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.

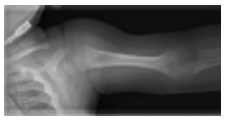
Diagnostic tests showed a high parathyroid hormone (PTH) level, severe vitamin D deficiency, normal phosphorus, elevated alkaline phosphatase (ALP), but no urinary calcium loss (urinary Ca/creatinine : 0,44 mmol/mol creatinine [0,034-0,690 mmol/mol creatinine]).

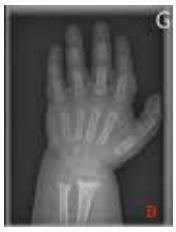
Radiographic findings were typical of rickets (Figure 1) and also showed cardiomegaly. Echocardiography showed mild cardiac dysfunction with dilated left ventricle, but without clinical impact.

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.

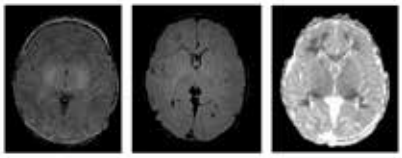


Figure 2: Day 10. From left to right: cerebral MRI in T1, FLAIR, and diffusion-weighted image. The first image shows hyperintense lesions in the white matter, especially in the frontal and the parietal regions. The frontal white matter shows signs of necrosis. Diffusion - restricted lesions are found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

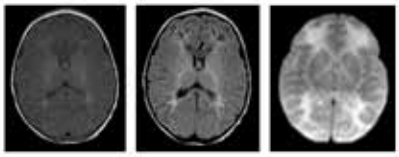
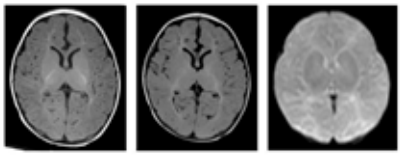


Figure 3: Week 6. From left to right: cerebral MRI in T1, FLAIR, and diffusion-weighted image. This MRI shows the regression of the diffusion restricted lesions, followed by the appearance of white matter lesions in the frontal cortex with the appearance of cavitation, predominantly on the left side.



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.

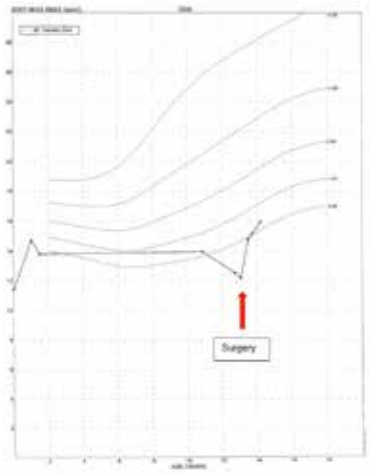
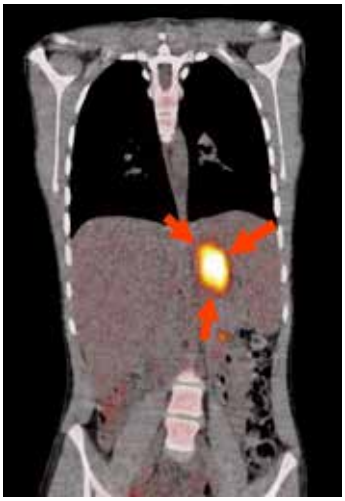


Figure 2:
PET-CT shows a hypermetabolic lesion in the left suprarenal fossa.



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.

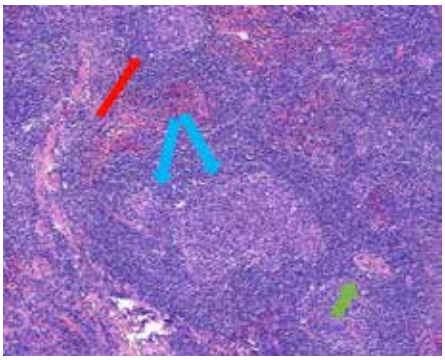
Fecal calprotectin, IgA transglutaminase, anti-Neutrophil cytoplasmic antibodies (ANCA), antisaccharomyces cerevisiae antibodies (ASCA), abdominal ultrasound, gastric endoscopy and colonoscopy were normal.

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.

