Kinsbourne syndrome as complication of a *Mycoplasma pneumoniae* infection

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Keywords

Mycoplasma pneumoniae ; Kinsbourne syndrome ; opsomyoclonus-ataxia.

Abstract

Kinsbourne syndrome also known as opsoclonus-myoclonus-ataxia syndrome (OMAS) or more commonly dancing eyes and feet syndrome is a rare neurological disorder. This disorder affects children at an average age of 6 to 36 months. It associates opsomyoclonias and ataxia with behavioral disturbances. The pathophysiology is not well understood but seems to involve a dysimmunitary process; its etiology is often either paraneoplasic or parainfectious. Spontaneous resolution without immunomodulatory treatment has been described.

We describe here the case of a young five-year-old patient with Kinsbourne syndrome associated with *Mycoplasma pneumoniae* infection.

Case presentations

A five-year-old boy with no medical history was admitted to the emergency department with acute respiratory distress in a context of a week-long febrile upper respiratory tract infection. He was diagnosed with a left-sided bronchopneumonia complicated by a large pleural effusion (Figure 1A). The child was admitted to the intensive care unit where a pleural drain was placed and local fibrinolysis with urokinase was administered. The drain was removed after 9 days,. Non-purulent pleural fluid was drained and bacteriologic analyses were performed. *Mycoplasma pneumoniae* infection was confirmed in both initial blood samples and pleural fluid, first by serology and then by PCR. There was a significant clinical improvement after initial antibiotic therapy with amoxicillin/clavulanic acid (100 mg/kg/d) and clarithromycin (15 mg/kg/d) for 5 days followed by moxifloxacin (10 mg/kg/d) for 15 days (Figure 1B, 1C). On the 10th day of treatment, he presented with rapid, irregular and multidirectional eye movements consistent with opsoclonus, orthostatic ataxia, and myoclonus of the extremities, upper limbs and face. All of these new neurological symptoms disappeared at rest but were exacerbated during attention-grabbing tasks and activities. He also suffered from sudden behavioral changes and sleep disturbances (low frustration tolerance, frequent nocturnal awakenings). An extensive work-up was performed to exclude a neoplastic phenomenon such as neuroblastoma, but all investigations were negative (Table I).

It was thought that this opsoclonus-myoclonus-ataxia syndrome was provoked by the *Mycoplasma pneumoniae* infection, leading to the diagnosis of a rare entity: post-infectious Kinsbourne syndrome. The boy had a slow but favorable evolution with spontaneous resolution and complete disappearance of symptoms within 6 weeks after the initial presentation of the *Mycoplasma pneumoniae*.

Discussion

Mycoplasma pneumoniae is commonly responsible for upper and lower respiratory tract infections, and may be associated with extrapulmonary manifestations (e.g. meningoencephalitis, arthritis, hepatitis, myocarditis, pericarditis…) . Neurological manifestations occur in 0.1% of infections (1) . The diagnosis of a *Mycoplasma pneumoniae* infection is challenging due to the tedious culture conditions and the persistence of IgM antibodies long after acute infection. Culture remains the gold standard for confirming the diagnosis but due to its inherent difficulties, simpler tests have been developed. Among these, PCR (on blood or respiratory fluid) has a higher sensitivity than serology during the first two weeks of the disease, as antibodies tend to appear only one to two weeks after the onset of the infection. During this same period, the serologic response to detect an infection is positive in 23% to 56% using IgM detection versus 96% to 100% using PCR (2). Beyond this period, blood PCR detection remains positive in some patients, for up to 7 weeks after disease onset, with a transition to a clinically asymptomatic carrier state. The bacterial load gradually decreases over time. The rise in IgG levels is still used to confirm the infection, but is not helpful in acute clinical management as their titer usually rise in the convalescent phase after more than 40

Figure 1: Paraclinical work-up done in our patient and its results. Overview of the different differential diagnoses.

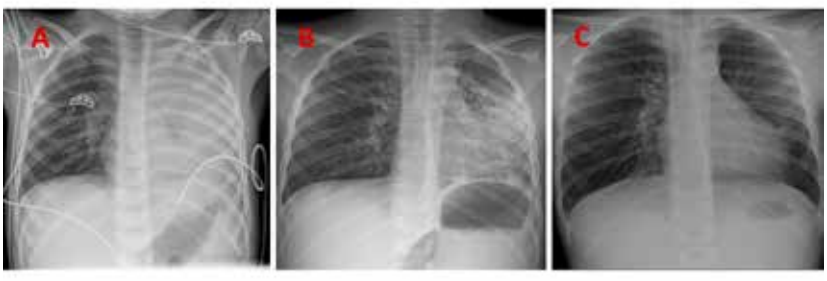

Figure 1: Radiological evolution after initiation of antibiotic therapy.

(A) Chest radiography at Day 0 showing a major left pleural effusion; (B) Day 9 of treatment: reappearance of partial left lung ventilation, persistent mediastinal shift to the left; (C) Day 86: persistence of a minimal residual lingular infiltrate without pleural reaction.

Investigation	Etiology	Results
Thyroid hormone assay	Hyperthyroidism	Normal.
Thyroid ultrasound	Secondary hyperthyroidism	No lesion or nodule. Normal appearance.
Abdominal ultrasound	Neuroblastoma, Hepatoblastoma Expansive tumor phenomenon	Normal.
Chest X-ray	Neuroblastoma. Expansive tumor phenomenon	Slight persistent pleural reaction on the left. No mass. No adenopathy.
Lumbar puncture	Meningitis	Cytology, culture, and multiplex PCR negative.
Blood determination of neuron-specific enolase (NSE)	Neuroblastoma Other tumor of neuroectodermal or neuroendocrine origin.	Normal.
Urinary determination of catecholamines	Neuroblastoma	Normal.
Ophthalmologic examination	Oculomotricity disorder	Normal examination except for opsoclonus.
Electroencephalogram (EEG)	Convulsions	Normal.
Cerebral MRI	Intracranial expansive, infectious or inflammatory process.	Normal.

days post infection (2). Newer diagnostic tests such as Elispot have been proposed but to date it is still difficult to confirm the diagnosis. Therefore, the combination of PCR with serological detection of IgM is the most sensitive method to confirm *Mycoplasma pneumoniae* infection taking into account the specificity and sensitivity of both techniques. In our case, we had less reason to doubt the diagnosis because there was strong evidence for ongoing *Mycoplasma pneumoniae* infection as PCR was positive in both blood and pleural effusion.

Treatment consists of antibiotic therapy with a macrolide which, in addition to its antimicrobial activity, has anti-inflammatory and immunomodulatory properties (3). Antibiotics remain the mainstay of treatment for *Mycoplasma pneumoniae* infection, with or without associated extrapulmonary manifestations. Treatment of neurological manifestations may vary whether these are secondary to active infection (need to prescribe an antibiotic with good brain penetration) or as post-infectious (consider combination with immunosuppressive therapy).

Among these manifestations, Kinsbourne syndrome, also known as opsoclonus-myoclonus-ataxia syndrome (OMAS) or more commonly as "dancing eyes and feet syndrome", is a rare neurological disorder that affects adults and children, with a peak incidence in the pediatric population most often between the ages of 6 and 36 months (1,3,4). It usually associates opsoclonus, myoclonus, truncal and appendicular ataxia with walking difficulties. Behavioral changes such as irritability, attention and sleep disturbances have also been described (4,5). The clinical picture varies from one patient to patient and the expression of the different neurological symptoms can be heterogeneous. Opsoclonus may be intermittent and may appear many weeks after ataxia. Behavioral disturbances can appear several weeks before the onset of typical neurological signs (1). The diversity of the clinical expression makes the diagnosis of OMAS difficult to make in some patients. The etiology of Kinsbourne syndrome is paraneoplastic or parainfectious (1,4,6).

In children, the neoplastic / paraneoplastic etiology must be ruled out first. It is therefore essential to exclude malignant phenomena, in particular neuroblastoma (or another neural crest tumor) which may present with the syndrome of opsomyoclonus and ataxia (5). Central imaging is mandatory. Several other infectious pathogens (EBV, CMV, HCV, HSV, Rotavirus, Coxsackie, Influenza, Salmonella...), have recently been newly associated with the onset of OMAS and are considered to be the primo movens. Emamikhah et al. have recently described cases secondary to COVID-19 (7). Rare cases in the literature mention and describe *Mycoplasma pneumoniae*, a pathogen well known in pediatrics, as an infectious agent responsible for the genesis of OMAS (6). The infectious workup remains essential in patients in whom a neoplastic/paraneoplastic etiology has been excluded as OMAS secondary to medication has not yet been described (6).

The pathophysiology of OMAS is not fully understood, but autoantibodies have previously been detected in some patients and appear to involve an immune process with dysregulation of humoral and cellular systems (6,8). Antineuronal nuclear autoantibodies type 2 (ANNA2) have been described in particular in paraneoplastic conditions (anti-Ri, anti-Yu, anti-Ho) (5,9). To date, no diagnostic biomarker has been identified despite the progress made in the understanding and genesis of this syndrome. Krasenbrink et al. support the idea of a genetic predisposition in OMAS, regardless of the etiology, without having identified or incriminated a specific gene (10). Their study showed that the prevalence of autoimmune diseases and autoantibodies is higher in parents of children with OMAS compared to the control group of parents of children of the same age and sex (3,10).

Kinsbourne syndrome is therefore considered an autoimmune disease whose etiology may be paraneoplastic or postinfectious, may involve several infectious agents, and may have other etiologies yet to be discovered.

In addition to treatment of the underlying cause, which often, but not systematically, leads to an improvement or even resolution of the symptoms, there is also a supportive component to the treatment for which there is no consensus or guidelines (8). Corticosteroids, adrenocorticotropic hormone (ACTH) and immunoglobulins are the most commonly used immunomodulatory agents in pediatrics as first-line therapy. In certain refractory situations, plasmapheresis may be considered. Immunosuppressive treatments, such as cyclophosphamide, cyclosporine A or azathioprine have been used as a last resort, regardless of etiology, because they block the antibody production that may be involved in the process (4,8,10).

Our patient received no treatment and spontaneously improved with nearly complete recovery in less than 6 weeks. Treatment with corticosteroids was considered but not started because of the spontaneous progressive improvement. This is one of the only case reports demonstrating a favorable evolution without any specific treatment.

The prognosis may depend on the etiology and the time of onset of treatment. Idiopathic and parainfectious forms generally have a good prognosis and may resolve spontaneously without treatment. Relative learning difficulties, mild motor, cognitive and behavioral sequelae may persist and may affect the child's future development. Only a few cases have been reported to define their prevalence/incidence and the long-term evolution.

Conclusion

Mycoplasma pneumoniae, a pathogen regularly encountered in respiratory tract infections, can be responsible for numerous extrapulmonary

manifestations. Among these is Kinsbourne syndrome or opso-myoclonus-ataxia syndrome, first described in 1962, an autoimmune disease whose etiology may be paraneoplastic or infectious. Autoimmunity is thought to be at the basis of this syndrome. Only a few cases have been reported in the literature. This case report illustrates the diversity of the clinical picture of an infection with this particular pathogen.

In Kinsbourne syndrome, it is essential to exclude an underlying malignant process at first and to identify the etiologic cause early on in order to target the therapy and determine the prognosis. If a post-infectious etiology is suspected, the diagnosis of *Mycoplasma pneumoniae* remains difficult, due to the lack of specificity/sensitivity of PCR and serology and both tests need to be combined. Corticosteroids and adrenocorticotropic hormone (ACTH) remain the first-line treatment, although there is no consensus or therapeutic guidelines. It should be noted that spontaneous recovery can be achieved without immunomodulatory treatment, as in our case.

Conflict of interest

The authors have no conflicts of interest in relation to the subject matter of this manuscript.

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Catch-up growth in infants and young children with faltering growth

Statement and expert opinion to guide general clinicians

QR code to the full publication

THE ISSUE : What is Known?

Faltering growth (FG) in infants and young children (<2 years of age) is a common problem for general clinicians to see in clinical practice, especially in low-income settings.

FG is associated with a range of adverse outcomes and there may be benefits in promoting catch-up growth where this is indicated.

Healthcare professionals may be deterred from adequately addressing the problem, due to the misconception that addressing faltering growth may promote accelerated growth.

CONSEQUENCES OF FALTERING GROWTH

High-income

Disease related FG: Short term consequences

Studies on mixed populations of hospitalized children have shown that malnutrition is associated with an increase in infectious complications and an increased length of stay.

Disease related FG: Long term consequences

In the longer term malnourished children also have increased rates of impaired cognitive function and behavioral problems, including impaired communication skills and attention-deficit hyperactivity disorders.

Non-disease related FG: Short term consequences

The consequences of faltering growth may include an impact on schooling and cognitive achievements, short stature, and socioeconomic outcomes.

Middle-income

Faltering growth in low and middle-income countries commonly occurs together with numerous health and social outcomes, including poor brain development and delayed cognitive performance; delayed attainment of milestones; greater susceptibility to some infections; higher overall and disease-specific mortality in childhood; lower physical work capacity in adulthood; poorer earnings; and diminished human capital.

Low-income

MANAGEMENT

Nutritional management of disease-related and non-disease-related faltering growth

Nutritional management of disease- and non-disease-related faltering growth requires a **balanced ratio of energy and protein in addition to micronutrients for optimal catch-up**.

Breastfeeding should be supported in both disease- and non-disease-related faltering growth by ensuring assessing technique and supply and only **where appropriate** infant milk fortification, cup feeding or **supplementary formula should be considered**.

In formula fed infants **ready to use energy dense therapeutic feeds with proven efficacy** should be used, where available; if these are not available suitable locally available powdered feeds can be used, applying WHO hygiene safety for mixing.

Modular additions of only fat and carbohydrates to feed and food **should be avoided**, as this reduces the protein to energy ratio.

Nutritional management for both medical and non-medical faltering growth should include **either/both the fortification of accepted foods and advice on foods that are naturally energy dense** and locally available.

The nutritional management plan should include a target for **appropriate catch-up growth that is monitored** at an interval that is deemed appropriate by the healthcare professional, the available healthcare service and the severity of the faltering growth.

Cooke R, et al. J Pediatr Gastroenterol Nutr. 2023; 77(1):7-15.

Important: Breastfeeding is the ideal nutrition for infants.

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Onze referentie bij inhaalgroei

Van 0 tot 18 maanden of tot 9 kg

- Voldoet aan de **WHO aanbevelingen** voor inhaalgroei: min. 8,9-11,5 En% eiwit[1]
- Onze unieke **prebiotische mix scGOS/lcFOS** ter ondersteuning van de darmmicrobiota[5]
- **Volledige medische voeding voor zuigelingen** (10 En% eiwitten)
- **Positieve stikstofbalans** vanaf dag 1[15]
- **Volwaardige wei/caseïne-eiwitverhouding 60:40** vergemakkelijkt de maaglediging en vermindert braken en kokhalsreflexen[6-9]
- **LCPs (DHA en ARA)** die de gezichtsscherpte en cognitieve ontwikkeling ondersteunen[3,4]
- **Lage osmolariteit voor een betere tolerantie**[8] wat het risico op gastro-oesofagale reflux[11] en/of osmotische diarree verlaagt[12]
- **Nucleotiden** die het immuunsysteem stimuleren[10]
- **Kant-en-klaar,** wat het risico op bacteriële contaminatie en bereidingsfouten vermindert[13,14*]
- 40% **meer micronutriënten** per 100 ml dan een energieverrijkte zuigelingenvoeding. Dus minder volume nodig om in de behoefte voor zuigelingen te voorzien[2]
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*voor Infatrini 125 ml, 500 ml

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Idiopathic infantile hypercalcemia in a child presenting with failure to thrive: a case report

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Keywords

Idiopathic infantile hypercalcemia ; CYP24A1 ; failure-to-thrive ; case report.

Abstract

Idiopathic infantile hypercalcemia is caused by loss-of-function mutations in the *CYP24A1* gene, which encodes an enzyme that degrades vitamin D. The disease is characterized by nonspecific symptoms. In this case study, the infant merely presents with failure to thrive and dehydration, giving rise to a broad differential diagnosis. Ultrasound revealed bilateral nephrocalcinosis. Genetic research showed two compound mutations in the *CYP24A1* gene. Following a diet low in calcium and vitamin D and starting calcium-lowering therapy, led to adequate weight gain and normalized calcium levels. The case highlights the importance of determining full serum electrolytes in children with failure to thrive.

Introduction

The fat-soluble vitamin D plays a substantial role in calcium- and phosphate homeostasis (1). For this purpose, supplementation of 400-600 international units (IU) per day (depending on skin color) is routinely recommended in all newborns up to the age of 6 years (2). The degradation of active vitamin D or calcitriol is catalyzed by CYP24A1, a member of the cytochrome P450 family. Loss-of-function mutations in this enzyme cause a disease called 'idiopathic infantile hypercalcemia (IIH) type 1', which presents with nonspecific symptoms such as hypotonia, polyuria, dehydration and feeding difficulties due to hypercalcemia (1). Once diagnosed, calcium-lowering therapy should be initiated and vitamin D supplementation discontinued immediately. Caution should be taken in asymptomatic carriers, as in this case, external factors like excessive calcium or vitamin D intake may still cause late sequalae (3). We describe a case of an infant with IIH merely presenting with failure to thrive (FTT) and dehydration.

