Gait Disturbance … of Red Herrings, Oranges, and Lemons – A Case of Missed Vitamin C Deficiency and Lessons Learnt

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ABSTRACT

Vitamin C deficiency resulting in scurvy, is considered to be a rare nutritional disorder in developed countries, thus leading to underdiagnosis with exposure to unnecessary investigations and delay in appropriate treatment. The wide myriad of clinical signs and symptoms with which vitamin C deficiency can present (including haematological, musculoskeletal and vague constitutional symptoms that overlap with other common medical conditions), also contributes to this diagnostic challenge. Despite scurvy being habitually thought to be present in children with neurodevelopmental conditions such as autism spectrum disorder, other important at-risk groups that frequently tend to be forgotten include children with persistent fussy eating behaviour, and children with abnormal vitamin C metabolism. We hereunder present a case of a 10-year-old boy who presented to an acute general hospital for further investigation with gait disturbance. The lack of detailed nutritional assessment on presentation in the first instance led to a missed diagnosis of vitamin C deficiency, thus exposing the child to a wide array of unnecessary investigations and treatments. The added perplexity to the case resulting from false positive results of investigations performed as part of this child's workup, is also discussed.

KEYWORDS

Scurvy; ascorbic acid deficiency; pediatrics; nutritional deficiency; child nutrition disorder; nutrition assessment; case report

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INTRODUCTION

Scurvy secondary to vitamin C deficiency is considered to be a rare nutritional disorder in developed countries given the high level of nutrition standard in general. Given the important role that vitamin C holds for skin and soft tissue function including iron absorption, wound healing, and collagen biosynthesis; vitamin C deficiency causes a myriad of clinical signs and symptoms. These include haematological abnormalities, musculoskeletal complaints, and an extensive range of other constitutional symptoms (1, 14, 15). Despite all the latter clinical manifestations, vitamin C deficiency can still be overlooked and challenging to diagnose clinically (2).

Vitamin C deficiency within the paediatric population tends to occur in children with very restrictive diets (3). This group of children includes those with neurodevelopmental disorders, in particular autism spectrum disorders. This tends to be a result of unbalanced nutritional intakes and food selectivity. However, it can also occur in children without clear autism or neurodisability (4). We hereunder present an interesting case of a child presenting with vitamin C deficiency and scurvy, with special emphasis on the importance of considering vitamin C deficiency as part of the differential diagnosis for children presenting with vague constitutional symptoms and gait disturbance. We thereby advocate nutritional and behavioural assessment to be included more routinely as part of clinical paediatric reviews, given the valuable information that these can provide as a clue to the diagnosis, thus avoiding unnecessary investigations.

CASE REPORT

A 10-year-old boy, presented to the paediatric outpatient clinic with a 2-month history of progressively worsening pain in his lower back, bilateral anterior thighs and both knees. As a result of his increasing pain, he eventually also developed an antalgic gait, with difficulty standing up from squatting, and difficulty with walking short distances unaided, requiring a wheelchair to mobilise. Symptoms were reported to be worse towards the end of the day. There was no history of fever, trauma, or recent illness. The child denied urinary or faecal incontinence.

On review, mild rectus femoris atrophy could be observed together with reduced power of grade 4– proximally in both lower limbs and 4+ proximally in the upper limbs using the Medical Research Council (MRC) muscle power scale. Tone, deep tendon reflexes and sensation were normal throughout. Lordotic posturing was noted on standing and mild tenderness could be elicited on the lower back. There were no signs of arthropathy. Gait was observed to be slow, antalgic, narrow based, but not clearly ataxic. There were no cerebellar signs elicited. Romberg sign was negative and cranial nerves were fully intact. Systemic examination was otherwise normal.

Initial blood investigations including a full blood count, inflammatory markers, rheumatology screen and creatine kinase levels were normal. Magnetic resonance imaging (MRI) of the head, spine and thighs was also performed to exclude intracranial, spinal, and demyelinating abnormalities and on initial review these were reported to be normal. Somatic symptom conversion disorder was also discussed as a possibility.

