Pediatric manifestations of vitamin B12 deficiency include failure to thrive, delayed development, movement disorders and megaloblastic anemia[20]
- The role of Vitamin B12 deficiency in association with hyperhomocysteinemia and atherosclerosis promotion leading to cardiovascular events[9] and dementia[22] needs further evaluation.

LABORATORY EVALUATIONS IN VITAMIN B12 DEFICIENCY

1. Common hematologic indices performed

These include anemia and peripheral blood smear may reveal oval macrocytes, anisocytosis, poikilocytosis and Howell-Jolly bodies. The mean corpuscular volume (MCV) is usually greater than 100 fL. The MCV correlates with estimated vitamin B-12 level[3, 4]:

- MCV of 80-100 fL (normal) has less than 25% probability of vitamin B12 deficiency
- MCV of 115-129 fL indicates a 50% probability
- MCV greater than 130 fL indicates a 100% probability

Other hematologic manifestations include[3,20]

- Megaloblastic changes are observed in all three hematopoietic cell lines
- Pancytopenia with leucopenia and thrombocytopenia reflecting severity of vitamin B12 deficiency
- Hemolytic anemia with elevation in serum bilirubin, lactic dehydrogenase, and low haptoglobin due to ineffective erythropoiesis
- Megaloblastic changes in bone marrow smear

Differential diagnosis of <u>common causes for macrocytosis include</u>[3]:
Folic deficiency, reticulocytosis, liver disease, hypothyroidism, hyperlipidaemia, erythropoietin usage, alcohol abuse, myelodysplastic syndrome, multiple myeloma and other plasma cell disorders, leukemia and aplastic anemia.

2. Definition of vitamin B12 deficiency state

<u>Plasma vitamin B12 assay</u>

There is no consensus on the level to define vitamin B12 deficiency due to variation in reference values associated with different assays (immunologic based chemiluminescence or radioassay)[3,13] . Use of the older microbiologic and radioisotopic methods had yield 97% sensitivity for clinical vitamin B12 deficiency and had stood up to scrutiny by independent studies. The results may be considered as follows[3,19]:

- a level of < 200 pg/ml (<148 pmol/L) is consistent with clinical vitamin B12 deficiency
- a level of 200 – 300 pg/ml(148-221 pmol/l) is a borderline result with possible vitamin B12 deficiency
- level greater than 300 pg/ml or 221 pmol/l as normal result.

Cobalamin assay may be affected in pregnancy, transcobalamin deficiency, folate deficiency, myeloma, medications and its specificity and sensitivity debatable[13,19,23].

Despite these issues, cobalmin assay is still considered the primary tool for diagnosis of vitamin B12 deficiency due to its relatively low cost and easy availability.

<u>Assay of specific metabolic markers</u>

Assays of serum and urinary MMA and plasma total homocysteine are useful in equivocal states of vitamin B12 deficiency, both clinical and biochemical, with greater sensitivity compared to plasma vitamin B12[9,13,14,19].

Serum and urinary MMA has similar sensitivity to plasma total homocysteine assay and higher specificity compared with plasma total homocysteine assay. The latter assay has high sensitivity but poor specificity. MMA could be confounded in the presence of congenital inborn error of metabolism disorders, renal impairment, volume contraction, and lab assays; homocysteine assay could also be affected by renal impairment, low folate level,

hypothyroidism, alcohol abuse, vitamin B6 deficiency and various medications.

These assays have the following downside, namely not readily available, costly, requiring more attention in sample collection and lack of consensus in reference values[13,16].

Plasma holo-transcobalamin II (holo-TCII)

Assay of plasma holo-transcobalamin II (holo-TCII) which measures the biologic active cobalamin-TCII complex had recently approved by FDA for diagnosis of B12 deficiency[13,24]. Claims of it as the earliest marker for vitamin B12 deficiency, issues of specificity and influences on holo-TCII need to be evaluated further[19].

Trail of therapeutic response with vitamin B12

Trail of therapeutic response with vitamin B12 may serve as a diagnostic tool for deficiency in doubtful cases[13,19,23] and should be accompanied by improvement in clinical picture or metabolic changes.

- **Vitamin B12 deficiency** state may thus be defined by presence of clinical manifestations with plasma cobalamin level below reference range, or by borderline cobalamin level with evidence of at least one raised metabolic markers or decreased holo-TCII level[13,19].
- A state of ***subclinical vitamin B12 deficiency*** may be identified based on absence of clinical disease but may be elicited through abnormal electrophysiologic neurologic abnormalities, low or low normal cobalamin level and at least one abnormal metabolic markers present[19].