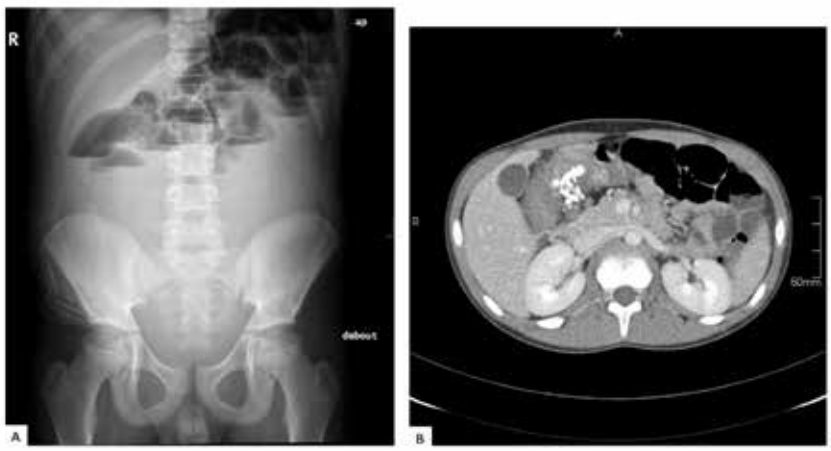


Figure 2:
A and B : Colonoscopy showed an annular, irregular mass with an ulcerated aspect totally obstructing the lumen.

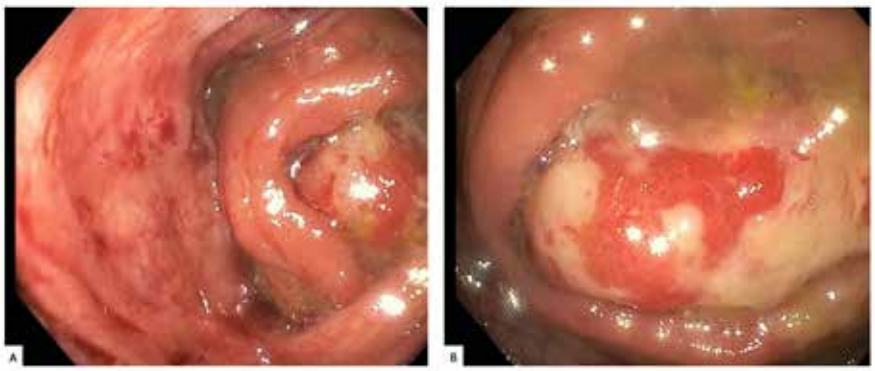
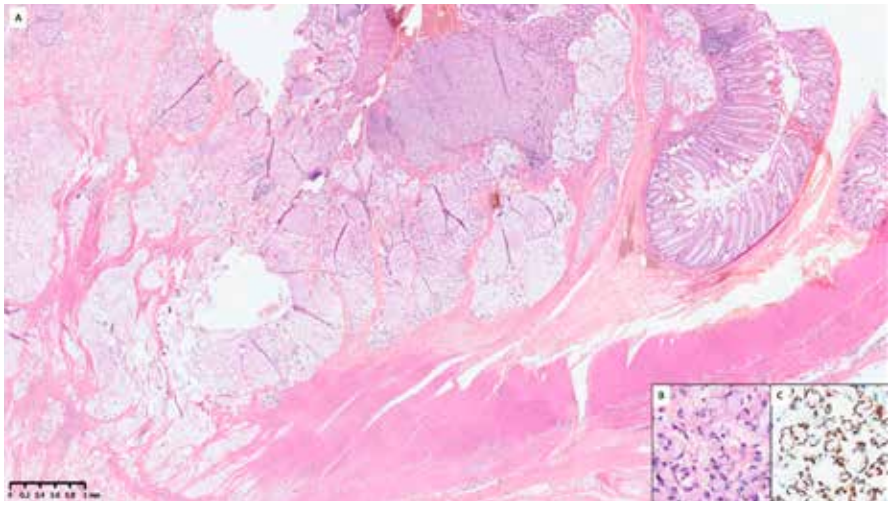


Figure 3:
A. Histopathology of the lesion. H&E staining of the tissue showing tumoral lesions characterized by abundant extracellular mucin with numerous floating signet-ring cells.
B. H&E staining - x40- Isolated tumor cells with an eccentric nucleus and mucus vacuole.
C. x40- Immunohistochemical stains 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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