In view of normal initial investigation results, a watch-and-wait approach was initially adopted, with regular physiotherapy input and adequate analgesia cover. Despite this, minimal improvement was seen over the following days. At this point, the mother mentioned a similar episode of gait disturbance and lower limb pain associated with fleeting arthralgias mainly involving the knees, ankles and hip joints, two years earlier at 7 years of age which resolved spontaneously over a few months. The history given by the mother was unclear, but allegedly the episode had been attributed to post streptococcal reactive arthritis and/or viral myositis in view of influenza A being detected on his respiratory screen together with high anti-streptolysin O titre levels on his blood results. A missing part of her history involved the child's history of restricted food intake, mainly consisting of pasta, bread, butter, cereal, milk, water. Review of past investigations performed later during the child's stay in fact revealed that a low Vitamin C level of <1.0 mg/L had been noted, and the child was advised to start vitamin C supplementation, with which he had been uncompliant but was not further followed up given that his symptoms had gradually resolved spontaneously over a few weeks.

Given the child's clinical findings and lack of improvement, nerve conduction studies were performed which excluded large fibre polyneuropathy. Cerebrospinal fluid and serum blood antibody analysis (including anti-acetylcholine receptor antibodies, anti-muscle specific kinase and anti-ganglioside antibodies) revealed positive anti-ganglioside monosialic 2 and GD1b antibody titres. Therefore, despite the clinical picture not being consistent with classical Guillain-Barré syndrome and considering the small possibility of a sensory painful inflammatory polyneuropathy, it was decided to attempt a trial of intravenous immunoglobulin (IVIG) administration, again with only mild improvement noted.

Admission on the ward allowed for the opportunistic observation of the boy's behaviour and dietary eating habits. The child was noted to exhibit elements of anxious behaviour and strict routines. He was also noted by the nursing staff to refuse most food provided, including that prepared by the mum herself. Further in-depth questioning revealed a longstanding history of restrictive eating habits with very minimal intake of fruit and vegetables, which had not been previously highlighted as yet during the clinical reviews performed since his current admission. The mum also confirmed that the child had always had relatively strict behavioural routines and had been noted to become seemingly increasingly anxious during the past year, mainly related to school performance. The child had allegedly already been seen by the child development assessment unit in the past, but no definitive diagnosis had been made yet with regards to his behaviour and development.

Considering this new information, a full nutritional and endocrine screen including iron profile, thyroid functions tests, coeliac screen, folate, vitamins A, B12, C, and

D together with early morning cortisol were performed, and the child was started on iron and folate supplements in view of borderline low levels. Dietician and neuropsychology input was sought to improve nutritional intake and to identify possible problematic dietary habits including avoidant/restrictive food intake disorder (ARFID). Over the course of the next few days, his pain was noted to worsen with progressive lower limb proximal muscle weakness. He was also noted to develop a bilateral petechial symmetrical non-tender and palpable rash over both lower limbs together with gum ulcers, gum mucositis and skin bruising. In light of these new symptoms pointing towards possible scurvy, a course of oral high dose vitamin C was initiated. In the interim, vitamin C level results had become available which confirmed very low Vitamin C levels once again. Retrospective review of the MRI images revealed bilateral symmetrical high STIR signal and low T1 signal at the proximal and distal femoral metaphyses. Subtle widening of both distal femoral physis and similar changes throughout the pelvic rim were also seen. These changes were consistent with hypovitaminosis C. Prompt improvement was in fact seen after 3 days of starting treatment, with eventual complete resolution of symptoms over the following weeks.

Tab. 1 Figure showing clinical signs and symptoms of scurvy together with associated imaging, biochemical and haematological findings. Information adapted from Agarwal A. et al. (2015).

System	Clinical Manifestations and Investigation Findings
General	Irritability, Appetite loss, Fever, Iron deficiency anemia, Endocrine disturbance, Cytopenia, Acquired thrombocytopathy, Other vitamin deficiencies
Skin	Petechiae, Rashes, Poor wound healing, Bruising, Hyperkeratosis, Cork screw hairs, Alopecia
Bone (typically symmetrical)	Limp, Arthralgia, Myalgia, Joint swellings, Generalised limb swellings, Scorbutic rosary at costochondral junctions, Sternum depression
	X-ray: Groundglass bone appearance, Osteopenia with cortical thinning, Epiphyseal slipping, Radiodensity metaphyseal physis (line of Franke), Wimburger's sign (radiodense ring around epiphysis), Cupping of distal femoral metaphysis, Subperiosteal haemorrhage in long bones, Pelkan spurs
	MRI: Increased T2 signals in metaphysis of long bones, Widened and striated physis, Haemorrhages at site of fractures
	Ultrasound: bony irregularity, bulky subcutaneous plane, intramedullary/periosteal mass, subperiosteal haemorrhages, multifocal symmetrical signal abnormalities involving metaphyses with associated marrow enhancements
Gums	Swelling, Bleeding, Teeth loosening, Ecchymoses
Mood/psychological	Low moods, Behavioural disturbance