Case report

A 5-month-old girl presented to the emergency department because of poor feeding that had worsened over the past week. During this week she had fever that resolved spontaneously. According to the parents, there was no associated vomiting or diarrhea and urine production was still adequate.

There were no peculiarities in her past history. She was born at term with a normal birth weight. The infant was still exclusively breastfed at the time of presentation. Both parents were of Romanian origin, there was no consanguinity and all siblings were in good health. The infant was not receiving any medications in addition to the recommended daily dose of 400 IU of vitamin D per day.

Physical examination showed a lean and listless infant with mild signs of dehydration. There were no symptoms of infection and no syndromic stigmata. She had lost 160 grams over the past 6 weeks and the growth chart indicated that her weight had decreased 2.5 standard deviations over the previous two months.

Initial blood results revealed mild leucocytosis with normal C-reactive protein (CRP) level, acidosis, hyponatremia and hyperkaliemia. The nasopharyngeal aspirate was positive for Influenza A. Intravenous (IV) rehydration was started. On admission to the hospital, subsequent blood tests showed elevated levels of both total calcium (4,07 mmol/L, reference range 1,95-2,80 mmol/L) and free calcium (2,04 mmol/L, reference range 1,15-1,27 mmol/L). Phosphate levels were normal. Parathyroid hormone (PTH) was suppressed with a value of <6 ng/L (reference range 15-65 ng/L). 25-hydroxy vitamin D3 was markedly raised (> 100 ng/mL, reference range 10-44,8 ng/mL) with also high levels of 1,25-dihydroxy vitamin D3 (198,7 pg/mL, reference range 19-95 pg/mL). Urinalysis showed hypercalciuria with a calcium/creatinine ratio of 3,380 mg/mg (reference range <0,6 mg/mg). Renal ultrasound showed nephrocalcinosis.

The parents denied any excessive use of vitamin D supplements. No evidence of malignancy, granulomatous disease or congenital disorders was found. Genetic analysis revealed two compound heterozygous mutations in the CYP24A1 gene: c443T>C, p. (Leu148Pro) in exon 2 and c.1186C>T, p. (Arg396Trp) in exon 9.

Intravenous hyperhydration and formula low in calcium and vitamin D were started, and supplemental vitamin D was discontinued. A daily low dose of fluconazole, which can reduce the formation of 1,25-dihydroxy vitamin D3, was started. In addition, two doses of bisphosphonates were given to lower calcium levels more rapidly. Calcium and PTH levels returned to normal within three months. Feeding difficulties resolved, solid foods could be introduced, and adequate weight gain was achieved.

Discussion

Idiopathic infantile hypercalcemia was first described in the early 1950s when formula milk, heavily fortified with vitamin D, caused symptoms such as failure to thrive, vomiting, dehydration or even death in children with intrinsic hypersensitivity to vitamin D. However, it was not until 2011 that Schlingmann et al. described mutations in the CYP24A1 gene that explained this hypersensitivity (1). Later, pathogenic variants in the SLC34A1 gene, which encodes a sodium-phosphate IIa cotransporter, were found to be another molecular basis for IIH (type 2) by causing renal phosphate wasting, leading to an inappropriate increase in 1,25-dihydroxy vitamin D3 synthesis (3,4). In the presented case, both genetic mutations were investigated, although normal serum phosphate levels suggested the diagnosis of IIH type 1. The two compound loss-of-function mutations in this patient were previously described in De Paolis et al. as causing IIH type 1 (3).

The CYP24A1 enzyme catalyzes the breakdown of 1,25-dihydroxy vitamin D3 (active form) and its precursor 25-hydroxy vitamin D3 into metabolites that can be excreted (1). Low calcium levels stimulate the production of PTH which in turn downregulates CYP24A1. This process leads to an increase in concentration of active vitamin D and thus to an increase in calcium levels through intestinal absorption and renal reabsorption. In IIH type 1, loss-of-function mutations in the CYP24A1 gene prevent the breakdown of active vitamin, causing calcium levels to rise to pathological levels (3).

IIH often manifests early, usually at 3 to 7 months of age (5). Affected children may present with a variety of symptoms, including vomiting, polyuria, dehydration, anorexia, constipation and weight loss. Lethargy and muscular hypotonia may also occur (3,5,6). Sometimes, the disease can be accompanied by seizures, pancreatitis or psychiatric symptoms (6). Our patient presented with failure to thrive, which is described in about three quarters of the cases reported in literature (7). If the initial symptoms go undetected, other problems such as kidney stones, renal failure, osteoporosis or calcium deposition in the cornea or joints may develop. Patients who are carrier of a mutation may also show these latent symptoms, mainly when vitamin D is taken in excess (3,5).

Typical laboratory findings are hypercalcemia, hypercalciuria and supressed PTH levels (3). 1,25-dihydroxy vitamin D3 is usually slightly elevated but tends to normalize due to downregulation by PTH (5). Another diagnostic clue is an elevated ratio of serum 25-hydroxy vitamin D3 to its catabolite 24,25-dihydroxy vitamin D3 (5,8). In some patients, abdominal ultrasound may reveal nephrocalcinosis (1).

Failure to thrive can be caused by a wide range of conditions. The finding of PTH-independent hypercalcemia with normal to high calcitriol levels suggests the possible diagnosis. In children, congenital causes, such as IIH types 1 and 2, are more common than acquired etiologies. Early onset of the condition, consanguinity, a family history of hypercalcemia or a history of multiple or recurrent kidney stones, should raise the suspicion of a genetic disorder (3). Some congenital syndromes associated with hypercalcemia, such as William syndrome, Down syndrome, and Jansen disease, can be identified by dysmorphic features (6,8). PTH-independent hypercalcemia may also be seen in some rare inborn errors of metabolism such as blue diaper syndrome, hypophosphatasia, congenital lactase deficiency or disaccharide intolerance (6). Among the acquired disorders, (accidental) intoxication with vitamin D, vitamin A or some drugs should be considered first (6). Extrarenal overproduction of vitamin D occurs in granulomatous disorders or malignancies such as lymphoma or ovarian dysgerminoma. In neonates, subcutaneous fat necrosis is a rare and reversible cause of hypercalcemia, caused by the formation of a granulomatous infiltrate in the necrotic area (6,8).

Children diagnosed with IIH require prompt treatment. Hyperhydration with or without loop diuretics will stimulate calcium excretion and rapidly reduce calcium levels. A diet low in calcium and vitamin D has to be prescribed (3,8). In the next phase of treatment, a more prolonged reduction of calcium levels should be achieved. Several options have been explored, including the use of corticosteroids, especially for hypercalcemia due to granulomatous disease, or the use of calcitonin, although its effect is short-lived (3,6). A 2- to 3-day course of bisphosphonates can be given to inhibit osteoclast activity and thereby lowering calcium levels. This course can be repeated every 6 to 8 weeks (3,6). In addition, azole antifungals are known to be general inhibitors of the cytochrome P450 complex. Consequently, they also interfere with the function of the 25-hydroxylase and 1-alpha-hydroxylase enzymes, thereby reducing the production of vitamin D. Ketoconazole is a more potent inhibitor with a higher risk of hepatic and renal toxicity than the more readily available fluconazole (3,5,9). Rifampicin is an inducer of the CYP3A4 enzyme, which could act as different approach to break down vitamin D (6). It is important that these medications are gradually reduced as calcium levels normalize (5).

In the literature little is known about the natural course and prognosis of IIH. According to some studies hypercalcemia resolves spontaneously in most children at the age of one to three years. In a small number of patients, suboptimal calcium levels persist into adulthood (5,6). Long-term adverse outcomes have been reported, including mild to moderate intellectual disability, anxiety and hyperactivity (5). The implications on bone development also remain unclear, as both low, normal and high bone mineral density have been described (8). In the presented case, the patient showed a rapid catch-up growth after initiation of diet and calcium-lowering therapy. Treatment with fluconazole could be weaned after approximately three months.

Conclusion

When a child presents with failure to thrive, hypercalcemia needs to be excluded by performing a complete serum electrolyte panel during the diagnostic evaluation. A genetic cause of hypercalcemia should be considered in the presence of early onset of disease or conspicuous family or medical history. In these cases, IIH should be considered in the differential diagnosis. High-dose vitamin D supplementation should be used with caution, as it may endanger children with *CYP24A1* mutations. Finally, more research is needed on the natural course and the long-term impact of IIH.

Conflict of interest

All authors declare that they have no conflict of interest in relation to the realization of this case report.

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Si vous ne recommandez pas la vaccination contre le MenB à vos patients,

qui le fera ?

81% des parents considèrent leur médecin comme la source principale d'information concernant la vaccination de leurs enfants (n=800)[2]

BEXSERO
Vaccin méningococcique groupe B
(ADNr, composant, adsorbé)

BEXSERO est indiqué pour l'immunisation active des sujets à partir de l'âge de 2 mois contre l'infection invasive méningococcique causée par *Neisseria meningitidis* de groupe B.[1]

RÉSUMÉ ABRÉGÉ DES CARACTÉRISTIQUES DU PRODUIT : Veuillez vous référer au Résumé des Caractéristiques du Produit pour une information complète concernant l'usage de ce médicament. **DÉNOMINATION DU MÉDICAMENT :** Bexsero suspension injectable en seringue préremplie. Vaccin méningococcique groupe B (ADNr, composant, adsorbé) ; EU/1/12/812/001 ; EU/1/12/812/002, EU/1/12/812/003, EU/1/12/812/004. Classe pharmacothérapeutique : vaccins méningococciques, Code ATC : J07AH09. **COMPOSITION QUALITATIVE ET QUANTITATIVE :** Une dose (0,5 ml) contient : Protéine de fusion recombinante NHBA de Neisseria meningitidis groupe B[1, 2, 3] : 50 microgrammes • Protéine recombinante NadA de Neisseria meningitidis groupe B[1, 2, 3] : 50 microgrammes • Protéine de fusion recombinante fHbp de Neisseria meningitidis groupe B[1, 2, 3] : 50 microgrammes • Vésicules de membrane externe (OMV) de Neisseria meningitidis groupe B, souche NZ98/254 mesurée en tant que proportion de l'ensemble des protéines contenant l'antigène PorA P1.4[2] : 25 microgrammes • [1] produite dans des cellules d'E. coli par la technique de l'ADN recombinant - [2] adsorbée sur hydroxyde d'aluminium (0,5 mg Al^{3+}) - [3] NHBA (antigène de liaison à l'héparine de Neisseria), NadA (adhésine A de Neisseria), fHbp (protéine de liaison du facteur H). Pour la liste complète des excipients, voir rubrique 6.1 du RCP complet. **FORME PHARMACEUTIQUE :** Suspension injectable. Suspension liquide blanche opalescente. **DONNÉES CLINIQUES : Indications thérapeutiques :** Bexsero est indiqué pour l'immunisation active des sujets à partir de l'âge de 2 mois contre l'infection invasive méningococcique causée par Neisseria meningitidis de groupe B. L'impact de l'infection invasive à différentes tranches d'âge ainsi que la variabilité épidémiologique des antigènes des souches du groupe B dans différentes zones géographiques doivent être pris en compte lors de la vaccination. Voir rubrique 5.1 du RCP complet pour plus d'informations sur la protection contre les souches spécifiques au groupe B. Ce vaccin doit être utilisé conformément aux recommandations officielles. **Posologie et mode d'administration :** Posologie : **Tableau 1. Résumé de la posologie : Age lors de la première dose :** Nourrissons de 2 à 5 mois[a]. **Primovaccination :** Trois doses de 0,5 ml chacune. **Intervalles entre les doses de primovaccination :** 1 mois minimum. **Rappel :** Oui, une dose entre l'âge de 12 et 15 mois avec un intervalle d'au moins 6 mois entre la primovaccination et la dose de rappel[b, c] - Primovaccination : Deux doses de 0,5 ml chacune. **Intervalles entre les doses de primovaccination :** 2 mois minimum. **Rappel :** Oui, une dose entre l'âge de 12 et 15 mois avec un intervalle d'au moins 6 mois entre la primovaccination et la dose de rappel[b, c]. **Age lors de la première dose :** Nourrissons de 6 à 11 mois. **Primovaccination :** Deux doses de 0,5 ml chacune. **Intervalles entre les doses de primovaccination :** 2 mois minimum. **Rappel :** Oui, une dose au cours de la deuxième année de vie avec un intervalle d'au moins 2 mois entre la primovaccination et la dose de rappel[c]. • **Age lors de la première dose : Enfants de 12 à 23 mois. Primovaccination :** Deux doses de 0,5 ml chacune. **Intervalles entre les doses de primovaccination :** 2 mois minimum. **Rappel :** Oui, une dose avec un intervalle de 12 à 23 mois entre la primovaccination et la dose de rappel[c]. • **Age lors de la première dose : Enfants de 2 à 10 ans. Primovaccination :** Deux doses de 0,5 ml chacune. **Intervalles entre les doses de primovaccination :** 1 mois minimum. **Rappel :** Selon les recommandations officielles, une dose de rappel peut être envisagée chez les sujets présentant un risque continu d'exposition à infection méningococcique[d]. • **Age lors de la première dose : Adolescents (à partir de 11 ans) et adultes*. Primovaccination :** Deux doses de 0,5 ml chacune. **Intervalles entre les doses de primovaccination :** 1 mois minimum. **Rappel :** Selon les recommandations officielles, une dose de rappel peut être envisagée chez les sujets présentant un risque continu d'exposition à infection méningococcique[d]. • [a] La première dose ne doit pas être administrée avant l'âge de 2 mois. La sécurité et l'efficacité de Bexsero chez les nourrissons de moins de 8 semaines n'ont pas encore été établies. Aucune donnée n'est disponible. - [b] En cas de retard, la dose de rappel ne devrait pas être administrée audelà de l'âge de 24 mois. - [c] Voir rubrique 5.1 du RCP complet La nécessité et le moment d'administration d'autres doses de rappel n'ont pas encore été déterminés. - [d] Voir rubrique 5.1 du RCP complet. - * Il n'existe aucune donnée chez les adultes de plus de 50 ans. Mode d'administration : Le vaccin est administré par une injection intramusculaire profonde, de préférence dans la face antérolatérale de la cuisse chez le nourrisson ou dans la région du muscle deltoïde du haut du bras chez les sujets plus âgés. Des sites d'injection distincts doivent être utilisés si plusieurs vaccins sont administrés simultanément. Le vaccin ne doit pas être injecté par voie intraveineuse, souscutanée ni intradermique et ne doit pas être mélangé avec d'autres vaccins dans la même seringue. Pour les instructions concernant la manipulation du vaccin avant administration, voir la rubrique 6.6 du RCP complet. **Contreindications :** Hypersensibilité aux substances actives ou à l'un des excipients mentionnés à la rubrique 6.1 du RCP complet. **Effets indésirables :** Résumé du profil de sécurité : La sécurité de Bexsero a été évaluée lors de 17 études, dont 10 essais cliniques randomisés contrôlés portant sur 10 565 sujets (âgés de 2 mois minimum) ayant reçu au moins une dose de Bexsero. Parmi les sujets vaccinés par Bexsero, 6 837 étaient des nourrissons et des enfants (de moins de 2 ans), 1 051 étaient des enfants (entre 2 et 10 ans) et 2 677 étaient des adolescents et des adultes. Parmi les nourrissons ayant reçu les doses de primovaccination de Bexsero, 3 285 ont reçu une dose de rappel au cours de leur deuxième année de vie. Chez les nourrissons et les enfants (de moins de 2 ans), les réactions indésirables locales et systémiques les plus fréquemment observées lors des essais cliniques étaient : sensibilité et érythème au site d'injection, fièvre et irritabilité. Dans les études cliniques menées chez les nourrissons vaccinés à 2, 4 et 6 mois, la fièvre (≥ 38 °C) était rapportée chez 69 % à 79 % des sujets lorsque Bexsero était coadministré avec des vaccins de routine (contenant les antigènes suivants : pneumococcique heptavalent conjugué, diphtérie, tétanos, coqueluche acellulaire, hépatite B, poliomyélite inactivée et Haemophilus influenzae de type b), contre 44 % à 59 % des sujets recevant les vaccins de routine seuls. Une utilisation plus fréquente d'antipyrétiques était également rapportée chez les nourrissons vaccinés par Bexsero et des vaccins de routine. Lorsque Bexsero était administré seul, la fréquence de la fièvre était similaire à celle associée aux vaccins de routine administrés aux nourrissons pendant les essais cliniques. Les cas de fièvre suivaient généralement un schéma prévisible, se résolvant généralement le lendemain de la vaccination. Chez les adolescents et les adultes, les réactions indésirables locales et systémiques les plus fréquemment observées étaient : douleur au point d'injection, malaise et céphalée. Aucune augmentation de l'incidence ou de la sévérité des réactions indésirables n'a été constatée avec les doses successives du schéma de vaccination. Liste tabulée des effets indésirables : Les effets indésirables (consécutifs à la primovaccination ou à la dose de rappel) considérés comme étant au moins probablement liés à la vaccination ont été classés par fréquence. Les fréquences sont définies comme suit : Très fréquent : (≥ 1/10) - Fréquent : (≥ 1/100 à < 1/10) - Peu fréquent : (≥ 1/1 000 à < 1/100) - Rare : (≥ 1/10 000 à < 1/1 000) - Très rare : (< 1/10 000). Fréquence indéterminée : (ne peut être estimée sur la base des données disponibles). Dans chaque groupe de fréquence, les effets indésirables sont présentés par ordre de sévérité décroissante. Outre les événements rapportés lors des essais cliniques, les réactions spontanées rapportées dans le monde pour Bexsero depuis sa commercialisation sont décrites dans la liste ci dessous. Comme ces réactions ont été rapportées volontairement à partir d'une population de taille inconnue, il n'est pas toujours possible d'estimer de façon fiable leur fréquence. Ces réactions sont, en conséquence, listées avec une fréquence indéterminée. **Nourrissons et enfants (jusqu'à l'âge de 10 ans) :** Affections hématologiques et du système lymphatique : Fréquence indéterminée : lymphadénopathie. Affections du système immunitaire : Fréquence indéterminée : réactions allergiques (y compris réactions anaphylactiques). Troubles du métabolisme et de la nutrition : Très fréquent : troubles alimentaires. Affections du système nerveux : Très fréquent : somnolence, pleurs inhabituels, céphalée. Peu fréquent : convulsions (y compris convulsions fébriles). Fréquence indéterminée : épisode d'hypotonie-hyporéactivité, irritation des méninges (des signes d'irritation des méninges, tels qu'une raideur de la nuque ou une photophobie, ont été rapportés sporadiquement peu de temps après la vaccination. Ces symptômes ont été de nature légère et transitoire). Affections vasculaires : Peu fréquent : pâleur (rare après le rappel). Rare : syndrome de Kawasaki. Affections gastrointestinales : Très fréquent : diarrhée, vomissements (peu fréquents après le rappel). Affections de la peau et du tissu souscutané : Très fréquent : rash (enfants âgés de 12 à 23 mois) (peu fréquent après le rappel). Fréquent : rash (nourrissons et enfants âgés de 2 à 10 ans). Peu fréquent : eczéma. Rare : urticaire. Affections musculosquelettiques et systémiques : Très fréquent : arthralgies. Troubles généraux et anomalies au site d'administration : Très fréquent : fièvre (≥ 38 °C), sensibilité au niveau du site d'injection (y compris sensibilité sévère au site d'injection définie par des pleurs lors d'un mouvement du membre ayant reçu l'injection), érythème au site d'injection, gonflement du site d'injection, induration au site d'injection, irritabilité. Peu fréquent : fièvre (≥ 40 °C). Fréquence indéterminée : réactions au site d'injection (incluant un gonflement étendu du membre vacciné, vésicules au point d'injection ou autour du site d'injection et nodule au site d'injection pouvant persister pendant plus d'un mois). **Adolescents (à partir de 11 ans) et adultes :** Affections hématologiques et du système lymphatique : Fréquence indéterminée : lymphadénopathie. Affections du système immunitaire : Fréquence indéterminée : réactions allergiques (y compris réactions anaphylactiques). Affections du système nerveux : Très fréquent : céphalée. Fréquence indéterminée : syncope ou réaction vasovagale à l'injection, irritation des méninges (des signes d'irritation des méninges, tels qu'une raideur de la nuque ou une photophobie, ont été rapportés sporadiquement peu de temps après la vaccination. Ces symptômes ont été de nature légère et transitoire). Affections gastrointestinales : Très fréquent : nausées. Affections de la peau et du tissu sous-cutané : Fréquence indéterminée : rash. Affections musculosquelettiques et systémiques : Très fréquent : myalgies, arthralgies. Troubles généraux et anomalies au site d'administration : Très fréquent : douleur au point d'injection (y compris douleur sévère au point d'injection définie par une incapacité à mener à bien des activités quotidiennes normales), gonflement du site d'injection, induration au point d'injection, érythème au site d'injection, malaise. Fréquence indéterminée : fièvre, réactions au site d'injection (incluant gonflement étendu du membre vacciné, vésicules au point d'injection ou autour du site d'injection et nodule au site d'injection pouvant persister plus d'un mois). Déclaration des effets indésirables suspectés : La déclaration des effets indésirables suspectés après autorisation du médicament est importante. Elle permet une surveillance continue du rapport bénéfice/risque du médicament. Les professionnels de santé déclarent tout effet indésirable suspecté via le système national de déclaration : **Belgique :** Agence Fédérale des Médicaments et des Produits de Santé - Division Vigilance - Boîte Postale 97 - 1000 Bruxelles - Madou - Site internet: www.notifieruneffetindesirable.be - e-mail: adr@afmps.be. **Luxembourg :** Centre Régional de Pharmacovigilance de Nancy ou Division de la pharmacie et des médicaments de la Direction de la santé. Site internet : www.guichet.lu/pharmacovigilance. **TITULAIRE DE L'AUTORISATION DE MISE SUR LE MARCHÉ :** GSK Vaccines S.r.l.,Via Fiorentina 1, 53100 Sienne, Italie. **DATE D'APPROBATION DU TEXTE :** 26/04/2023 (v15). **MODE DE DELIVRANCE :** Sur prescription médicale.