3. Establish causes of vitamin B12 deficiency

The various causes of vitamin B12 deficiency should be identified and could be guided by history taking and initial clinical examination. Some of these evaluations may include:

- Antibodies to IF, which has a higher sensitivity and specificity than antibodies to parietal cells in making a diagnosis of Pernicious Anemia[3,14]
- Schilling test for detection of pernicious anemia is now of historical interest and replaced by serologic tests for presence of the autoantibodies antibodies[3,9]
- Other causes according to evaluations, for example Crohn's disease, TB infection of ileum.

TREATMENT IN VITAMIN B12 DEFICIENCY

Definitive treatment of underlying cause of vitamin B12 deficiency if possible. These may include treatment in blind loop syndrome, Crohn's Disease, TB ilealitis, fish tapeworm infection or improved nutrition intake. Pharmacological preparations available for vitamin B12 replacement include cyanocobalamin, hydroxycobalamin and methylcobalamin. There is no evidence of superiority of the use of the co-enzyme form, methylcobalmin[13].

Traditionally, parenteral vitamin B12 has been the definitive treatment and administered by intramuscular injections. Cyanocobalamin, in 1000mcg is the usual preparation. There is no consensus on injection regimes. The usual regime would have daily injections for a few days, followed by weekly injections, and subsequently, monthly to three monthly injections. The ultimate aim is to load the body with vitamin B12 and subsequently, for maintenance doses for a duration to be determined by the underlying causes[3,9,13]. These injections may involve visits to the clinics and cause patient discomfort.

Oral preparations, consumed daily, have been found to be reasonable alternative to injections. Cyanocobalamin in doses of 1000mcg and 2000mcg are the usual preparations that have been utilised to achieve hematological and neurological responses in vitamin B12 deficient patients[25,26]. Absorption of vitamin B12 is through passive diffusion in the ileum independent of intrinsic factor. Supplemental B12 absorption is unlikely to be affected by use of H2 receptors blockers and proton pump inhibitors or even gastrectomy[6, 9]. Time-released formulations are not advised[3].

Concerns have been raised about the effect of oral vitamin B12 treatment in patients with severe neurological manifestations, and parenteral route is preferred. Caution to be exercised when compliance to oral medication is an issue[13]. Oral vitamin B12 treatment has been adopted by British Columbia Ministry of Health (see website at http://www.health.gov.bc.ca/gpac/guideline_b12.html).

Nasal and sublingual preparations[3] are available but erratic absorption and patient acceptance are issues to be considered.

Blood transfusion may sometimes be needed in symptomatic patient with severe anemia presenting with heart failure.

Marked hypokalemia may develop during early treatment of cobalamin deficiency due to increased hematopoietic activity. Treatment of iron and folate deficiency needs to be considered especially in the early stage of cobalamin replacement[13]. No adverse effects have been reported with excessive use of vitamin B12[3].

Management of patients with subclinical vitamin B12 deficiency is not well defined[13]. One management option may be to initiate vitamin B12 replacement and monitor for clinical changes and to continue with treatment in the presence of such improvement. The second option would be to continue patient evaluation for progression of clinical state within a year.

MONITORING VITAMIN B12 RESPONSE

Clinical improvement, hematologic and metabolic responses should be monitored with initiation of vitamin B12 therapy[3]. Neurologic abnormality may improve slower over 6 months, and is dependent on extent and duration of disease and may be irreversible[19,21]. Diagnosis of cognitive impairment especially more than 6 months after onset may not improve significantly with vitamin B12 treatment[4,27].

Laboratory monitoring may elicit the following changes[3,4]

- Reticulocytosis response in 3-4 days
- Hemoglobin concentration rise within 10 days with full correction by 8 weeks
- Hypersegmented neutrophils improve by 10-14 days
- Decrease in serum methylmalonic acid and homocyteine within 5-10 days of stating vitamin B12 replacement.

Cobalamin level is not used as monitoring of adequate response to treatment as it rises invariably after replacement[19].

Patients with pernicious anemia may have an increase incidence of gastric or colorectal adenocarcinoma, but the data are not entirely conclusive[3]. Periodic fecal occult blood testing is an acceptable tool for screening for malignancy[3]. Endoscopic examination for gastric malignancy may be suggested every 5 years for the young patients with pernicious anemia[13].