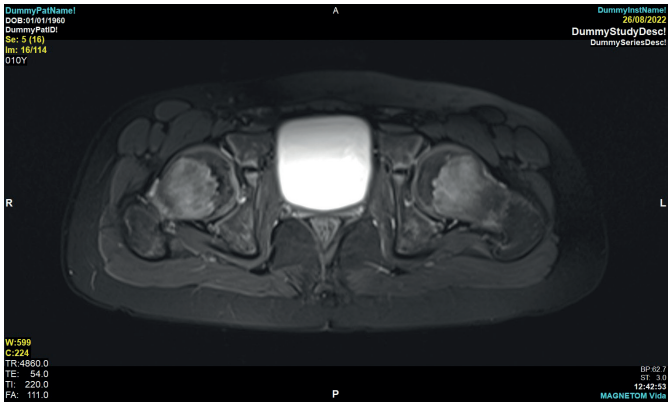

Fig. 1 Axial STIR imaging through both hips and thighs demonstrates the presence of bilateral symmetrical fluid signal characteristics (STIR hyperintense) affecting both the proximal and distal femoral metaphyses.

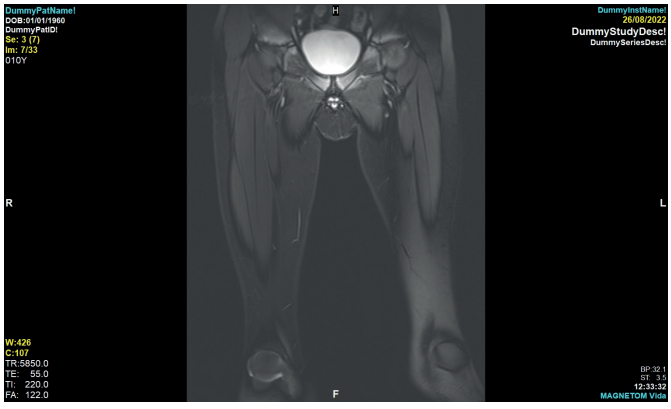

Fig. 2 Coronal STIR imaging through both hips and thighs demonstrates the presence of bilateral symmetrical fluid signal characteristics (STIR hyperintense) affecting both the proximal and distal femoral metaphyses.

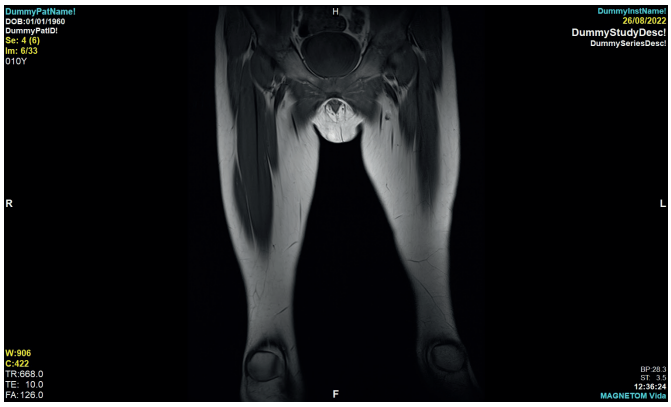

Fig. 3 Coronal T1 weighted view through pubic symphysis showing significant symmetrical marrow oedema like signal changes on either side, along with mild oedema like signal changes extending into the proximal left adductors.

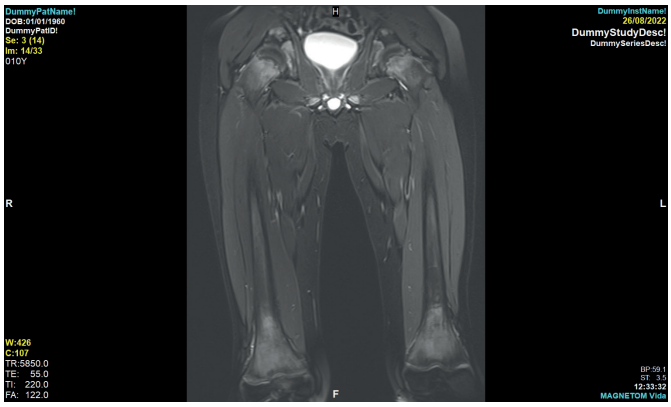

Fig. 4 Subtle, again symmetrical widening of both distal femoral growth plates was also appreciated, as best seen on coronal large FOV STIR imaging.