Références : 1. SmPC Bexsero. **2.** Schmitt JH, Booy R, Astron R, et al. How to optimize the coverage rate of infant and adult immunisations in Europe. BMC Med. 2007;5:11. doi:10.1186/1741-7015-5-11.

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GSK

Severe persistent hypocalcemia occurring despite vitamin D and calcium supplementation in children with symptomatic vitamin D deficiency

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Keywords

Hypocalcemia ; vitamin D ; vitamin D deficiency ; treatment ; child.

Abstract

This article describes two cases of severe persistent hypocalcemia occurring despite vitamin D and calcium supplementation in children with symptomatic vitamin D deficiency. We compared these cases with hungry bone syndrome (HBS) occurring after parathyroidectomy. Studies of hypocalcemia due to vitamin D deficiency suggest a potential risk of hungry bone (HB)-like syndrome if calcium treatment is inadequate at the start of vitamin D supplementation. This article highlights the pitfalls of hypocalcemia management. Hypocalcemia should be actively treated with calcium boluses and continuous infusion to avoid the possibility of HB-like syndrome.

Introduction

The incidence of vitamin D deficiency is increasing in developed countries (1–4). Complications from vitamin D deficiency and hypocalcemia include rickets, seizures, cardiomyopathy, and has a significant impact on morbidity and mortality in children (1–5).

We present two cases of children with symptomatic hypocalcemia, and an unexpected severe worsening after initiation of calcium and vitamin D treatment, resembling hungry bone syndrome (HBS).

The aim of our presentation is to compare our 2 cases with HBS, which has been described mainly after parathyroid or thyroid removal surgery (5,6).

Studies on hypocalcemia due to vitamin D deficiency, suggest a potential risk of hungry bone (HB)-like syndrome if calcium treatment is inadequate at the start of vitamin D supplementation (7,8).

Case presentations

Case 1

A 6-month-old male was admitted to the emergency department after a third episode of brief seizures without accompanying fever.

This full-term healthy child, born from to an inbred family from Pakistan, was breastfed and received fruit and vegetable supplements. He received all scheduled vaccines but no vitamin supplementation. His growth was normal. The mother and the child had dark skin and wore traditional clothing. There was no family history of epilepsy. The mother wasn't taking any medications or vitamins.

On admission, physical and neurological examinations were normal. Plasma biology (Table 1) revealed anemia, vitamin B12 and iron deficiency, and severe hypocalcemia (Ca 1.4 mmol/L [N 2.25-2.75 mmol/L]).

Cerebrospinal fluid analysis, brain CT scan, and electroencephalogram were normal. He was treated with intravenous (IV) calcium gluconate (24 mg/kg/day of elemental Ca) and oral cholecalciferol 800 units/day.

After a few days of treatment, the hypocalcemia worsened (Ca 1.27 mmol/L), and new episodes of seizures occurred.

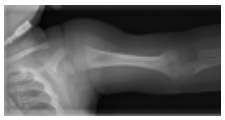
Diagnostic tests showed a high parathyroid hormone (PTH) level, severe vitamin D deficiency, normal phosphorus, elevated alkaline phosphatase (ALP), but no urinary calcium loss (urinary Ca/creatinine : 0,44 mmol/mol creatinine [0,034-0,690 mmol/mol creatinine]).

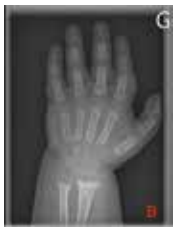
Radiographic findings were typical of rickets (Figure 1) and also showed cardiomegaly. Echocardiography showed mild cardiac dysfunction with dilated left ventricle, but without clinical impact.

Table 1: value at admission and etiological assessment.

	Value	Unit	Standards
Hemoglobin	10,7	g/dL	10,5-13,5
White cells	11 030	/mm^3	6000-17500
C-reactive protein	7,82	mg/L	<0,5
Calcium	1,4	mmol/L	2,25-2,75
Ionized calcium	0,65	mmol/L	1,12-1,32
Magnesium	0,78	mmol/L	0,63-1,05
Phosphorus	1,7	mmol/L	1,15-2,15
Parathyroid hormone	94,9	ng/L	<49
25-OH-vitamin D	<0,5	mcg/L	30-80
Iron	36	mcg/dL	40-100
Albumin	43,4	g/l	38-54
Alkaline phosphatase	864	UI/L	<449

Figure 1:
A and B : Left arm and wrist of case 1 : poorly demarcated, widened and frayed distal ends of radius and ulna, characteristic of rickets. Same symptoms on the ankle.





Calcium administration was increased to 210 mg/kg/day of oral elemental calcium, and 36 mg/kg/day of intravenous (IV) elemental calcium. Vitamin D administration was increased to 3000 units per day and alfacalcidol was added to the treatment.

On day 3 (D3) the child was transferred to the Paediatric Intensive Care Unit (PICU) due to lack of improvement in calcemia. Notably, after admission to the PICU, the patient developed hypophosphatemia (0.88 mmol/L [1,15 - 2,15 mmol/L]).

In the PICU, the patient received an IV bolus of calcium chloride followed by continuous intravenous infusion of calcium chloride from D3 to D6 (maximum 60 mg/kg/day of elemental calcium). Normocalcemia was achieved on D5. Intravenous calcium administration was continued until D6. Oral calcium carbonate, vitamin D and iron therapy were started.

The exact amount of calcium administered is shown in Table 2.

The mother was vitamin D and iron deficient and was supplemented.

Case 2

A 19-day-old male infant was admitted to the emergency department with cough, nasal congestion and breathing difficulties. The child was afebrile. The mother reported that the infant had clonic movements of the upper limbs for the past two days. He was born at full term but had intrauterine growth restriction (birth weight below the third percentile on Fenton curves). He was born to Syrian healthy parents with dark skin.

Plasma biology on admission revealed hypocalcemia (1.58 mmol/L) and hypovitaminosis D (5.3 mcg/L [N 30-80 mcg/L]). PTH was low (39 ng/L [N <49 mg/L]), ALP was normal and phosphorus was high. There was no urinary calcium loss (Ca/creatinine 0.682 mmol/mol creatinine). Nasopharyngeal microbiology showed a respiratory syncytial virus. The cerebrospinal fluid analysis after lumbar puncture was normal. The child was initially treated with empiric antibiotic therapy and a bolus of 100 mg/kg of Ca gluconate (9.3 mg/kg of elemental Ca). The child also received respiratory support with continuous positive airway pressure (CPAP).

Table 2: Amount of calcium administered.

	Day 0	Day 1	Day 2	Day 3	Day 4	Day 5	Day 6	Day 7	Day 8
Case 1									
Per os	Cholecalciferol 800 units	Cholecalciferol 800 units Calcium carbonate 50mg/kg of EC	Cholecalciferol 800 units Alfacalcidol 0,25 mcg Calcium carbonate 105mg/kg of EC	Cholecalciferol 3000 units Alfacalcidol 0,3mcg Calcium carbonate 210 mg/kg of EC	Cholecalciferol 3000 units Calcium carbonate 210 mg/kg of EC	Cholecalciferol D 3000 units Calcium carbonate 210mg/kg of EC	Cholecalciferol 3000 units Calcium carbonate 210mg/kg of EC	Cholecalciferol 3000 units Calcium carbonate 160mg/kg of EC	Cholecalciferol 3000 units Calcium carbonate 160mg/kg of EC
IVC	Calcium gluconate 24mg/kg of EC	Calcium gluconate 24mg/kg of EC		Calcium chloride 60mg/kg of EC	Calcium chloride 60mg/kg of EC	Calcium chloride 30mg/kg of EC	Calcium chloride 6mg/kg of EC		
IVD			Calcium gluconate 36mg/kg of EC	Calcium chloride 0,2 ml/kg (5,5 mg/kg of EC)					
Case 2									
Per os		Cholecalciferol 1000 units Calcium gluconate 50mg/kg of EC	Cholecalciferol 1000 units Alfacalcidol 0,3 mcg Calcium gluconate 75 mg/kg of EC	Cholecalciferol 1000 units Alfacalcidol 0,4 mcg Calcium gluconate 75 mg/kg of EC	Cholecalciferol 1000 units Alfacalcidol 0,4 mcg Calcium gluconate 75 mg/kg of EC	Cholecalciferol 1000 units Alfacalcidol 0,4 mcg Calcium gluconate 75 mg/kg of EC	Cholecalciferol 1500 units Alfacalcidol 0,4 mcg Calcium gluconate 50 mg/kg of EC	Cholecalciferol 1500 units Alfacalcidol 0,4 mcg Calcium gluconate 75 mg/kg of EC	Cholecalciferol 1500 units Alfacalcidol 0,4 mcg Calcium gluconate 75 mg/kg of EC
IVC		Calcium gluconate 50mg/Kg of EC	Calcium gluconate 50mg/kg of EC	Calcium gluconate 50mg/kg of EC	Calcium gluconate 50mg/kg of EC	Calcium gluconate 55mg/kg of EC	Calcium gluconate 25mg/kg of EC	Calcium gluconate 25mg/kg of EC	
IVD	Calcium gluconate 9,3 mg/kg of EC	Calcium gluconate 18,6 mg/kg of EC		Calcium chloride 5 bolus 0,1ml/kg (9,1 mg/kg of EC)	Calcium chloride 1 bolus 0,1ml/kg (1,8 mg/kg of EC)				

On D1, the hypocalcemia worsened (Ca 1.33 mmol /L); an IV bolus of 48 mg/kg of elemental calcium was administered and the child was transferred to the PICU.

PTH concentration (48.5 ng/L) and ALP increased. The child received continuous intravenous calcium gluconate (50 mg/kg/day of elemental calcium) and vitamin D supplementation (alfacalcidol and cholecalciferol). Calcemia did not improve and on D3, the child presented with new episodes of clonic movements and a cardiogenic shock with left heart dysfunction requiring the administration of 5 boluses of calcium chloride (9.1mg/kg of elemental calcium), ventilatory support and inotropic drugs. The amount of intravenous calcium gluconate was adjusted to the blood calcium level (maximum 55 mg/kg/day of elemental calcium), as was the amount of oral calcium (maximum 75 mg/kg/day of elemental calcium).

Normocalcemia was achieved on D6. On D 8, calcium supplementation was changed to enteral only.

Genetic investigation was normal, excluding DiGeorge's syndrome, and the child fully recovered one month after this acute episode and did no longer required calcium supplementation.

The exact amount of calcium administered is shown in Table 2.

The mother was also vitamin D deficient (25-OH-vit D <5 mcg/L, PTH 190 ng/L).

Discussion

The two children presented with hypocalcemia of different etiologies.

The first child presented hypocalcemia with elevated PTH, suggesting vitamin D deficiency. He had several risk factors for vitamin D deficiency: breastfeeding, poor dietary diversification, lack of synthetic vitamin D intake, skin color (2,3,9).

The second child had hypocalcemia with low PTH. In neonates, late onset neonatal hypocalcemia is frequently associated with paradoxically normal or low PTH (1,10). This may be explained by a delayed maturation of the parathyroid axis in the neonatal period (7,11,12). The source of calcium then depends on calcium absorption from the gastrointestinal tract. In vitamin D deficiency, calcium absorption cannot meet bone metabolic requirements. The typical biological findings in this situation are low calcium, normal or high phosphorus, and paradoxically normal or a low PTH as seen in our patient (11,13,14,15,16). In this case, the hypocalcemia is also exacerbated by the intrauterine growth restriction, which reduces calcium intake during the third trimester. Maternal hyperparathyroidism secondary to vitamin D deficiency is also thought to play an inhibitory role in hypoparathyroidism in children (10). This suggests a late-onset neonatal hypocalcemia exacerbated by vitamin D deficiency.