CONCLUSIONS

Making a diagnosis of vitamin B12 deficiency requires an high index of suspicion is high risk groups of patients, namely, those at risk of pernicious anemia, gut surgery, the elderly, those with neurological, gastrointestinal, neuropsychiatric, and cardiovascular symptoms. In the child, B12 deficiency may be cause in failure to thrive. It needs to be noted that B12 deficiency may be missed because of the dissociation of clinical and biochemical findings. Early institution of vitamin B12 replacement is needed especially to reduce irreversible neurological injuries. The family physician as the first contact physician is well placed to make an earlier diagnosis and institute investigations and proper treatment.

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LEARNING POINTS

- **Vitamin B12 deficiency is not an uncommon condition.**
- **Certain patient groups at risk include elderly, pure vegans, relatives of patients with pernicious anemia and patients with gastrectomy or ideal conditions.**
- **Potentially serious complications especially with neuropsychiatric conditions could occur.**
- **Hematological indices changes and plasma cobalamin may not be reliable in diagnosis of deficiency.**
- **Plasma MMA, plasma homocyteine and holo-TC II assays may be useful as adjunct.**
- **Oral vitamin B12 replacement therapy could be an alternative to the traditional parenteral route, but monitoring for improvement is needed.**

CASE STUDY: MYOTONIC DYSTROPHY

A 49-year-old lady with a sad, lifeless sleepy expression and inability to walk

Dr Farhad Fakhrudin Vasanwala, Dr Matthew Ng, Dr Lee Kheng Hock

CASE PRESENTATION

Madam P, 49-year-old housewife, was admitted to SGH FMCC on 1/3/2008 with a fever of 38 degrees Celsius and left leg swelling for the past 2 days. She did not experience any pain. Clinical features are consistent with cellulitis of the left leg and she was treated with antibiotics.

During the clinical ward round, Madam P was noted to have a hatchet look (sad, lifeless and sleepy expression). She was also unable to walk and was wheelchair bound, without any history of trauma. Further questioning revealed that she had progressive lower limb weakness since her 30s. She was initially investigated in the 1970s at Tan Tock Seng Hospital. She had a muscle biopsy done and she was told that she had "muscle weakness". She subsequently defaulted from follow up. Madam P married at the age of 27-year-old, delivered her first baby at age 31. She underwent a caesarian section at Mount Elizabeth Hospital as she was unable to push out her baby. Since then, over the decades, she noticed progressive lower limb weakness, resulting her being unable to stand from the sitting position for the last 4 years.

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PAST MEDICAL HISTORY

She had a past medical history of:

- Lower limb swelling and wound debridement for narcotizing fascitis in May 2002 at SGH. On reviewing the anesthesia charts she was noted to have a prolonged recovery period after the anesthesia[8,9].
- Chronic duodenal ulcer diagnosed via oesophago-duodenoscopy (OGD) in 2002. She underwent triple therapy with resolution of symptoms.
- Post RIA hypothyroidism for Grave's Disease in the 1980s.
- Left lower limb deep vein thrombosis in 1989.

CLINICAL EXAMINATIONS

On examination, she had a left lower limb swelling with a fluctuant mass 3x3 cm over the previous old debridement scar, accompanied with surrounding erythema and swelling. Tinea pedis was present in between web space of the left third toe.

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Her cardiovascular, respiratory, and abdominal examination was unremarkable. She had a blood pressure of 110/75 mmHg, pulse rate 90 per min, and respiratory breaths 15 per min. Clinically, she was afebrile and there was no pallor of the conjunctiva. Madam P was orientated to time, place, and person. She was noted to have frontal balding and dysarthria.

Neurologically, her pupils were equal and reactive to light. She had bilateral 7th lower motor neuron lesions accompanied weakness and bilateral ptosis. Her range of eye movement was normal. There were no cerebellar signs. Motor power was 4/5 for her upper limbs and 2/5 for her lower limbs. Her sensation and proprioception were intact. No reflexes were elicited for both her upper and lower limbs including reinforcement. Her jaw jerk was present. There was no winging of her scapular. Plantars were down going for both her lower limbs. Percussion myotonia was present.