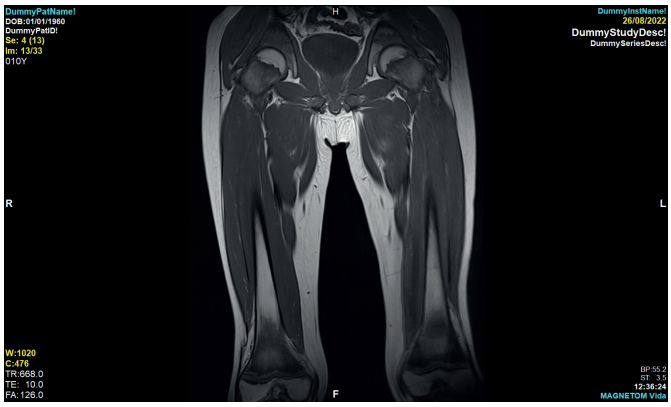

Fig. 5 Coronal T1 weighted imaging through both hips and thighs demonstrates the presence of bilateral symmetrical fluid signal characteristics (hypointense) affecting both the proximal and distal femoral metaphyses. No involvement of the long bone diaphyses or epiphyses was demonstrated.

DISCUSSION

Identification of a high-risk child is of ultimate importance in diagnosing scurvy. At risk groups include not only those with neuropsychiatric or developmental disorders, but also conditions which might affect absorption of water-soluble vitamins (e.g. gastrointestinal conditions), increased vitamin C requirements (e.g children on chemotherapy) or accelerated vitamin C catabolism (e.g conditions with iron overload such as haemochromatosis) (6, 7). Those following special diets including the ketogenic diet are also at risk of developing scurvy and require supplementation and monitoring.

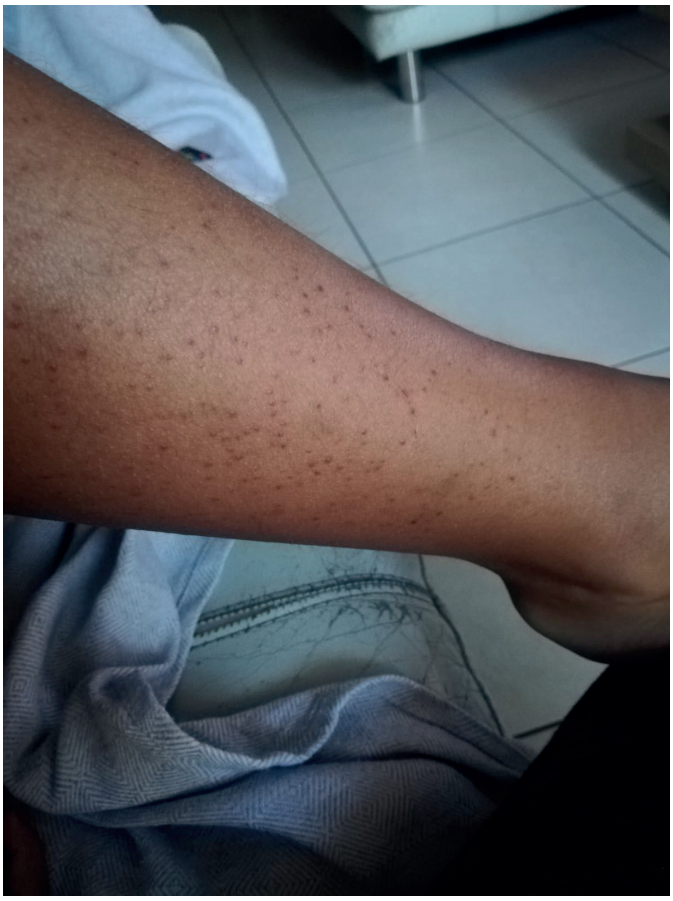

Fig. 6 Image showing the bilateral petechial symmetrical non-tender and palpable rash which had developed over both lower limbs, representative of a diagnosis of hypovitaminosis C.