These two cases of symptomatic hypocalcemia with prolonged time to successful resolution, but more importantly, worsening plasma calcium concentrations after initiation of calcium and vitamin D administration, suggest a possible HB-like syndrome. Studies on the treatment of hypocalcemia due to vitamin D deficiency suggest a potential risk of HB-like syndrome if calcium treatment is inadequate at the start of vitamin D supplementation (7,8).

In case 1, we hypothesize that intravenous calcium initiates a flux of calcium from the blood to the bones, stopping the process of calcium resorption from the bones as with rickets ("hungry bone-like"). The first patient presented had several risk factors for HBS described in adults studies: elevated ALP and PTH, and bone lesions from rickets (4,6).

In the second case, there is a physiologically high bone turnover due to the young age, worsened by vitamin D deficiency. We suspect that this high bone turnover is the cause of the worsening of calcemia at the start of treatment, with a shift of calcium from the blood to the growing bone ("hungry bone-like"). There were no signs of rickets or bone injury on the chest x-ray and we did not expect bone abnormalities because there was no elevated PTH and the duration of the calcium deprivation was short. In fact, in neonates, hypocalcemia may be symptomatic before bone changes occur due to the physiological period of high metabolic bone demand (4, 14, 15, 17).

HBS is an uncommon cause of hypocalcemia in children (6). This syndrome is mainly described as a postoperative complication of parathyroidectomy but also during treatment of hyperthyroidism or osteoblastic metastases of prostate or breast cancer (18,19). In all these conditions, there is a phenomenon of high metabolic bone turnover. HBS is characterized by a flow of calcium from the blood to the bones, due to a change from an osteoclastic to an osteoblastic process in the bone, leading to hypocalcemia lasting more than four days despite calcium supplementation (6). It is often associated with hypomagnesemia, hypophosphatemia and hyperkalemia (5,6). In the case of parathyroidectomy, a high bone turnover due to high PTH leads to bone injury. The decrease in PTH after surgery results in a shift from osteoclastic to osteoblastic process and a possible HBS.

There is no clear consensus on the treatment of HBS (20).

Lima Ferreira et al. propose a postoperative management protocol for parathyroidectomy to better manage hypocalcemia by identifying risk factors for HBS, and defining the amount of calcium and calcitriol needed based on blood calcium levels. They demonstrate that implementation of this protocol improves detection of HBS and reduces the duration of hypocalcemia (8).

The amount of calcium required for HBS is highly variable (6-12g/day in adult studies) (20).

Treatment of HB-like syndrome would consist of high-dose calcium and vitamin D administration. In the case of symptomatic hypocalcemia, calcium should be started with a bolus of 1-2 mg elemental calcium/kg followed by a continuous intravenous infusion of 1-3 mg elemental calcium/kg/hour (5). Oral treatment should be started as soon as possible to avoid the side effects of intravenous calcium administration (local irritation, tissue necrosis). Serum calcium levels should be monitored several times a day (every 4-6 hours) to adjust the treatment dose (16). Electrocardiographic monitoring is recommended because rapid changes in serum calcium may induce arrhythmias. The active forms of vitamin D are preferred (calcitriol/alfacalcidol). In our cases, optimization of treatment by increasing the doses of IV calcium and vitamin D administered has made it possible to treat the persistent hypocalcemia.

For the treatment of nutritional rickets, it is recommended to give at least 2000 IU/day of oral vitamin D for 3 months, and the intake of calcium should be 500 mg/day (dietary or supplements) (9). Magnesium treatment must also be initiated, as low magnesium levels exacerbate hypocalcemia (5,6,11,20).

Rickets, dilated cardiomyopathy and convulsions associated with hypocalcemia due to vitamin D deficiency are reversible after normalization of blood levels of vitamin D and calcium (2,3). If a child presents with hypocalcemia associated with dietary vitamin D deficiency, chest x-ray, bone x-ray if rickets is suspected (ankles and wrists, where growth plate enlargement may be seen as they are areas of rapid growth), and cardiac ultrasound should be considered (2, 3, 9).

Conclusion

We describe two cases of persistent hypocalcemia, occurring despite vitamin D and calcium supplementation in children with symptomatic vitamin D deficiency. This may be the consequence of a hungry bone-like syndrome in children whose growth is dependent on bone formation.

The term HBS should be reserved for situations in which a hypercatabolic state is converted to an anabolic process, which is not the case in vitamin D deficiency. Hungry bone-like syndrome could occur during vitamin D and calcium supplementation for hypocalcemia with vitamin D deficiency, especially if the patient has a significant bone turnover. For symptomatic hypocalcemia, calcium should be administered as a bolus and continuous intravenous infusion. If the calcemia falls after calcium administration, it suggests a HB-like syndrome and intravenous calcium bolus and vitamin D supplementation should be used to intensify treatment.

Complications of vitamin D deficiency are completely preventable with a good prevention strategy. It is the role of the pediatrician to educate

parents, monitor at-risk children and ensure that any child presenting with hypocalcemia receives appropriate diagnostic testing to elucidate the cause of hypocalcemia and detect potential complications.

Conflict of interest

The authors have no conflicts of interest in relation to the subject matter of this manuscript.

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Acute encephalopathy in a neonate associated with infection by SARS-CoV-2

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Keywords

Epilepsy ; punctuate white matter lesions ; SARS-CoV-2 ; meningo-encephalitis ; neonatal seizures.

Abstract

We present the case of a 5-day-old patient who was admitted to the emergency department with initially unilateral and then generalised seizures and lethargy. Cerebral MRI had shown diffusion-restricted symmetrical fronto-parietal lesions consistent with viral encephalitis due to SARS-COV-2. The control MRI showed signs of necrosis with the appearance of cavitation, predominantly on the left side. Neurological follow-up was performed at 1, 3 and 6 months of age and showed no significant neurodevelopmental delay.

Introduction

Our lives have been significantly affected by the SARS-COV-2 (known as COVID-19) pandemic since early 2020. This virus can cause a variety of disease symptoms ranging from asymptomatic carriers to a multisystem inflammatory syndrome in different age groups. Children appear to be less affected by this virus, often showing milder or no symptoms. However, an increasing number of cases have been reported in the literature describing severe disease, particularly neurological, such as lethargy, irritability, hypotonia, apnoea and seizures in young toddlers (1). We present a case of a neonate affected by COVID-19 with seizures due to encephalopathic white matter lesions.

Case report

The patient was a female born at 39 weeks by caesarean section for breech presentation. There were no other complications. The pregnancy was uneventful, except for controlled maternal hyperthyroidism. The Apgar scores were 9 and 10 at 1 and 5 minutes of life, respectively, and her birth measurements were within the normal range for her gestational age.

The patient was admitted to the emergency department because of abnormal movements and lethargy. In the emergency department, she had two further episodes of clonic movements, which started on the left side and then became generalised. There was no association with fever.

Initial blood tests were normal: normoglycaemia, mild leukopenia with 4340 WBC per microlitre, no other abnormalities in the haemogram, negative C-reactive protein, normal electrolytes, liver, and renal function, and basic coagulation tests showing no abnormalities. Empirical treatment with intravenous cefotaxime, amoxicillin, and acyclovir was started to cover the possibility of neonatal sepsis or herpes simplex virus encephalitis. After negative results of blood, urine and CSF cultures, antibiotics and antiviral treatment were discontinued. The seizures were initially controlled with intravenous phenobarbital and midazolam and then successfully managed with levetiracetam. She had no further convulsions.

On the day of admission, a CT-scan of the brain showed no abnormalities. However, a brain magnetic resonance imaging (MRI) scan showed symmetrical fronto-parietal signal abnormalities and restricted diffusion, predominantly on the fronto-polar cortex, precentral and central gyrus, anterior and posterior commissures of the corpus callosum, and postero-lateral regions of the thalami (Figure 1). These findings were consistent with neonatal encephalopathy.

A complete metabolic analysis, including blood, urine, and CSF amino acid levels, organic acid levels, and acylcarnitine profile, was performed to rule out a metabolic cause. All the results were normal. In addition, rapid exome sequencing revealed no significant pathological genetic mutations.

Analysis of cerebrospinal fluid (CSF) collected on days 1 and 3 showed normal cytology and normal glucose and protein levels (885 mg/L). A nasal swab tested positive for SARS-CoV-2 by reverse transcriptase polymerase chain reaction (rt-PCR). No other virus was found in her nasal swab, and we were able to rule out rhinovirus, enterovirus, influenza A&B, parainfluenza 1, 2, 3, 4, coronavirus (non-covid-19), cytomegalovirus (CMV). CMV was also tested by PCR on urine and CSF with negative results.

The patient's father had recently tested positive for SARS-COV-2 following mild respiratory symptoms. Her mother was asymptomatic, but her nasal swab tested positive for SARS-COV-2. The PCR SARS-COV-2 test on the CSF was negative. To exclude other viral causes, we tested the CSF for various neurotropic viruses such as herpes simplex virus types 1&2, enteroviruses, varicella-zoster virus, parechovirus, human herpesvirus 6 and CMV, all of which were negative. The patient had no respiratory symptoms related to her SARS-COV-2 infection, and two chest radiographs taken during her hospitalisation showed no specific abnormalities. Based on these findings, our presumptive diagnosis was viral encephalopathy probably due to SARS-COV-2, as this was the only virus detected.

Follow-up brain MRIs at 10 days (Figure 2) and 6 weeks (Figure 3) showed more defined lesions, reduced inflammation, and the appearance of cavitary zones. Spectroscopic analysis confirmed neuronal loss, supporting providing further evidence of a specific necrotizing encephalitis, with SARS-COV-2 being the only etiological factor detected.

Neurological follow-up at 1, 3, and 6 months of age showed no significant neurodevelopmental delay.

Discussion

There are many causes of neonatal encephalopathy, often related to acute brain injury during the perinatal period (2). The lesions described in this case did not correspond to the classic haemorrhagic or ischaemic lesions. Other aetiologies such as genetic or metabolic syndromes were ruled excluded by laboratory investigations. After excluding all other causes, including metabolic, genetic, haemorrhagic, thrombotic, and other bacterial and viral infections, it was concluded that the encephalopathy was due to SARS-COV-2 infection, which is now known to cause early neurological damage

Figure 1: Day 0. From left to right: cerebral MRI in T1, FLAIR, and diffusion-weighted image. Diffusion-weighted image shows a symmetrical restricted diffusion (hyperintensity of b-1000 and decrease of apparent diffusion coefficient) in the fronto-parietal regions, predominantly on the fronto-polar cortex, precentral and central gyrus, anterior and posterior commissures of corpus callosum, and the postero-lateral regions of thalami. It is associated with discreet flair hyperintensity in the same region. Also a discreet bilateral contrast enhancement in fronto-parietal leptomeninges is present.

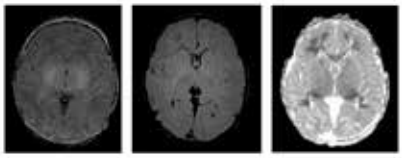


Figure 2: Day 10. From left to right: cerebral MRI in T1, FLAIR, and diffusion-weighted image. The first image shows hyperintense lesions in the white matter, especially in the frontal and the parietal regions. The frontal white matter shows signs of necrosis. Diffusion - restricted lesions are found in the corpus callosum.

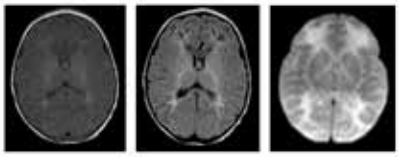
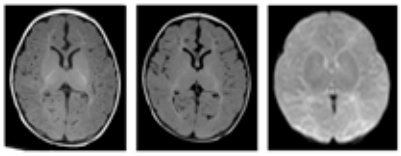


Figure 3: Week 6. From left to right: cerebral MRI in T1, FLAIR, and diffusion-weighted image. This MRI shows the regression of the diffusion restricted lesions, followed by the appearance of white matter lesions in the frontal cortex with the appearance of cavitation, predominantly on the left side.



in neonates (1). We emphasise on the fact that this diagnosis remains presumptive, as it is a diagnosis of exclusion.

Similar neurological lesions have been described in other viral encephalopathies, often associated with rotaviruses or enteroviruses (3, 4). Three similar cases associated with SARS-COV-2 infection have been (5-7). All cases had white matter lesions with restricted diffusion particularly in the corpus callosum and periventricular white matter. Our case, as well as a case described by Fragoso in 2022, showed cytotoxic white matter lesions transitioning into cavities. None of the described cases presented with respiratory symptoms. Of these cases, only one patient was treated with corticoids, in contrast to our patient (5).

The exact mechanism of these neurological lesions remains unclear. In none of these cases was SARS-COV-2 directly detected in the CSF. According to the International Encephalitis Consortium, the CSF pleocytosis is supportive, but not a necessary criterion for encephalitis, particularly in young infants. The major diagnostic criterion is an altered mental status lasting more than 24 hours without an alternative cause as evidence of neurological dysfunction. In addition, at least two additional minor criteria must be present, namely: fever ≥38°C within 72 hours, seizures, new focal neurological findings, CSF pleocytosis (≥5 white blood cells/μL), neuroimaging with brain parenchymal changes, or an electroencephalogram consistent with encephalitis (8). Young infants are more prone to have infectious encephalitis without pleocytosis, for example with enterovirus or parechovirus infections (8). Some authors suggest that central nervous system lesions may result from the virus accessing the central nervous system (CNS) directly or via an excessive cytokine release mechanism (1). The cytokine storm syndrome typically manifests as persistent fever, cytopenia, a high erythrocyte sedimentation rate, increased fibrinogen, and hyperferritinemia (5). However, our patient did not have any of these abnormalities. Studies conducted by Lindan have shown that the most commonly observed neuroimaging manifestation in children, not only neonates, is similar in appearance to ADEM (acute disseminated encephalomyelitis), with patchy or confluent areas of T2 hyperintensity in the grey and white matter, with or without reduced diffusion or enhancement (9).

We would like to emphasize that neurological symptoms due to SARS-CoV-2 represent a non-negligible proportion of affected neonates. A review of the literature on SARS-CoV-2 in neonates (both term and preterm) by Moraes et al in 2022 analysed data from a total of 87 neonates (1). Of these, 23% were asymptomatic. Those with symptoms usually had respiratory symptoms (57.5%) such as respiratory distress, tachypnoea, cough, and coryza. A total of 26.4% had fever. Neurological symptoms were observed in 26.4% of neonates, with lethargy being the most common (9.2%). Gastrointestinal symptoms such as vomiting, feeding intolerance and abdominal distension were seen in 21.8% of patients.

The long-term prognosis of affected children remains uncertain. The neurodevelopment of our patient seems to be completely normal at the age of 3 and 6 months of age, but it should be noted that the prefrontal regions become functional much later. Some other authors conducted a case-control study of newborns diagnosed with SARS-CoV-2 in Wuhan, China (10). A total of five newborns with SARS-CoV-2 were included. Despite a significant difference in the Hammersmith neonatal neurological examination score between infected and non-infected groups at the time of initial evaluation, there was no significant difference in neurobehaviour at 9 months of age. Larger studies with longer follow-up are needed to fully understand the impact of early-onset SARS-CoV-2 encephalitis.

Conclusion

Although our diagnosis is by exclusion and remains presumptive, it is important to consider SARS-CoV-2 infection in neonates presenting with atypical symptoms such as seizures, even in the absenceof respiratory distress. Imaging findings were also non-specific, although they are characteristic of viral encephalitis. Therefore, paediatricians should be aware of these possibilities and test for SARS-CoV-2 in patients with seizures and no other systemic involvement.

Conflict of interest

The authors have no conflict of interest to declare.

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Failure to thrive and hypergammaglobulinemia in a 13-year-old girl with Castleman Disease, a case report

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Keywords

Failure to thrive – Castleman Disease – Hypergammaglobulinemia - Lymphoproliferation.

Abstract

Castleman Disease is a rare, lymphoproliferative, non-malignant disorder with two subtypes, unicentric or multicentric, depending on the number of lymph node regions affected. Clinical symptoms may be extremely variable often making the diagnosis difficult or leading to delayed diagnosis. We describe a case of failure to thrive associated with late puberty, and severe hypergammaglobulinemia. Through this case report, we aim to recall the clinical features of this rare disorder and to insist on the importance of a broad differential diagnosis in the presence of failure to thrive especially with abnormal biochemical features.

Introduction

Failure to thrive (FTT) and late puberty are most frequently associated with endocrinopathies, syndromes, anorexia nervosa, inflammatory bowel disease or other chronic conditions. However, as we demonstrate in our case, Castleman Disease (CD), a rare and non-malignant lymphoproliferative disorder with very heterogeneous clinical phenotypes, should also be considered in the differential diagnosis. We describe the case of FTT associated with hypergammaglobulinemia and an inflammatory suprarenal mass.

Case report

We report the case of a 13-year-old girl who presented with FTT associated with late puberty (Figure 1). She has no past medical history and both her parents are healthy. Her birth weight and height were 2740 g and 49 cm, respectively. She has a healthy twin sister who is taller than her (BMI 17,2 kg/m^2, -1 SD). The patient's target height is 170 cm (0,6 SD).

Figure 1:
Body Mass Index curve (Flanders, 2004), red arrow indicates the time of surgery.