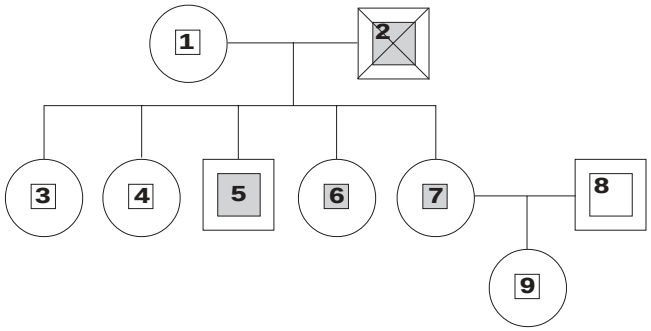
SOCIAL HISTORY

Madam P does not smoke nor drink. She is wheelchair bound. At home, she moves around the floor on a plate with rollers. Madam P is unemployed and currently stays with her disabled brother and sister. Her mother is the main caregiver. She is separated from her husband. Her house has no lift landing and has only squatting toilets.

FAMILY HISTORY

Legend

1: Madam P's mother (asymptomatic) now in her 80's
2: Madam P's late father, died in his 50s (symptomatic but intelligent)
3: Youngest sister, aged 44 years (asymptomatic)
4: Second youngest sister, aged 47 years (asymptomatic)
5: Madam P's brother, aged 53 years (symptomatic and intellectually challenged)
6: Third youngest sister, aged 48 years (symptomatic and intellectually challenged)
7: Madam P, currently aged 49 years (symptomatic but intelligent)
8: Madam P's husband, in good health
9: Madam P's 19-year-old daughter, her genetic destiny = ?



Questions

1. **Based on the above history and clinical examinations, what is the diagnosis?**
   a. **Myotonic dystrophy**
   b. **Becker muscular dystrophy**
   c. **Emery-Driefuss dystrophy**
   d. **Limb-girdle muscular dystrophy**
   e. **Congenital muscular dystrophy.**
2. **What is the pattern of inheritance?**
   a. **Autosomal recessive**
   b. **Mutifactorial**
   c. **Sex-linked recessive**
   d. **Autosomal Dominant**
   e. **Sporadic.**

CASE DISCUSSION

Madam P has Myotonia Dystrophy. This autosomal dominant disorder is among the most common forms of adult onset muscular dystrophy. However, it is more than simply a muscular dystrophy per se, since affected individuals may show cataracts, cardiac conduction abnormalities, infertility, and insulin resistant. As a consequence of its multisystemic nature, affected individuals can be presented to the family physician and different specialists before they are diagnosed.

Madam P was referred to neurologists who suggested nerve conduction study, electromyography and genetic counselling. Nerve conduction study of right upper and lower extremities showed borderline low CMAPs (compound muscle action potential amplitudes). Needle electrode examination of multiple muscles showed abundant myotonic potentials in all muscles tested.

TREATMENT AND MANAGEMENT IN THE WARD

Madam P was treated for left lower limb cellulites with oral antibiotics. The infection started to clear on the 7th day and she was given a total of 14 days of antibiotics. Miconazole cream was applied to her fungal infection in between her toes.

Madam P was referred to the occupational therapist and physiotherapist. She wished to be able to stand and walk again. However, these professionals felt that it may be more realistic and functional to aim for transfer and wheelchair mobilisation. As she had upper limb weakness that impaired her transfers, they felt that she might benefit from rehabilitation at the community hospital for upper and lower limb strengthening and transfer training.

Genetic counselling accompanied with relevant blood investigations was arranged at National Neuroscience Institute (NNI) after counselling was given to patient and her 19-year-old daughter.

The following investigations was done during admission:

Investigations	Results		Normal values
Creatine Kinase	34	U/L	38-164
Aldolase	5.9	U/L	2.0-12.0
Protein	57	G/L	62-82
AST	59	U/L	15-33
ALT	48	U/L	7-36
Albumin	28	G/L	37-51
Bilirubin, Total	12	UMOL/L	3-24
Alkaline Phosphatase	122	U/L	32-103
Hemoglobin	13.0	G/DL	12-16
WBC	9.8 $x10^9$/L		4.0-10.0
Platelets	259 x 10^9/L		140-440
ESR	33	MM/HR	3-15
CRP	106	MU/L	0.2-8.8
Gamma GT	97	U/L	7-39
Glucose fasting	4.9	MMOL/L	3.9-6.0
Free Thyroxine	10.3	PMOL/L	9.6-19.1
TSH	4.14	MU/L	0.36-3.24
Urine protein	Negative		
Blood cultures	Negative		
Electrocardiogram	Normal sinus rhythm		
Chest X-Ray	Normal		

TOPIC DISCUSSION: MYOTONIC DYSTROPHY[1]

Myotonic Dystrophy is also known as Dystrophica Myotonica (DM). The condition is composed of at least two clinical disorders with overlapping phenotypes and distinct clinical molecular genetic defects: Myotonic Dystrophy type 1 (DM1), the classic disease originally described by Steinert, and Myotonic Dystrophy type 2 (DM2), also called Proximal Myotonic Myopathy (PROMM).