Despite this, keeping in mind that scurvy can also occur in children without these specific risk factors, a detailed dietary history is important, particularly in unclear cases like the one described above. Fussy eating and selective eating habits are very frequently reported by parents within the paediatric population, especially in early childhood, and these are often disregarded given that this is common behaviour which resolves spontaneously in most. However, disregarded persistent unhealthy eating habits can lead to fundamental nutritional deficiencies and uncertainty regarding whether the abnormal eating behaviour was a cause or a result of an already present deficiency disorder, thus making early detection and treatment important (5). Moreover, given that scurvy is relatively easily treatable with adequate supplementation, timely diagnosis avoids unnecessary, expensive, and painful investigations for the child in question.

The first clinical manifestations of vitamin C deficiency usually appear after one to three months of inadequate intake. Moreover, the earliest signs and symptoms are usually very non-specific such as loss of appetite, low grade fever and malaise, which might not be concerning enough for the parents to seek medical advice. A further

additional diagnostic challenge results from the fact that signs or symptoms may present in an isolated and discontinuous manner, further misleading the clinician and thus contributing to diagnostic delay (8, 9).

Despite classical radiographic signs of scurvy on X-rays being well delineated in the literature, MRI findings are usually non-specific and inconsistent but may be evident earlier than those on X-rays (16–18). Retrospective review of MRI images in our case revealed bilateral symmetrical STIR hyperintensity at the proximal and distal femoral metaphyses, along with subtle widening of both distal femoral physis and similar changes throughout the pelvic bony ring, in keeping with a diagnosis of hypovitaminosis C as per below images.

In our case, the isolated detection of antiganglioside antibodies was misleading for the caring team, leading the team to believe that an immune-mediated nerve disorder was at play and the child was therefore unnecessarily treated with and exposed to IVIG. Monoclonal antiganglioside antibodies against ganglioside monosialic 1 are strongly associated with disorders affecting motor nerves, whilst polyclonal antibodies are found in a subset of patients with Guillain-Barre syndrome and its motor axonal variants. Like other laboratory methods, ganglioside antibody results have variable specificity and sensitivity. Their significance needs to be interpreted in the light of the clinical situation, thus avoiding arriving at a wrong diagnosis of Guillain-Barré Syndrome (GBS) (10, 11).

Measurement of serum vitamin C levels remains the gold standard for the diagnosis of scurvy, defined as levels lower than 2 mg/L. Serum vitamin C levels performed by laboratories are considered to be insensitive (despite being specific) given that they represent serum concentrations which do not always mirror the amount of ascorbic acid stored within body tissues. Moreover, recent vitamin C intake in any form can affect results. Therefore, a diagnosis of scurvy is based on a combination of clinical and radiological findings together with symptoms resolution on initiation of supplementation (12, 13, 21).

Vitamin C supplementation is a relatively cheap and effective medication. There are no standard treatment regimens in place, and individualised doses and treatment duration are advised depending on the severity of the case. Long term vitamin C supplementation is necessary for children who continue to show picky eating behaviour despite multidisciplinary intervention. Vitamin C daily requirements are up to 45 mg per day in children (19). Despite being relatively a safe medication given the body's limited capability to store vitamin C, toxicity from over supplementation has been reported in rare cases. This includes the formation of renal stones and calcium oxalate crystals within the renal tract (19). Commonly reported side effects usually involve gastrointestinal disturbances such as nausea, diarrhoea and abdominal pain, given the osmotic effect of unabsorbed vitamin C (20).

Dietician input in these cases is of utmost importance with reassessment of diet continuing well beyond the acute phase to avoid recurrence of deficiency. Communicating the cause of the child's deficiency and the necessary factors that need modification may be challenging, especially if the other family members have no deficiency and in cases of children with no clear neurodisability and challenging eating behaviour. This therefore necessitates educating and supporting both child and family throughout the entire process of treatment, recovery and follow up. Screening for concomitant vitamin and mineral deficiencies such as B12, folate, calcium, zinc and iron, is also encouraged given vitamin C's role in iron absorption and the high probability of coexistent vitamin deficiencies in children with restrictive food intakes.

CONCLUSION

Despite scurvy being considered to be rare in developed countries, nutritional education and assessment should be given more importance by clinical teams within their practice as part of routine care, with early liaison with dietetics teams for early intervention and early supplementation when indicated. Whilst special consideration should be taken for children within high-risk groups, vitamin C deficiency should be included within the list of differential diagnosis of children presenting with vague constitutional symptoms, haematological, musculoskeletal and mood disorders otherwise unexplained by routine investigations especially for perplexing clinical presentations.

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