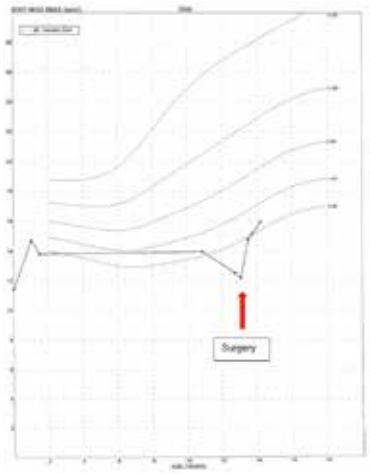
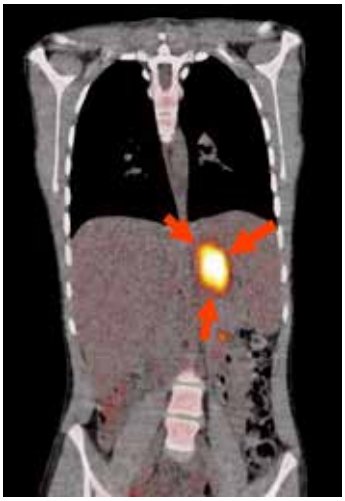


Figure 2:
PET-CT shows a hypermetabolic lesion in the left suprarenal fossa.



In addition to FTT and late puberty, the main symptoms were fatigue, a subfebrile state and a lack of appetite leading to often unfinished meals but frequent snacking. The possibility of anorexia nervosa was excluded based on the absence of food restrictions or the fear of gaining weight. She did not report any digestive symptoms but recalled a blood spot on the toilet paper.

On clinical examination, she was in good condition but lean and pale with a height of 148,8 cm (-1,5 SD); a weight of 27,1 kg (-3,6 SD); BMI of 12,2 kg/m^2 (-4,0 SD) and Tanner stage A1P1M1. She had no dysmorphic features and her vital signs were completely normal.

Complementary investigations revealed an anemia of chronic disease (Hb 7,7 g/dl [N 12-16], hematocrit 27.2% [N 36-46], MCV 63.1 µm3 [N 78-100], reticulocytosis 46.1x103/µl), elevated C-Reactive Protein (CRP 164.4 mg/L [N <5 mg/L]), elevated sedimentation rate (120 mm/h, [N 0-11 mm/h]) normal white blood cell count (7.72x103/µl), elevated platelets (432x103/µl) and normal levels of liver enzymes. Endocrine assessment was normal for prolactin, TSH and free T4, and FSH, LH, estradiol and IGF-1 in the prepubertal range.

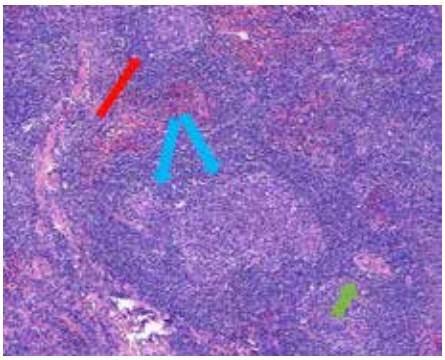
Fecal calprotectin, IgA transglutaminase, anti-Neutrophil cytoplasmic antibodies (ANCA), antisaccharomyces cerevisiae antibodies (ASCA), abdominal ultrasound, gastric endoscopy and colonoscopy were normal.

The following additional workup was performed: tuberculin intradermal test, chest x-ray, lymphocyte typing, and antinuclear factor, all of which were normal. However, a severe hypergammaglobulinemia (total IgG 26,17 g/L [N 5,8-14,5 g/L]) was found.

PET-CT showed a hypermetabolic lesion in the left suprarenal fossa (Figure 2). Transgastric biopsy was performed through echo-

endoscopy. Histologic sections (Figure 3) of the lymph node showed a mainly preserved architecture with hyperplastic lymphoid follicles of various sizes. Some showed slightly atrophic germinal centers surrounded by enlarged mantle cuffs sometimes arranged in concentric rings. Increased vascularity with penetration of radially-oriented hyalinized blood vessels in the germinal centers was also focally observed. Immunohistochemical staining was unremarkable and negative for human herpesvirus-8 disease. The Ebstein-Barr encoding region was negative. There was no evidence of Immunoglobulin heavy chain clonality on molecular analysis. The IgG4/IgG ratio was not elevated and there was no significant amount of IgG4 plasma cells. Folliculolysis and pictures reminiscent of progressive germinal center transformation were also observed. Overall, the histopathologic findings were consistent with a reactive germinal center with Castleman-like modifications.

Figure 3:
Biopsy sample of a suprarenal lymph node, magnification x5, stained with hematoxylin and eosin, shows twinning of the germinal centers (blue arrows), atrophic germinal center with concentric distribution of the mantle cuff (red arrow) and slightly hyalinized vessels penetrating the mantle zone (green arrow).



The suprarenal mass (5,5 cm x 4,5 cm x 3 cm) was surgically resected and the proposed diagnosis of unicentric Castleman Disease was confirmed histologically.. Subsequently, rapid remission ensued with restored appetite, weight gain, and onset of puberty observed. Likewise, biochemical parameters improved rapidly, including normalization of the gamma globulin levels. One year later, there were no signs of recurrence.

Discussion

This case illustrates the need for a stepwise but comprehensive biochemical and imaging workup in the setting of failure to thrive.

We first ruled out the most common diagnoses and then investigated rarer causes. Anorexia nervosa, endocrinopathy and chronic infectious disease were quickly ruled out based on the patient's behavior, endocrine and microbiologic analyses and gastroenterologic workup.

Severe hypergammaglobulinemia (>25g/l) orientated our diagnostic approach. In the largest cohort study of 442 pediatric patients with hypergammaglobulinemia (>20 g/L), Lo et al. reported that 95% of patients had identifiable disorders with nearly half of the patients affected by autoimmune diseases such as systemic lupus erythematosus (SLE), inflammatory bowel disease, as well as infectious diseases (EBV, CMV, HIV) and less commonly malignant, drug-related, and other diseases including CD (1).The authors observed that, higher IgG levels, lower white blood cell count, lower hemoglobin levels, lower C-reactive protein levels, as well as female gender were independent risk factors for autoimmune diseases.

Our patient presented with hypergammaglobulinemia and only the low hemoglobin level and the female gender were also in favor of autoimmune / autoinflammatory disease, but extensive workup ruled out such diseases. There was no evidence of chronic infectious disease. Biopsy samples of the suprarenal mass led to the exclusion of malignancy but confirmed reactional lymphoid hyperplasia with Castleman-like modifications.

First described by Benjamin Castleman in 1958, CD is divided into two subtypes depending on the number of affected lymph nodes. Unicentric Castleman Disease (UCD) involves one or more lymph nodes in a single region of the body with similar histopathologic features. UCD is a slowly progressive disease with no specific clinical manifestations (2). Multicentric Castleman Disease (MCD) involves multiple affected lymph node areas, with similar histopathologic characteristics. Patients with MCD present with systemic symptoms and generalized lymphadenopathy, hepatosplenomegaly, cytopenia and organ failure due to inflammatory cytokine secretion (3). In their 2015 study, Munshi et al. estimated the annual incidence of CD in the United States to be between 6500 and 7700 new cases, of which 75% were with UCD, which had a better outcome than patients with MCD (4).

The etiology of CD is unclear. Typical histopathologic aspects of affected lymph nodes are reactive changes, which could be observed with abnormal antigenic stimulation or in a low-grade neoplastic process (5). In the MCD subtype, half of the cases are associated with HHV8 infection, and the other half are HHV8-negative, termed idiopathic MCD (iMCD) (3). Immunological mechanisms such as elevated IL-6 levels are thought to mediate the lymphoproliferative mechanisms. The expression of a viral analog of IL-6 (vIL-6) by HHV-8 may play a role in the downstream mediation of plasmacytosis in the setting of HHV-8 infection (6). Nabel et al. suspected that UCD and or HHV8 negative MCD could be caused by other viruses, but they failed to establish a clear association with any other virus (7). Pediatric CD has similar clinical features compared to adult patients, but the disease mechanism may be different because most adult cases occur in a context of immunodeficiency associated with HIV and/or HHV-8 infection. In children, CD appears to be caused by a primary dysregulation of the immune system (8). In their 2018 retrospective cohort study, Sopfe et al, reported that 75% of their pediatric patients presented with UCD (9). As in our patient, children often present with systemic manifestations such as weight loss, chronic fatigue, fever, and abnormal laboratory results such as elevated erythrocyte sedimentation rate and CRP, microcytic anemia, thrombocytosis and hypergammaglobulinemia (9).

Diagnosis of CD is based on histopathologic findings and is classified into one of two subtypes - hyaline-vascular or mixed/plasmacytic subtype. The histologic differential diagnosis should include malignancies (Hodgkin lymphoma, Non-Hodgkin lymphoma, sarcoma), inflammatory diseases (SLE, systemic-onset juvenile idiopathic arthritis, Sjögren syndrome) or infectious diseases (EBV, CMV, HIV) (5).

The best treatment for UCD is surgery. If complete, surgical resection is usually curative. If surgery is incomplete, radiotherapy or embolization are complementary treatment options. In some cases of limited accessibility, simple clinical surveillance may be considered. Outcomes are excellent with no impact on life expectancy (9).

Although not curative, the management of MCD aims to limit complications due to inflammation and to improve patients' quality of life. In the past, corticosteroids and chemotherapy were used as first line treatments when surgery was not possible. However, their benefits were limited and adverse effects were considerable (8). Currently, new biologic therapies are available including anti-CD20, anti-IL1, and anti-IL6.The current first-line treatment suggested for pediatric patients with MCD is the use of tocilizumab, an anti-IL-6 receptor monoclonal antibody, but recommendations regarding treatment duration and adverse effects are still expected (8, 10).

Conclusion

Castleman Disease is a rare and clinically heterogeneous disorder frequently associated with FTT in children, systemic manifestations, and hypergammaglobulinemia. The diagnostic workup should include autoimmune/autoinflammatory diseases, infectious diseases, malignancies or lymphoproliferative disorders such as CD.

The prognosis of UCD, the most common form of CD in children, is generally excellent after surgical excision with rapid resolution of symptoms. The inflammatory symptoms associated with MCD are alleviated with new biologic therapies that help to improve patients' quality of life.

Conflict of interest

The authors have no conflict of interest to declare.

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Sporadic colorectal adenocarcinoma in children: an uncommon diagnosis

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Keywords

Colorectal cancer ; mucinous adenocarcinoma ; children.

Abstract

Colorectal cancer (CRC) is rare in the pediatric population. Low incidence and disease awareness among pediatricians often leads to delayed diagnosis. Compared with adult CRC, pediatric CRC is characterized by an advanced clinical stage at diagnosis and a higher frequency of unfavorable histopathology. We report the case of an 11-year-old boy diagnosed with an adenocarcinoma of the ascending colon without any predisposing factors.

Introduction

In the European Union, colorectal cancer is estimated to account for 12.7% of all new cancer diagnoses and 12.4% of all cancer deaths in 2020. It is the second most common cancer in adults after breast cancer and the second most common cause of cancer death in adults after lung cancer (1). In contrast, CRC is rare in children and adolescents, with an estimated annual incidence of one case per million (2).

Many small series and case reports suggest that children are more likely to present with advanced-stage disease than adults. This phenomenon can be explained by the non-specific symptoms and low awareness of the disease, leading to delayed diagnosis, and by the fact that the tumors found in children are often aggressive with unfavorable histology, suggesting a different pathophysiology.

Clinical case

An 11-year-old boy presented to the emergency department with a 3-month history of abdominal pain and weight loss of 2 kg.

He had been referred 1 month earlier by his general physician for hematochezia. Constipation was diagnosed at that time based on the history and the presence of a small anal fissure scar. A treatment was initiated. On admission, the pain had been increasing for one week and was associated with vomiting, nausea, and fever. He had no medical history except for asthma and no history of travel.

Physical examination revealed a relatively distended abdomen with diffuse rebound and tenderness, right lumbar pain and palpable stool. His vital signs were normal.

Abdominal ultrasound showed a distension of the right colonic frame with suspicion of paralytic ileus. The evaluation was completed with abdominal radiography and a computed tomography, which demonstrated the presence of a right colic flexure-centered mass causing intestinal subocclusion (Figures 1 A and B). Intestinal wall thickening and multiple adenopathies were also seen. A malignant lesion was suspected, yet tumor markers (CEA (carcinoembryonic antigen) and NSE (neuron-specific enolase)) were negative.

Figure 1:
A. An Abdominal X-ray was done at first showing air-fluid levels and a right paravertebral calcification at L2 level.
B. Abdominal computed tomography showed the presence of a right colic flexure centered mass causing intestinal subocclusion.

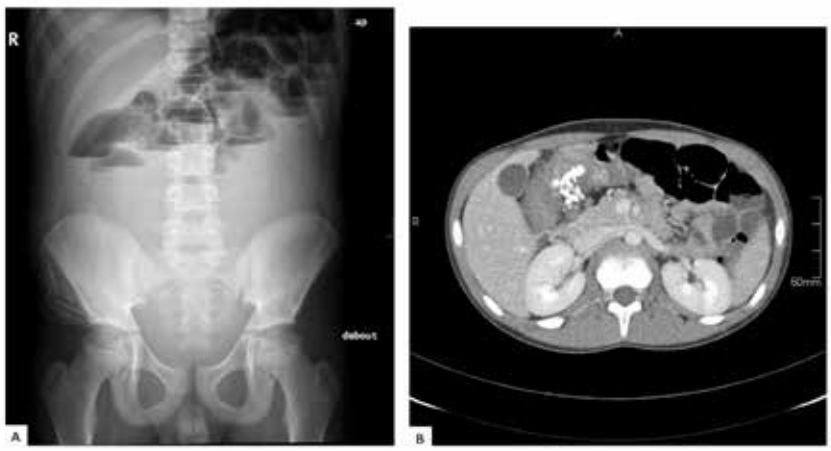


Figure 2:
A and B : Colonoscopy showed an annular, irregular mass with an ulcerated aspect totally obstructing the lumen.

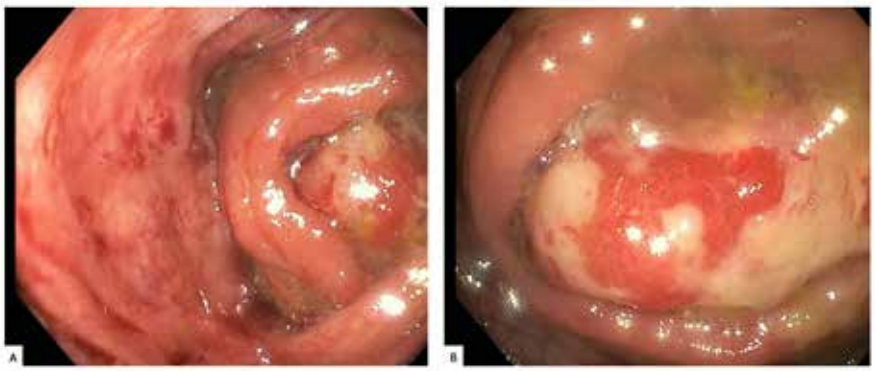
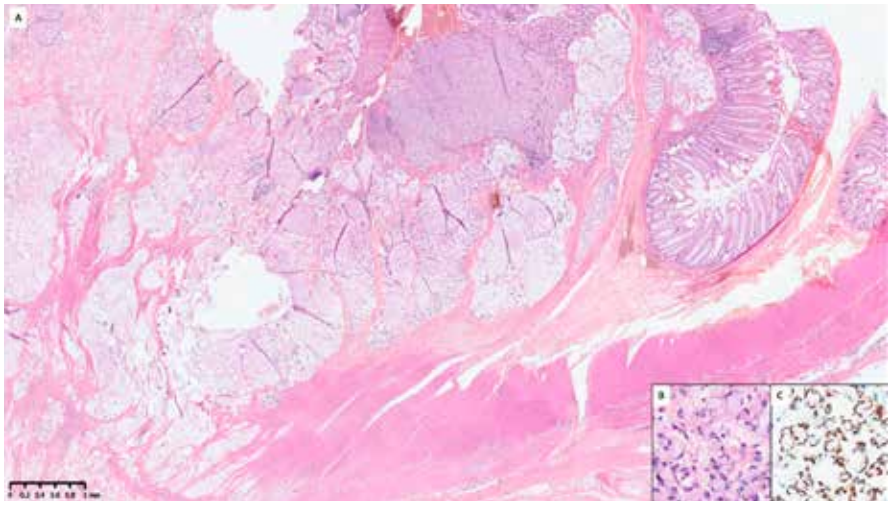


Figure 3:
A. Histopathology of the lesion. H&E staining of the tissue showing tumoral lesions characterized by abundant extracellular mucin with numerous floating signet-ring cells.
B. H&E staining - x40- Isolated tumor cells with an eccentric nucleus and mucus vacuole.
C. x40- Immunohistochemical stains are positive for Anti-CDX2, which is a transcription factor expressed in case of intestinal differentiation.
H&E = hematoxylin and eosin.