Clinical Features

The clinical expression of Myotonic Dystrophy varies widely and involves many systems other than muscle. Affected patients have a typical hatchet faced appearance due to temporalis, masseter and facial muscle atrophy and weakness. Frontal balding is characteristic of men with the disease. Neck muscles, including the flexors and sternocleidomastoids, and distal limb muscles are involved early. Weakness of the wrist extensors, finger extensors, and intrinsic hand muscles impairs function. Ankle dorsiflexor weakness may cause foot drop. Proximal muscles remain stronger throughout the course, although preferential atrophy and weakness of quadriceps muscles occur in many patients. Palatal, pharyngeal, and tongue involvement produce a dysarthric speech, nasal voice and swallowing problems. Some patients have diaphragm and intercostals weakness, resulting in respiratory insufficiency[5,6].

Myotonia, which usually appears by the age of 5, is demonstrable by percussion of the thenar eminence, the tongue and the wrist extensor muscles. Myotonia causes a slow relaxation of the handgrip after a forced voluntary closure. Advanced muscle wasting makes myotonia more difficult to detect[7].

Cardiac disturbances occur commonly in patients with DM1. ECG abnormalities include first-degree heart block and more extensive conduction system involvement. Complete heart block and sudden death can occur[5,10]. Congestive heart failure occurs infrequently, but may result from cor-pulmonale secondary to respiratory failure. Mitral valve prolapse also occurs commonly. Other associated features include intellectual impairment, hypersomnia, posterior subscapular cataracts, gonadal atrophy, insulin resistance, decreased esophageal and colonic motility.

Congenital myotonic dystrophy is more severe form of DM1 and occurs in approximately 25% of infants of affected mothers. It is characterised by severe facial and bulbar weakness, transient neonatal respiratory insufficiency, and mental retardation.

DM2, or PROMM, has a distinct pattern of muscle weakness affecting mainly proximal muscles. Other features of the disease overlap with DM1, including cataracts, testicular atrophy, insulin resistance, constipation, hypersomnia, and cognitive defects. Cardiac conduction defects occur, but are less common, and the hatchet face and frontal baldness are less consistent features. A very striking difference is the failure to identify a congenital form of DM2.

Laboratory Features

The diagnosis of Myotonic Dystrophy can usually be made on the basis of clinical findings. Serum CK levels may be normal or mildly elevated. EMG evidence of myotonia is present in most cases. Muscle biopsy shows muscle atrophy, which selectively involves type 1 fibers in 50% of the cases. Typically increased numbers of central nuclei can be seen. Necrosis of muscle fibers and increased connective tissue, common in other muscular dystrophies, do not usually occur in myotonic dystrophy.

Genetic Considerations

DM1 and DM2 are both autosomal dominant disorders. New mutations do not appear to contribute to the pool of affected individuals. DM1 is transmitted by an intronic mutation consisting of an unstable expansion of CTG trinucleotide repeats in a serine-threonine protein kinase gene (named DMPK) on chromosome 19q13.3. In general the severity of DM1 type phenotype correlates with the number of CTG repeat size, but there is considerable variability:

- Individuals with repeat size of 35 to 49 are asymptomatic.
- Mutations of 50 to 150 CTG is associated with mild disease, typically characterised by cataracts and mild myotonia[2,3].
- Longer repeats in the range of 100 to 100 are seen in individuals with classical myotonia (onset between the age of 12 to 50) with muscle weakness, wasting, myotonia, cataracts, cardiac conduction defects. The life span of these patients may be reduced.
- With CTG repeat length of 500 to 2,700, the Myotonic Dystrophy will manifest at birth with infantile hypotonia, respiratory distress and mental retardation.

The unstable triplet repeat in Myotonic Dystrophy can be used for prenatal diagnosis. Congenital disease occurs almost exclusively in infants born to affected mothers[4]; it is possible that sperm with greatly expanded triplet repeats do not function well.