A diagnostic laparoscopic surgery with concomitant colonoscopy was scheduled. An annular colon tumor with an ulcerated aspect was found in the right colonic frame, obstructing the lumen (Figures 2 A and B). Pathology of the tumor and lymph node biopsies revealed abundant extracellular mucin with numerous floating signet-ring cells, supporting the diagnosis of mucinous adenocarcinoma (Figure 3 A and B).

A right hemicolectomy was performed. Final pathology results confirmed high-grade mucinous adenocarcinoma extending through the visceral peritoneum. Seven lymph nodes out of the sixty-three removed were metastatic. There was no evidence of metastatic disease to the liver, and the preoperative PET scan was negative. The final staging was pT4aN2bMx according to the 8th edition of the Union for International Cancer Control.

The immunohistochemical profile of the tumor was CK20/CDK2/MUC2 confirming the colic origin, but no evidence of microsatellite instability was found (Figure 3C). Next-generation sequencing of the samples revealed no mutations in the *NRAS*, *KRAS* and *BRAF* genes, but identified a presumed pathogenic point mutation in the tumor suppressor gene *TP53*, a gene associated in about 40 to 50% of sporadic colorectal cancer cases in adults.

A constitutional mutation of TP53 was ruled out.. Further genetic testing for inherited cancer susceptibility syndromes (Hereditary Non-Polyposis Colorectal Cancer, Familial Adenomatous Polyposis (FAP), MUTYH-associated polyposis, Peutz-Jeghers syndrome, Juvenile polyposis syndrome and Cowden syndrome) was also negative.

The patient underwent a FOLFOX chemotherapy regimen consisting of 1 cycle of intravenous 5-fluoruracil and oxaliplatin every 2 weeks. To date, he has completed thirteen cycles of chemotherapy without complication. Follow-up imaging studies have shown no evidence of recurrent disease.

Discussion

While it is one of the most frequent malignancies among adults, colorectal cancer is a rare tumor in the pediatric population, with an incidence of approximately 1 per million. A recently published population-based study using the SEER database (1973-2005) calculated an age-adjusted incidence rate of 0.38 and 802 per million for children/adolescents and adults respectively (2).

Much of the existing literature focuses on young adults or "early-onset" colorectal cancer (< 50 years of age), while fewer series or studies focus on children or adolescents. The largest database study to date was published by Poles et al. in 2015. Using the National Cancer Database, they compared pediatric, early-onset, and older adult patients with a total of 918 pediatric patients (≤ 21 years) (3).

Common presenting signs and symptoms are abdominal pain, vomiting, altered bowel habits, weight loss and hematochezia. However, these are often underestimated because they are nonspecific and can mimic many common functional gastrointestinal disorders in children. In our case, the patient had a history of hematochezia with presence of a small anal fissure scar caused by constipation, itself due to the tumor.

As illustrated by our case, pediatric colorectal cancer is unanimously characterized in the literature by a high occurrence of aggressive histologic subtypes: poorly differentiated, signet-ring or mucinous adenocarcinoma. The cause of this observation has not been elucidated to date. Still, it is suggested that pediatric CRC may have a different pathophysiological process compared to the well-known multistep development described in adult CRC (which usually occurs over approximately 10 years) (4). It has been demonstrated that even in adult CRC, there are significant differences in molecular alterations between mucinous and non-mucinous colorectal adenocarcinoma. Mucinous colorectal adenocarcinoma is characterized by an overexpression of the MUC2 and MUC5AC proteins, high-frequency microsatellite instability and mutations of the *RAS/MAPK* pathway (5).

High-frequency microsatellite instability (MSI) is caused by defects in the mismatch repair system (MMR). It has been found mainly in Hereditary Non-Polyposis Colorectal Cancer (HNPCC) but also in about 15% of sporadic CRC in adults. Few articles suggest a more frequent occurrence of MSI in early-onset sporadic colorectal carcinomas than in late-onset tumors. Furthermore, a different pattern of genetic alterations between both groups has been suggested to cause the altered function of the MMR system. (6-7)

An advanced stage at diagnosis is also a hallmark of pediatric CRC. This is illustrated in the population-based study by Poles et al., in which 62% of

pediatric patients presented with stage 3 and 4 disease at presentation, compared to 49.7% and 37.3% in the early-onset adult and older adult populations respectively (3).

The reason why children present more often at a later stage than adults is still unclear, but the possible explanations include an intrinsically more aggressive behavior of the disease and a delayed diagnosis, itself due to low incidence, non-specific symptoms and lack of awareness by physicians. In their review, Hill et al. compared patients whose time to diagnosis was less than 2 months (20 patients) with those whose diagnosis occurred 2-6 months (12 patients) after symptom onset. This comparison showed that patients with a longer delay to diagnosis tended to have a lower disease stage (p= 0.063) and better overall survival (p=0.014), making it less likely that delayed diagnosis alone explains advanced disease at presentation (8).

CRC most frequently develops sporadically in children. The main known predisposing factors are inflammatory bowel disease and inherited cancer susceptibility syndromes such as FAP and HNPCC, which are inherited autosomal dominant disorders associated with early-onset tumors. However, they seem less frequent in the pediatric population, representing an average of 10% of the cases (9). Several authors, such as Weber et al., have presented evidence suggesting that pediatric patients with predisposing syndromes (mainly HNPCC) have a better prognosis than those with sporadic disease (10).

However, in the case of HNPCC, strict adherence to follow-up guidelines does not seem to explain this observed better prognosis as there are currently no specific recommendations for the follow-up of children. The onset of surveillance colonoscopy is advised to be stratified based on the associated gene, with 25 years being the earliest recommended age.

To date, there are no therapeutic recommendations specific to pediatric CRC, so adult protocols are used. Surgery is considered the keystone of the treatment and should be radical. Complete surgical resection and lymph node dissection are decisive for cure. Saab et al. reported that the common factors among long-term survivors of pediatric CRC were low-stage disease and complete resection.

Depending on the disease stage, surgery may be followed by adjuvant chemotherapy. Oxaliplatin and 5–fluorouracil–based antineoplastic agents are commonly used chemotherapy combinations. For patients with metastatic disease, resection of all metastatic lesions is needed. Therefore, neoadjuvant chemotherapy may be advised (9).

Predictors of poor outcome in addition to disease stage are incomplete resection, mucinous histology, proportion of signet-ring cells > 10 %, and the absence of an in-situ component (2, 8).

Pediatric CRC is also characterized in the literature by a poorer survival rate than in adults. In the population-based study by Sultan et al. using the SEER database, the estimated 5 and 10 years overall survival rates were 40% ± 4,2% and 31% ± 4,4% respectively, in the children/adolescent population. This compares to 60 % ± 0,1% and 54 % ± 0,1% in the adult population. They also observed an improved outcome over time in adults, while no major differences were observed in children and adolescents (2).

Conclusion

Pediatric CRC differs from adult-onset CRC in several aspects. It is characterized by a high occurrence of aggressive histologic subtypes, an advanced clinical stage at diagnosis and, probably due to these aforementioned aspects, a poorer prognosis than adults.

There is evidence that an intrinsically different tumor biology may partially explain these features. In the absence of specific pediatric treatment recommendations, adult protocols are currently used. However, given the possibility of a different pathogenesis, the response to treatment may also be different from adult cancers. This is supported by the fact that even within adult populations, early-onset colorectal cancer is associated with differences in tumor behavior. With this in mind, further studies are needed to adapt the management of pediatric CRC, starting with a better understanding of the physiopathological process.

Due to its rarity and the non-specific nature of the symptoms, it is challenging to provide specific recommendations to general pediatricians regarding suspicion of CRC. Our suggestion is to be vigilant for warning signs and to emphasize the need to re-evaluating the outcomes of any therapeutic intervention.

Conflict of interest

The authors have no conflicts of interest to declare with regard to the topic discussed in this manuscript.

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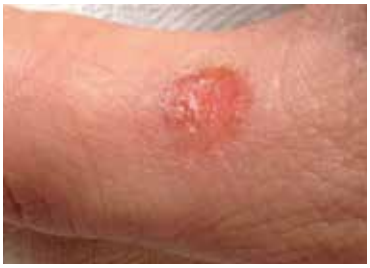
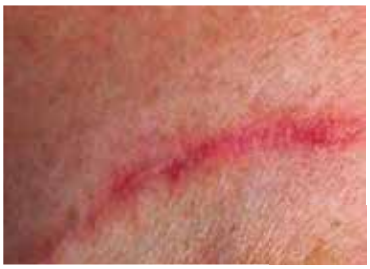


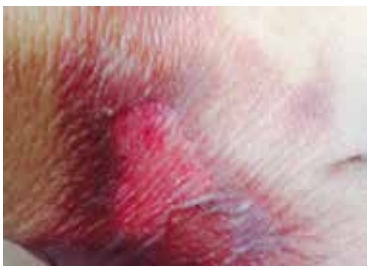
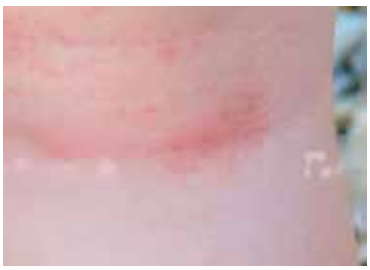

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Birth-related neonatal rib fracture: a case report

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Keywords

Rib fracture ; birth injury ; neonate ; case report.

Abstract

Rib fractures due to birth trauma are rare, other mechanisms of trauma need to be considered. We report the case of a large for gestational age newborn in the maternity ward with an isolated rib fracture due to birth trauma. Birth was complicated with shoulder dystocia after a vacuum extraction.

Introduction

Bone fractures resulting from birth trauma are not uncommon. Clavicle fractures are the most common with an incidence of up to 3.2% (1). Fractures also occur at other sites, such as the femur, humerus or skull. Rib fractures, however, are rare. Rib fractures are usually localised in multiple ribs and are often accompanied by clavicle fractures (2,3). In this article, we present a case study of a newborn with an isolated rib fracture, aiming to draw attention to this less common form of birth trauma.

Case report

Following an uncomplicated pregnancy a boy was born at a gestational age of 40 weeks and 5 days to a G1P0 mother. During vaginal delivery, vacuum extraction was necessary because of prolonged second stage of delivery. In total three tractions were needed. The delivery was complicated by shoulder dystocia. Suprapubic pressure and McRoberts manoeuvre were needed to lift the shoulder dystocia. APGAR-score was 7 at 1 minute and 9 at 5 minutes after birth. Birth weight was 4,220 gram (93th centile). Physical examination immediately after birth (day 1) showed normal, symmetrical movements and reflexes, and a caput succedaneum. Twelve hours after admission to the maternity ward, the mother heard a cracking sound during movement of the right arm, which reappeared the day after. A second physical examination on the first day was normal. On day 2, however, physical examination revealed a distinct cracking sound when the right arm was moved and a 'crack' could be felt under the right scapula. Range of motion of the arm was normal, apart from abduction of the right shoulder, which was limited to 75°. There were no signs of Erb's or Klumpke's paresis. There was no sign of pain during the clinical examination. A chest radiograph showed no clear fractures of the humerus and scapula, but there was uncertainty regarding a possible fracture at the level of the anterior part of the third and fourth rib. According to the radiology department, a rib fracture following a complicated birth would be expected to occur posteriorly rather than anteriorly. The familial history was negative for underlying diseases causing bone fractures. There were no arguments for non-accidental injury. On day 3, the cracking sound was still heard during spontaneous, painless movements. There was no residual limitation of movement of the right arm and shoulder. The boy was discharged from the hospital. Conservative treatment with physiotherapy was started. At follow-up after one week, the parents reported that their child sometimes cried when changing clothes, but there were no signs of pain when picking him up. The cracking sound diminished, but was still present. Clinical examination withheld a cracking feeling at the right side of the back, but no movement limitations. An anterior-posterior oblique ('3/4') radiograph (Figures 1 and 2) showed a minimally displaced fracture posterolateral to the seventh rib on the right side. As full recovery was expected, no clinical follow-up was scheduled. A telephone follow-up at nine months reported that the 'crack' had disappeared and motor development was normal.

Figure 1: fracture of posterolateral side of the right 7th rib.

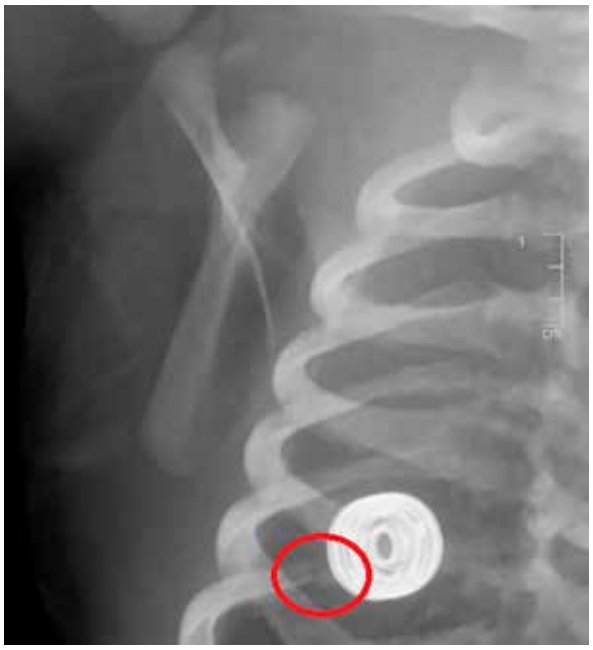
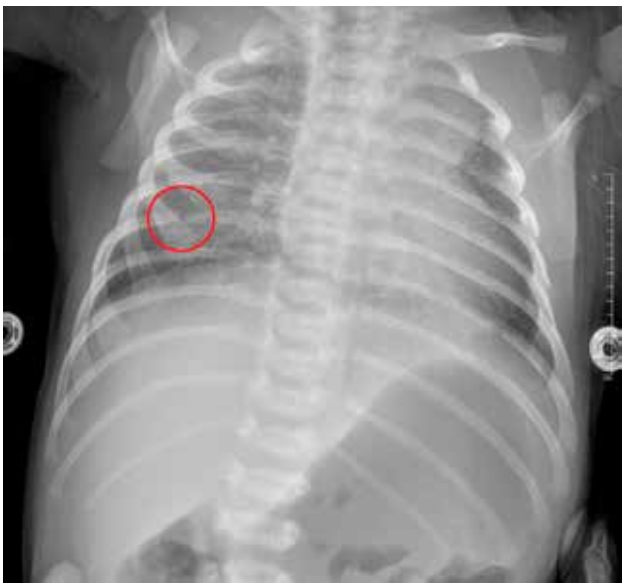


Figure 2: Fracture of posterolateral side of the right 7th rib, anterior-posterior oblique view.



Discussion

The incidence of fractures in the neonatal period varies amongst different studies. A single centre study in the United Kingdom by Rehm et al. mentioned a 0.075% fracture rate amongst all live births (1). In a nationwide Swedish study, conducted by Högberg et al., a 0.29% fracture rate was observed in all newborns (2). Another single centre study, conducted in Wales by Wei et al., reported a fracture rate of 1.6% in the neonatal intensive care department, which included more premature infants having metabolic bone disease (4). The incidence of fractures is possibly underestimated because children might lack symptoms and not every child will get a radiological evaluation.

Up to 95.5% of all neonatal fractures are located in the clavicle, with maternal short stature or obesity, large for gestational age child, instrumental delivery and shoulder dystocia being the main risk factors (2).

Very little literature is available on rib fractures due to birth trauma in the neonatal period. Van Rijn et al. reviewed all 10 published cases of rib fractures caused by birth trauma until 2008 and added 3 new cases. In all cases rib fractures were located in multiple ribs; in 6 cases an associated ipsilateral clavicle fracture was found and 9 out of 13 neonates were large for gestational age with birth weight >4 kg (3). In the study conducted by Rehm et al., one rib fracture was found in a total of 66 fractures in 84,761 live births. (1) In the nationwide Swedish study mentioned above, only 10 out of 5,336 fractures (= 0.002%) found in 1,855,267 live born neonates were rib fractures. In all of the cases rib fractures were associated with an ipsilateral clavicle fracture. Half of them had a birth weight over 4kg, four of them had shoulder dystocia and in four cases vacuum extraction was used. (2) In our case the neonate was large for gestational age (>4kg) and birth was complicated by shoulder dystocia. The rib fracture was not associated with a clavicle fracture and it was localized in only one rib, which is rare considering in all previously published cases, multiple rib fractures were found.