DM2 has been linked to chromosome 3q13.3-q24. At this locus, a DNA expansion mutation consists of a CCTG repeat in intron 1 of the *ZNF9* gene. The gene is believed to encode an RNA binding protein expressed in many different tissues, including skeletal and cardiac muscle. In DM2 there is no definite correlation between repeat length and disease severity[2].

How the DNA expansion in DM1 and DM2 impairs function of the muscle and other cells is not well understood. They may alter expression of an adjacent protein kinase gene (DM1), inactivate an important RNA binding protein (DM2), or influence other neighboring genes. In both DM1 and DM2, the mutant RNA appears to form intranuclear inclusions composed of aberrant RNA.

Treatment

The myotonia in Myotonic Dystrophy rarely warrants treatment. There is no disease modifying therapy available, treatment is symptomatic. Phenytoin is the preferred agent for the occasional patient who requires an antimyotonic drug; other agents, particularly quinine and procainamide, may worsen cardiac conduction[7, 11]. Cardiac pacemaker insertion should be considered for patients with unexplained syncope or advanced conduction system abnormalities with evidence of second-degree heart block, or trifascicular conduction disturbances with marked prolongation of the PR interval. Molded ankle-foot orthoses help prevent foot drop in patients with distal lower extremity weakness.

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NURSE EDUCATOR PROGRAMME

Health Promotion Board

Why have a Nurse Educator Programme?

About 1 in 4 Singaporeans have at least 1 chronic disease, such as diabetes, hypertension and high blood cholesterol. The National Health Survey 2004 showed that almost 30% of known diabetics had unacceptable blood glucose control and half the known hypertensives had poor blood pressure control.

There is good evidence that, in addition to compliance with medication, lifestyle changes - e.g. regular exercise and healthy diets – are crucial to keep these conditions well controlled, and to prevent or delay the onset of life-threatening complications requiring expensive hospital admissions

In Singapore, most individuals with chronic diseases are managed by doctors in polyclinics and private practices. Most polyclinics have a Nurse Educator or Case Manager whose role is to support management of the chronic disease patient by providing counselling on self-management skills, and advice on nutrition, exercise and target setting.

The main aim of the Nurse Educator Programme that has been recently launched by the Health Promotion Board (HPB) is to make this type of resource available to GP clinics. With this in mind, the programme has been launched, for a start, at 6 Community Centres :

- MacPherson CC – serving the MacPherson area
- Punggol Park CC – serving the Punggol South area
- Ulu Pandan CC – serving the Ghim Moh area
- Kebun Bahru CC – serving the Ang Mo Kio area
- Jalan Besar CC – serving the Jalan Besar area
- Marine Parade Community Club – serving the Marine Parade area

GPs (whether in these areas or not) may now refer their chronic disease patients for counselling and structured workshops by the Nurse Educators at these venues.

Who are the Nurse Educators and what do they do?

The Nurse Educators, recruited by the HPB, have undergone an intensive 10-day training course. The training curriculum includes a clinical update on the key chronic diseases – hypertension, diabetes and lipid disorders; Motivational Interviewing skills to help individuals change their health behaviour and self-management skills.

The Nurse Educators will conduct workshops in the CCs for those with chronic diseases (diabetes, hypertension or hypercholesterolemia). There will also be a workshop for individuals at risk of developing chronic diseases – i.e. those with a BMI > 27.5kg/m^2 and those who have Impaired Glucose Tolerance. In addition to imparting skills to manage chronic conditions better, the Nurse Educator will also work with the individual patient, in partnership with the GP, to set targets in relation to weight, blood pressure and HbA1c measurements.
Each workshop will consist of 3 structured sessions held over a period of 3 - 4 weeks. The total cost of the 3 sessions is $10.

The Nurse Educators and you, the GP

refer your chronic disease patients for the workshops or for more information about this programme please call 6435-3221 or email **hpb_nurse_educator@hpb.gov.sg** or visit **www.hpb.gov.sg/chronicdisease/nep** In addition to empowering individuals with chronic diseases to make better lifestyle choices, and manage their conditions better, the Nurse Educators will play a key role in ensuring that patients follow-up regularly with their GPs and adhere to treatment protocols. It is hoped that the Nurse Educators, working in close partnership with GPs and their patients, will make a difference in the management of chronic diseases in Singapore.