Birth trauma as a cause of rib fractures is very rare, therefore it is always necessary to consider other differential diagnoses. Firstly, non-accidental injury (NAI) has to be excluded. No studies on NAI and rib fractures that includes only neonates are available. Barsness et al. reported a positive predictive value of 95% for rib fractures as an indicator of NAI in children under the age of 3 (5). In two studies in infants by Bulloch et al. and Cadzow and Armstong, respectively 82% and 83% of rib fractures were caused by NAI (6,7). Differentiating birth trauma from non-accidental injury is difficult, since both have similar trauma mechanisms and predispose to a similar type of rib fractures. In some forms of NAI, the abuser applies anterior-posterior compression to the thorax when encircling the thorax with both hands, shaking and gripping the child with consequent anterior displacement of the vertebrae. This pressure results most often in posterior rib fractures, but also lateral fractures. Childbirth also circular exerts pressure on the thorax through the narrow birth canal, combined with rotational forces, leverage over the pubic symphysis and relative fixation of one side of the thorax, resulting in mid-posterior, unilateral rib fracture (3,8). A second differential diagnosis for neonatal rib fractures is cardiopulmonary resuscitation (CPR). CPR results in rib fractures in 0-2% of resuscitations. After changing the technique of CPR from the two-finger technique to the two-thumbs method, some studies reported an increase in rib fractures, while others did not (9). Thirdly, accidental injury can result in neonatal rib fractures as well. In the study by Högberg et al. 7.4% of fractures in neonates were caused by accidental trauma, 92.6% by birth trauma (2). At last, several underlying conditions and diseases can predispose to rib fractures. In premature neonates metabolic bone disease facilitates fractures. Osteogenesis imperfecta (OI), hyperparathyroidism and familial hypocalciuric hypercalcemia (FHH) have also been described as predisposing to neonatal rib fractures (3).

Chest radiograph is the golden standard for diagnosing fractures. Considering the fracture site is mainly posterior, anterior-posterior oblique views are necessary to image rib fractures as they might be missed in normal anterior-posterior views, as was in our case. Ultrasound can be a safe alternative to X-ray in diagnosing fractures. A recent study by Liu indicates 100% sensitivity and specificity of ultrasound for detecting fractures in infants (10).

No specific guideline is available for treatment of rib fractures in neonates. In general a conservative approach is chosen with adequate analgesia and physiotherapy for mobilisation and positioning.

We suggest the following work-up for neonates with rib fractures. First, it is important to conduct a thorough anamnesis to detect risk factors of NAI and to screen for genetic predisposition to underlying conditions such as OI or FHH. Secondly, a full clinical investigation is carried out, searching for other fractures, bruises or signs of associated diseases such as blue sclerae in OI. Severe hyperparathyroidism and OI often result in multiple fractures, although in NAI also multiple fractures can be found (3). Associated clavicle fractures can point to birth trauma. Thirdly, when in doubt of the diagnosis of rib fractures, X-rays with oblique views can be helpful; if necessary additional radiographs can be made to exclude fractures in other sites. Finally, in cases with an aberrant family history, multiple fracture sites, other clinical features and no indications for traumatic birth, a blood test for underlying diseases is indicated, including calcium, phosphorus, alkaline phosphatase, parathormone and vitamin D levels (3). Additional genetic testing can be considered.

In our case, the lack of arguments for NAI, the negative family history and clinical investigation were reassuring. X-rays for the diagnosis of the posterior rib fracture showed no other fracture sites. The birth weight was high (>4kg), vacuum extraction was carried out and birth was complicated with shoulder dystocia, three arguments that increase the risk of birth trauma. Therefore no further work-up was carried out.

Conclusion

Rib fractures in neonates due to birth trauma are rare. Risk factors might be a large for gestational age child, instrumental delivery, shoulder dystocia and associated clavicle fractures. Always consider alternative trauma mechanisms such as non-accidental injury or underlying diseases. The golden standard for diagnosing rib fractures due to birth trauma is chest X-ray, including oblique views since the fracture site is usually posterior.

Conflict of interest

The authors have no conflict of interest to declare.

Informed consent

Written informed consent was obtained from the parents of the patient for publication of this article.

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Systeemorgaanklasse Frequentie Infecties en parasitaire aandoeningen Zeer zelden: fungemie in patiënten met een centraal veneuze katheter en in patiënten in kritieke toestand of immuungecompromitteerde patiënten (zie rubriek 4.4 van de SKP), mycose door *Saccharomyces boulardii* CNCM I-745. Frequentie niet bekend: sepsis bij patiënten in kritieke toestand of immuungecompromitteerde patiënten (zie rubriek 4.4 van de SKP) Immuunsysteemaandoeningen Zeer zelden: anafylactische shock Bloedvataandoeningen Zeer zelden: anafylactische shock Ademhalingsstelsel-, borstkas- en mediastinumaandoeningen Zeer zelden: dyspneu Maagdarmstelselaandoeningen Zeer zelden: verstopping, epigastralgie, abdominaal meteorisme (epigastralgie en abdominaal meteorisme werden waargenomen in klinische studies) Huid- en onderhuidaandoeningen Zeer zelden: jeuk, exantheem, Quincke-oedeem Algemene aandoeningen en toedieningsplaatsstoornissen Zeer zelden: dorst Melding van vermoedelijke bijwerkingen Het is belangrijk om na toelating van het geneesmiddel vermoedelijk bijwerkingen te melden. Op deze wijze kan de verhouding tussen voordelen en risico's van het geneesmiddel voortdurend worden gevolgd. 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New insight in sepsis capillary leak syndrome: alpha 1 AMPK, from the comprehension of key molecular mechanisms to the exploration of a new therapeutic approach

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Keywords

alpha 1 AMPK ; sepsis ; canagliflozin ; endothelial permeability ; VE-cadherin ; connexin 43 ; heat shock protein 27 ; actin cytoskeleton.

Introduction

Sepsis is a major health concern worldwide, and is defined as a syndrome of dysregulated host response to infection causing life-threatening organ dysfunction.

Despite significant advances in the understanding of the disease, the therapeutic management of septic patients primarily relies on supportive care and mortality rates remain unacceptably high, around 40% (1). Sepsis capillary leak syndrome (SCLS), mainly caused by vascular hyperpermeability, is a critical process in sepsis pathophysiology and has been demonstrated to be an independent prognostic factor of survival (2). Moreover, growing evidence supports that maintenance of vascular barrier integrity improves sepsis outcome (3). However, no therapeutic proposal that targets SCLS has so far reached the clinical trial stage. SCLS is caused by vascular barrier disruption. Under healthy conditions, endothelial cells are sealed to one another by inter-endothelial junctions (IEJs) that effectively control the passage of molecules in a size-selective manner. Vascular endothelial cadherin (VE-Cad), the major component of adherens junctions (AJs), is a protein essentially involved in this regulation (4). Its stability depends on the actin cytoskeleton, whose polymerization is notably regulated by the phosphorylation of heat-shock protein of 27 kDa (HSP27), downstream of the p38 MAP kinase (p38MAPK) (5). Upon sepsis, stress mediators trigger signalling cascades that induce actin cytoskeleton contraction, AJs disruption, and loss of endothelial barrier function (6). This event is characterized by the formation of intercellular gaps, leading to plasma leaking through the endothelium and resulting in widespread oedema, finally compromising microcirculation (7).

The catalytic subunit of AMP-activated protein kinase (AMPK) is primarily expressed under its α1-isoform within the microvascular endothelium; there, it acts as a major regulator of the actin cytoskeleton and IEJs (8).

Canagliflozin, an inhibitor of sodium-glucose co-transporter 2 (SGLT2i), is currently prescribed as oral glucose-lowering agent to patients with diabetes. Independently of modulating glucose transport, clinically relevant canagliflozin concentrations also activate AMPK in different cell types, including human endothelial cells (9).

Interestingly, in addition to increasing renal glucose excretion, strong evidence supports that canagliflozin exerts significant cardiovascular protective effects, whose exact mechanisms are still poorly understood (10). On account of its effect on AMPK activity, we hypothesized that canagliflozin may constitute a new therapeutic option to target SCLS. In this thesis, we aimed (a) to characterize the role of endothelial α1AMPK in endothelial barrier function during sepsis, (b) to identify the molecular mechanisms involved in this regulation (c) to demonstrate the potential (AMPK dependent) protective effect of canagliflozin against SCLS.

Methods

α1AMPK expression and/or activity was modulated in human dermal microvascular endothelial cells (HMECs) using either α1AMPK-targeting small interfering RNA or the direct pharmacological AMPK activator 991, prior to lipopolysaccharide (LPS) treatment. Western blotting was used to analyse the expression and/or phosphorylation of proteins that compose cellular junctions (zonula occludens-1 (ZO-1), vascular endothelial cadherin (VE-Cad), connexin 43 (Cx43)), or that regulate actin cytoskeleton (p38 MAPK; heat shock protein 27 (HSP27)). Functional endothelial permeability was assessed by *in vitro* Transwell assays, and quantification of cellular junctions in the plasma membrane was assessed by immunofluorescence. Actin cytoskeleton remodelling was evaluated through actin fluorescent staining.

A mouse model of specific and conditional endothelial α1AMPK deletion was generated (e-AMPK WT/KO). Canagliflozin was administered by oral gavage, and endotoxemia was induced by intraperitoneal injections of sublethal doses of LPS. Capillary leak was monitored with Evans Blue Dye (EBD) and plasmatic albumin levels.

Results

First, we have demonstrated the pivotal role of α1AMPK in the regulation of endothelial barrier function. *In vitro*, we described that α1AMPK invalidation is associated with increased endothelial permeability, while AMPK activation by 991 leads to endothelial barrier reinforcement against LPS injury. In vivo, EBD detection on myocardial sections showed that specific endothelial α1AMPK deletion is associated with increased vascular leakage in response to endotoxemia, while its pharmacological activation protects against this mechanism in e-AMPK WT, but not KO animals.

Second, we investigated the underlying molecular mechanisms of this protective effect, and demonstrated that α1AMPK deficiency is associated

with reduced expression of CX43, ZO-1, and VE-Cad. The drastic loss of CX43 is likely responsible for the subsequent decreased expression and localization of ZO-1 and VE-Cad in the plasma membrane of endothelial cells. Moreover, α1AMPK activation by 991 protects against LPS-induced endothelial barrier disruption by reinforcing cortical actin cytoskeleton. This is due to a mechanism that involves the phosphorylation of p38 MAPK and HSP27, which is nonetheless independent of the small GTPase Rac1.

Third, we described protectives effects of canagliflozin on endothelial barrier function submitted to sepsis conditions. *In vitro*, we reproduced the protective effects previously described with the pharmacological activator 991. We described that their abrogation appears inconstant in AMPK depleted cells, indicating that AMPK-independent mechanisms seem involved. In vivo, canagliflozin administration drastically reduced LPS-induced myocardial oedema and maintained albumin plasma levels. Endotoxemia-induced myocardial oedema and hypoalbuminemia persisted despite canagliflozin treatment in e-AMPK KO animals, demonstrating that canagliflozin protection involves endothelial α1AMPK. We confirmed that this protection involves both activation of p38MAPK/HSP27 pathway and preservation of VE-Cad integrity.

Finally, we validated these results in human endothelial cells submitted to human plasma collected from volunteers (HV) or septic shock (SS) patients. Immunostainings show that both HV and SS plasma affect VE-Cad architecture, with SS plasma inducing higher VE-Cad disruption. Of major interest, canagliflozin importantly preserved VE-Cad integrity while slightly enhancing its membrane expression in HMECs exposed to both HV and SS plasma.

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IMPORTANCE DE L'HYDRATATION DU NOURRISSON DURANT LA PÉRIODE HIVERNALE

Chez les nourrissons et les jeunes enfants, le maintien d'un apport adéquat en liquides est physiologiquement important tout au long de l'année. Cependant, il faut être particulièrement vigilant en hiver, saison durant laquelle le risque de nombreuses infections dont les principaux symptômes sont associés à une déshydratation est accru.[1,2]

La masse corporelle des nouveau-nés est composée d'environ 75% d'eau. Ce pourcentage diminue rapidement au cours de la première année de vie pour atteindre 60%, et reste relativement stable tout au long de l'enfance jusqu'à l'adolescence. La maturation progressive de la fonction rénale vers 2 ans ainsi qu'un rapport surface corporelle/masse corporelle plus élevé, se traduisant par une perte d'eau plus importante à travers la peau, expliquent en partie pourquoi les besoins en eau sont plus élevés chez l'enfant par rapport aux adultes.[1]

L'EFSA (European Food Safety Authority) a défini les apports adéquats en fonction des groupes d'âge (Tableau). Néanmoins, ces besoins peuvent varier d'un nourrisson à l'autre, et l'apport adéquat nécessite parfois un ajustement en fonction du niveau d'activité et des conditions environnementales telles que la chaleur et l'humidité.[3]

Recommandation de l'EFSA sur les apports adéquats en eau chez les nourrissons de 0 à 36 mois.

Groupe d'âge	Apports adéquats
0-6 mois	100-190 ml/kg sous forme de lait
6 à 12 mois	800-1000 ml/jour
1 à 2 ans	1100-1200 ml/jour
2 à 3 ans	1300 ml/jour

Les nourrissons et les jeunes enfants sont particulièrement sensibles aux maladies diarrhéiques et à la déshydratation en raison d'un métabolisme plus élevé, de leur incapacité à communiquer leurs besoins ou à s'hydrater eux-mêmes, d'une transpiration plus importante au cours des premiers mois de la vie, ou de processus pathologiques entraînant une perte de liquide.[4]

Déshydratation chez le nourrisson: attention aux maladies hivernales

Dans la majorité des cas, la déshydratation des nourrissons est la conséquence d'une gastro-entérite, affection fréquente pendant les mois d'hiver, responsable de symptômes favorisant les pertes hydriques: diarrhée, vomissements et fièvre.[4]

Les infections virales, notamment les rotavirus, les norovirus et les entérovirus, sont à l'origine de 75 à 90 % des cas de diarrhée infectieuse. En cas d'infection bactérienne, les principaux agents pathogènes incluent Salmonella, Shigella et Escherichia coli.[4]

Une hydratation adéquate des tissus corporels est essentielle à la santé et à la vie. Une perte de poids corporel, qui correspond à une perte d'eau corporelle, d'environ 1% est normalement compensée dans les 24 heures. En l'absence de compensation et lorsque les pertes d'eau corporelle continuent d'augmenter, des réductions des performances physiques et cognitives, de la thermorégulation et de la fonction cardiovasculaire se produisent. Une perte de 10% ou plus d'eau corporelle peut être fatale.[3]

Recommandations pour la consommation d'eau par les nourrissons

L'eau qui convient généralement à l'alimentation des nourrissons comprend l'eau de source répondant aux normes de sécurité et l'eau en bouteille commerciale (eau de source naturelle ou eau traitée à faible teneur en minéraux).[5] Dans le choix de la source d'eau utilisée soit comme boisson, soit dans la préparation du lait maternisé, il est important de veiller à ce que celle-ci contient un minimum de nitrates, source potentielle d'intoxication.[6] Dans tous les cas de figure, l'eau utilisée pour l'alimentation des nourrissons doit être stérilisée pour les enfants de moins de 4 mois.[5]

En cas de perte d'eau pendant une maladie (fièvre, diarrhée...), il faut continuer à donner du lait maternel ou une préparation pour nour-rissons plutôt que de l'eau, afin d'éviter des déséquilibres électrolytiques. Une thérapie de réhydratation orale peut être nécessaire.[5]

L'eau est essentielle à la vie, elle est également essentielle pour le devenir des nourrissons. En effet, l'acquisition d'habitudes de consommation saines est importante dès la petite enfance car de nombreux comportements alimentaires acquis pendant l'enfance persistent à l'âge adulte. Les enfants qui boivent peu d'eau deviendront des adultes qui en boivent peu, avec des conséquences potentielles sur la santé rénale et métabolique ainsi que sur les troubles cognitifs et de l'humeur.[1]

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Working towards an optimal nutritional status in people with Cystic Fibrosis

PhD thesis presented on 25/08/2022 at Ghent University, Ghent, Belgium

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Keywords

Cystic Fibrosis, nutritional status, sodium, sodium status, enteral nutrition, enteral tube feeding, cystic fibrosis related diabetes, continuous glucose monitoring.

Background

Cystic Fibrosis (CF) is an autosomal recessive disease caused by cystic fibrosis transmembrane conductance regulator (CFTR)-gene mutations affecting chloride secretion, sodium reabsorption, and water transport in epithelial cells. This leads to dehydrated mucus secretions impacting multiple organs (1, 2). Exocrine pancreatic insufficiency (EPI) is the earliest CF manifestation and respiratory failure is the primary cause of death. In Europe, the incidence of CF is approximately 1/3500 Caucasian births, with an incidence of 1/2850 births reported in Belgium (3). CF is associated with co-morbidities such as Cystic Fibrosis related Liver Disease, Cystic Fibrosis Related Bone Disease and Cystic Fibrosis Related Diabetes (CFRD) (2).

EPI impacts nutritional status by causing maldigestion and malabsorption of nutrients in the absence of supplemented pancreatic enzymes. There is a well-established association between nutritional status (expressed as BMI) and pulmonary function (expressed as forced expiratory volume in 1 second, FEV1, percent predicted (pp)), which ultimately affects survival. Therefore improving nutritional status is a cornerstone of CF therapy (2).

The ESPEN-ESPGHAN-ECFS guidelines on nutrition care for infants, children and adults with CF highlighted the need to increase knowledge on nutritional demand and nutritional status in CF (2). This thesis aimed to answer the following research questions (RQ): (a) "Does enteral nutrition have a long-term effect on the nutritional status of children and adults with CF?", (b) "How can the sodium status in children and adults with CF be evaluated?", and (c) "What's the impact of impaired glucose metabolism on nutritional status and pulmonary function?"

Method

As an introduction to the thesis, a narrative review was conducted, focusing on the reconsideration of nutritional therapy in people with CF (pwCF) (1). The narrative review was limited to evaluating the use of growth charts, body composition, pancreatic enzyme therapy, and protein intake and digestion. A literature search was performed across three databases: PubMed, Scopus, and Web of Science, form June 2014 to June 2017.

To study the impact of enteral tube feeding (ETF) on nutritional status and pulmonary function, data from the Belgian CF Registry (BCFR) was used in a retrospective case – control study design (4). All patients (n=1482) in the BCFR were considered. Children and adults who received ETF between 2000 and 2013 and met the inclusion criteria were included. Statistical analysis was performed on 113 cases receiving ETF and 226 age, sex, pancreatic status and genotype class-matched controls. As the BCFR lacked data on growth velocity, a subsequent retrospective case – control multicentre study (UZ Brussel (UB) and Ghent University Hospital (GUH)) was performed (5). This second study aimed to explore the long-term effect of ETF on nutritional status, growth velocity, and pulmonary function in children with CF, comparing the timing of ETF initiation to current European guidelines (2). Children with CF who started ETF between 2006 and 2016 were included. Data from the patients' medical records 3 years before and five years after the start of ETF were collected. A total of 24/197 patients (UB+GUH) and 18 controls (GUH) were included for analysis, matched for age, sex, and pancreatic function.

A narrative review on sodium status and replacement in pwCF served as an introduction to the third part of the thesis (6). In June 2019, an electronic literature search was conducted in the databases PubMed, Web of Science, and Scopus. The literature search was limited to publications in English, focusing on primary research studies published since 1951. Twelve originals studies were identified and analysed. The narrative review addressed the evidence on the pathophysiology, prevalence, and clinical influence of sodium deficiency in people with CF, the indistinct recommendations for infants, children and adults, and the methods to assess sodium status. Based on the results of this review, a prospective study was performed (7). The aim was to evaluate urinary salt parameters as a surrogate for fractional excretion of sodium (FENa) in a large group of children and adults with CF in order to facilitate future follow-up of the sodium status using a spot urine sample. Between January 2019 and December 2020, urine and blood samples were collected from 222 patients followed at the GUH during an annual follow-up visit. FENa and urinary surrogate parameters for sodium status were calculated. The hypothesis was that the urinary sodium/creatinine ratio corresponding to the FENa ≥ 0.5% would differ across age categories in patients with CF.

In the fourth study, we examined the impact of impaired glucose metabolism on nutritional status and FEV1pp in pwCF who were not previously diagnosed with diabetes (8). Since the insidious nature of CFRD and the lack of clinically relevant continuous glucose monitoring (CGM) indices, we studied diurnal and nocturnal CGM-derived glycaemic patterns. Additionally, CGM-derived indices of glycaemic control were studied in relation to FEV1pp and nutritional status. Patients with an impaired OGTT and/or increased HbA1c were recommended to wear a CGM (Dexcom® G4) for seven days. CGM data of 47 pwCF, followed at the Ghent University Hospital (children, n = 26) was analysed.

All studies were approved by the Ethical Committee of the Ghent University Hospital.

Results

"*Does enteral tube feeding have a long-term effect on the nutritional status of children and adults with CF?*"

To address this RQ the findings from our longitudinal registry study and multicentre study will be discussed (4, 5). Some pwCF are unable to consume an adequate amount of nutrients, affecting weight gain and growth. CF centres use ETF to increase nutrient intake (2). In our longitudinal study, age of ETF initiation varied widely. Approximately 50% of the patients were < 10 years of age, and ± 25% were ≥ 18 years of age. All ETF-patients had lower BMI and height z-scores at the first registration in the BCFR compared to controls. After 3 years, their BMI z-scores recovered to the levels observed approximately 4 years before starting ETF but never reached the recommended threshold. We did not observe significant improvements in height z-scores in children.

In our multicentre study, we found a delay in ETF initiation compared with the guidelines, with 60% of the patients already having a BMI z-score < 1.3 three years before starting ETF (5). This percentage increased to 80% at ETF initiation, with six out of 24 patients already stunted. After starting ETF, growth velocity increased in the first year, but patients remained below their genetic potential for height. We could not recommend an ideal ETF start time, but younger patients showed greater height z-score improvement. Overall, ETF prevented further decline in BMI and FEV1pp over a period of five years but should be commenced in time (4, 5).

"How can the sodium status in children and adults with CF be evaluated?"

PwCF have hypertonic sweat which increases the risk for electrolyte disturbances. Monitoring sodium status in individuals with CF, especially in infants, is imperative. Relying solely on serum sodium as a clinical parameter may delay the diagnosis of deficiency. FENa is cumbersome as it requires simultaneous urine and blood samples. Since sodium requirements and thus supplementation change based on patients' circumstances, repeated measurements are necessary. In our study we observed a strong age-dependent correlation between FENa cut-offs and the urinary sodium/urinary creatinine ratio (Una+/Ucreat) (7). In the future, monitoring UNa+/Ucreat will be important as variant-specific therapies in CF reduce salt losses via sweat. Salt supplements and diet will need to be adjusted accordingly.

" What's the impact of an impaired glucose metabolism on nutritional status and pulmonary function?"

CGM has revealed abnormal glucose profiles in pwCF even when fasting and post-OGTT glucose levels are normal. Glucose tolerance tends to decline over time, progressing from normal to impaired glucose tolerance and eventually diabetes. CFRD is associated with a worse nutritional status and pulmonary function (9). We observed in our study cohort disrupted circadian CGM-profiles in all but two adult patients. We found no significant associations between CGM-indices and FEV1pp or BMI in the paediatric cohort, but in our adult cohort, we observed a strong association between moderate hyperglycaemia during night and a worse concurrent pulmonary function. Specifically, every increase of 1% time > 140 mg/dL during the night associated with a 0.76% lower FEV1pp. Our study was the first to explore nocturnal and diurnal glycaemic profiles in children and adults with CF, revealing deviations from healthy individuals' profiles. While this is relevant in establishing CGM cut-offs, associations between CGM-indices and CF outcomes were absent in our small paediatrics cohort, suggesting the need for age-specific indices. Thirdly, the increase in nocturnal glycemia may challenge current CF nutritional interventions, warranting a reconsideration.

Conclusion

Therapy in CF has dramatically evolved in the last decade which is expected to increase life expectancy, but as a consequence, an increase in co-morbidities is expected. Optimizing nutritional status remains a pillar in CF therapy. Our findings can set the path for a further improvement of nutritional care in CF.

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Public health impact of environmental pollution on children in North and South. A focus on air and metal pollution in Antwerp (Belgium) and Lubumbashi (DR Congo)

PhD thesis presented on February 17th 2023 at Ghent University, Belgium

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Keywords

Infant ; child ; environmental pollutants ; particulate matter ; vulnerable populations ; developing countries ; asthma.

Research in context

Emerging infectious diseases like Zika, COVID and Ebola have shown clearly that disrupting ecological systems can lead to epidemics and pandemics. Therefore WHO developed the 'One Health' concept, an 'interdisciplinary approach stressing connections between human, animal and environmental health' (1). The distressing amount of environmental health problems from the last 20 years clearly shows that we must broaden our definition of 'public health', and include '**Planetary (One) Health**', focusing on the *(human and animal) health impact of disrupted ecosystems.* Currently we are not only facing climate change and its health consequences, but also a lack of water and land, diminishing biodiversity and different kinds of pollution. All these problems are closely connected. To understand all these challenges – and react to them – we need to increase collaboration between disciplines and countries, if we want to keep our planet (and its inhabitants) healthy (2, 3).

The magnitude of the current environmental problems is endangering humanity itself (by nutritional crises resulting in population displacement and conflict, pandemics and the serious health impact of pollution) (3). **Air pollution** and '**chemical / toxic substances**' (of which metals are the most important) are the **two most important 'areas of work**' of WHO's 'Public Health and Environment' (PHE) strategy (4). The purpose of this PhD thesis was to fill a few knowledge gaps about the health impact of air and metal pollution on children in the Global North and South.

Evidence before this PhD

It is well known in paediatrics that the first 1000 days (from conception onwards) are very important in terms of proper nutrition and (psychosocial) development (5, 6). In this thesis we aimed to demonstrate that also environmental '**early life exposures**' are very important. South African researchers from the 'Drakenstein Child Health Study' have shown that **antenatal exposure** to household air pollution (HAP) already affects the incidence and severity of '*lower respiratory tract illness*' (remark that they call it LRT 'illness' and not 'infection') in their offspring (7, 8). Antenatal outdoor 'ultrafine particle' (UFP; with an aerodynamic diameter < 0.1 micrometre) exposure was also linked to '*asthma development in children*' in the US (mostly when the exposure took place late in pregnancy) (9). Foetuses and infants are extremely vulnerable to pollution exposure because of their rapid development and immature immune system, particularly those in Low- and Middle-Income Countries (LMIC) where poverty and lack of resources compound the effects (10).

Environmental health effects are the largest in **disadvantaged or vulnerable populations**: this can be because of age (the youngest and the oldest are more 'fragile'), disease, race and poverty (11). There is a clear link between poverty and unhealthy living environment, also in Belgium (12). People in 'low resource settings' are even a lot more 'exposed' to several environmental pollutants than disadvantaged people in the global North, because there are less stringent environmental laws in LMIC (13).

Added value of this PhD and knowledge gaps

In our 'health impact assessment' (HIA) of 'Ringland' we have calculated that the impact of improved air quality by moving the entire Antwerp Ring Road into a tunnel, would especially have a significant impact on 'all cause' mortality (21 deaths, 95%CI 7-41, avoided annually in the population living in a perimeter of 1500m around the ring road), and on child lung function development (forced vital capacity improvements of 3-64ml in 356 of the 430 schools around the ring road) (14). In the 'BronchiolAir' study (in publication), we found a trend that children hospitalized for bronchiolitis appear to be more exposed to air pollution, but the study was too small to draw definite conclusions. This trend does however confirm that the already existing evidence from the US on the association between bronchiolitis and air pollution, does probably also count for the urban environment of Antwerp. Larger studies are needed to consolidate the impact of air pollution on bronchiolitis in Europe; and even more so in LMIC.

In a case-control study in a mining area in southern Katanga (Democratic Republic of the Congo, DRC), we were able to associate paternal occupational mining (OR 5.5; 95%CI 1.2-25), and concentrations of Mn (OR 1.7; 95%CI 1.1-2.7) and Zn (OR 1.6; 95% CI 0.9-2.8) in cord blood and placental tissue, with the incidence of (visible) birth defects in newborns (15). Prospective studies could help to establish a causal relationship between metal pollution and congenital malformations.

We have added data to the increasing evidence that 'early life exposure' to environmental pollutants, is harmful in the Global North and South. Until a few decades ago, pollution was not considered a major determinant of health among children. The health impact of air and metal pollution on children is becoming more clear in recent years. And even if some things (like the relationship between metals and birth defects in DRC that we have shown) are just associations, according to the 'precautionary principle', this is enough to start protecting children from environmental 'early life exposures'. Even if there is uncertainty about the nature and magnitude of potentially harmful effects of several pollutants, the credible threat of these agents to the paediatric population provides a rationale for taking precautionary measures to prevent this exposure (16).

Policy implications of all the evidence available

WHO, UNICEF and The Lancet recently called for action to put '**children in all policies**' to build a healthier and more equitable world for future generations. This is especially important for policies on environmental pollution (17). Fossil fuel combustion has become one of 'the world's most significant threats to children's health' (10). The 'Ringland' and 'BronchiolAir' studies confirm that the **individualized motorized traffic** (and the liberty associated with it) has become one of society's largest problems. Air pollution, but also pollution of water and soil (by fossil fuels, but recently also by metals for batteries), global warming, destruction of biodiversity and liveable urban space for roads and car parks are just a few of the negative effects of the automobile industry (18).

It is exaggerated to state that lithium-ion batteries are '*the new oil*', but – as part of the 'low-carbon future' – high amounts of cobalt and smaller amounts of copper are needed. They are extracted in countries like DRC. The increased production makes that more children (and adults) are exposed to high amounts of metals, especially in vulnerable countries like DRC. Our 'Katanga Malformations Congénitales' study has shown that even unborn children are at risk. We must therefore prevent that batteries destroy more lives than they save the climate (19, 20). On a *global scale* **Big Tech companies should be held responsible** not only for where their metals come from, but also become key stakeholders in a real circular economy, by becoming accountable for the recycling of their own mobile devices, laptops, etcetera, when they can no longer be used (cf. the Recupel initiative) (21).

An important component of environmental health in *LMIC*, is '**better housing**'. Better housing means that dwellings are *climate-proof*, i.e. less hot and mosquito-free, but also free of *household air pollution (HAP)*. HAP can be reduced by cooking on porches that are well ventilated, with nets not only to keep mosquitos out, but also to let the smoke escape (22).

In HIC technical solutions that reduce industrial emissions, proper urban cycling networks, good public transport systems, clean power sources (wind, water, sun) and isolation of houses are essential (10). A '**Modal Shift**' towards more active transport and '**Road pricing**' (these two are currently part of the 'Ringland' plan), but also '**Low Emission Zones**' **(LEZ)**, preferably associated with 'circulation plans', are only first steps. More and more cities recommend to leave personal cars (especially for non-urban residents) in '*park and ride zones*' outside of the city. These zones should be equipped with charging stations (for electric cars) and be a lot better connected to the heart of the city by public transport and shared bicycle systems. **Transforming 'car parks' into 'real parks'** could also have additional salutogenic effects. The WHO recommendation is that all people should have access to ≥ 0.5 hectare (ha) open green space within 300 m linear distance from their home. Recently, the '**3-30-300 rule**' (or 'Vancouver rule') has been proposed by urban planners: they state that 'everybody should be able to see at least 3 trees from their home, that all neighbourhoods should have at least 30% tree cover, and that everyone should have access to "a green area of at least one hectare" within 300 metres' (23). Adding blue spaces to this '3-30-300 rule', could even increase its impact.

It has already been shown many times that investing in Public Health works. The 'fiscal multiplier' for investments in public health is 4.3. This means that for every euro invested in Public Health, the society in the end gains 4 euros (24). So, societies investing in healthier (pollution free) environments for children will also benefit financially from this. For example, Copenhagen is planning **Cycle Super Highways**, to improve mobility and reduce air pollution in the capital region. The planned 'Bicycle Super Highways', around the city (>500 km of bike paths), could reduce public health expenses by 40 million euro every year (25). 'Historically, cycle paths are an artifact of car thinking' (26). Originally streets were 'meeting places'. In a lot of cities worldwide pedestrians and cyclists are 'reclaiming the streets', by initiatives like the 'Critical Mass Bike Ride' (26).

Traffic remains an important cause of diverse forms of pollution that harm children. When planning transport, the purpose should be to maximize social/health benefits, and to minimize harm. Therefore some people argue that we should 'phase out' cars from our lives. For almost all journeys cars can easily be substituted (think of Pontevedra, Amsterdam or Copenhagen) (27).

Measuring works: 'Clear indicators' can be helpful to identify which populations are most vulnerable (and where you should act first). In New York City, e.g., the city council mapped green space and the 'urban heat island' effect: on this basis they decided which communities are the most at risk for heat-related mortality/morbidity and where they should thus prioritize cooling policies (28). The same could be done for places and populations most at risk for air pollution.

You can be unlucky with your genes and get cancer despite living an ultra-healthy life. But statistically, with a healthy lifestyle you are 79% less likely to develop a chronic condition. 'Quick wins' are not smoking, exercising, keeping your BMI under 30 and a healthy diet (no red meat and prepared meat; lots of vegetables and seeds) (29). It is now becoming increasingly clear that a healthy lifestyle also includes avoiding 'early life exposures' to a combination of pollutants. Pollution is like a symphonic orchestra: there's only a concert when several instruments play together.

'Bird perspective' on this PhD

We have to broaden our definition of 'public health' with the concept of 'planetary health'. Everything is connected. Climate warming, loss of biodiversity, but also environmental pollution are closely related to global health problems like infectious disease outbreaks (COVID-19, LRTI…) and 'non-communicable diseases' (malnutrition, asthma, allergies, renal problems, several cancers…) (30).

We must mutualize the 'commons' again. 'Commons' or 'le bien commun' are the things that are not supposed to be anyone's property; it's what we all inherit from our parents and pass on to our children. It's about air, water, the underground (and by extension also our climate) (31). We have an intergenerational responsibility to keep them clean. These 'commons' are important in the Global North, but perhaps even more so in the Global South, because there are less stringent environmental laws in LMIC.

This doctoral research was needed because we often do not realize how early in life an unhealthy living environment can already have long-lasting consequences. Since foetuses and young children cannot do anything about this themselves, society has a tremendous responsibility. The trend to more sustainable cities and a healthier world has been set. It can be slowed down by some politicians and policy makers (often protecting privileges of a selected group), but it cannot be stopped anymore. A 'tailored approach' depending on where you are, is needed. Think global, act local.

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