Failure to thrive, from a frequent symptom to a rare diagnosis

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Keywords

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Abstract

Niemann-Pick type C (NPC) disease is a neurometabolic disorder that causes premature death and rapidly progressive neurological disability. It affects 1 in 100,000 live births and has a heterogeneous presentation.
Case: We present a 3-month-old boy with significant failure to thrive that was initially misdiagnosed as acquired CMV infection. He had concomitant RSV bronchitis with acute respiratory failure.
Long follow-up, family history and genetic testing led to the diagnosis of Niemann-Pick type C disease.
Conclusion: Long-term follow-up is essential for the diagnosis of rare diseases.

Introduction

Failure to thrive (FTT) is a common sign in pediatrics. Its combination with developmental delay and organomegaly may indicate rarer underlying conditions. This case illustrates the complexity of establishing a specific diagnosis, the importance of ruling out differential diagnoses, and the importance of long-term follow-up for our patients.

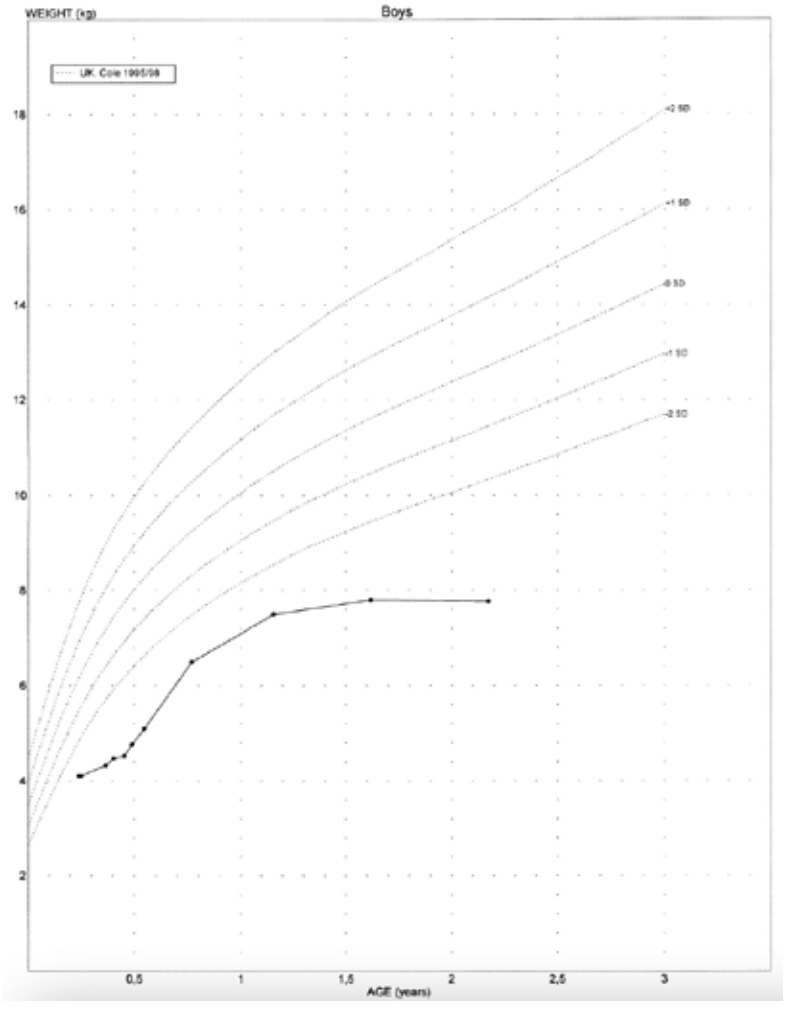
Case report

A three-month-old boy with a history of failure to thrive (FTT) had a lower respiratory tract infection for 3 days. On admission, his biometric measurements (weight, height and head circumference) were below the 3rd percentile on the WHO charts. Physical examination revealed a thin baby with grayish skin coloration. He was mildly dyspneic. Pulmonary auscultation revealed widespread rhonchi, crepitations, and wheezing. The abdomen was distended with massive hepatomegaly and an enlarged spleen, respectively 5 cm and 2 cm below the costal margin. Neurological examination revealed only axial hypotonia.

Initial investigations revealed a normocytic normochromic anemia with a hemoglobin of 9 g/dL [NL 9.5-13.5 g/dL]. Alanine aminotransferase and aspartate aminotransferase were elevated to 1.5 times the upper limit of normal (ULN). Gamma glutamyl transferase level was 3.3 times the ULN, and total bilirubin was 3 times the ULN (mainly indirect).

The international normalized ratio (INR) was within normal limits. A nasal swab was positive for respiratory syncytial virus (RSV). He was admitted to the hospital with a diagnosis of acute bronchiolitis and FTT. Chest radiographs supported the diagnosis of bronchiolitis.

Figure 1: Weight on the WHO curves from birth to the age of 2 years.



Further anamnesis revealed that the pregnancy was unremarkable except for intrauterine growth restriction. The family was from Syria. The parents are consanguineous in the 1st degree and the couple reported the death of a previous child at the age of 4 years due to an unknown neurological disorder with liver involvement.

Further biological investigations revealed a positive IgM serology for cytomegalovirus (CMV) and a positive CMV-PCR in urine. Acquired CMV-acquired infection was confirmed by a negative CMV-PCR in the newborn blood spot test. Because of hepatosplenomegaly, metabolic analyses were performed. No vacuolated lymphocytes were found. Lipid assessment was normal. Enzymatic assays for sphingomyelinase and glucocerebrosidase were normal, excluding acid sphingomyelinase deficiency (ex- Nieman-Pick type A/B diseases) and Gaucher's disease, respectively.

Measurements of Lyso509, chitotriosidase, oxysterols or lysosphingo-myeline-509 were not performed.

Abdominal ultrasonography (US) confirmed the hepatosplenomegaly without any other associated abnormalities. The infant developed respiratory failure requiring continuous positive airway pressure and oxygenation. After 42 days of hospitalization the patient was discharged home with a diagnosis of RSV-bronchiolitis and acquired CMV infection.

After hospitalization his weight and height progressed in harmony under 3rd percentile (Figure 1 and 2).

In the following months, the hepatosplenomegaly did not resolve. Generalized hypotonia persisted and global developmental delay became apparent. Multigene panel sequencing revealed a heterozygous frameshift variant (c.2972_2973delAG) in the NPC 1 gene on chromosome 18, identifying a Niemann-Pick type C disease. At the age of 2, the patient began to lose the ability to sit and slowly regressed. He died prematurely at the age of 2 years and 5 months.

Discussion

Failure to thrive is a common medical condition in pediatrics. Poor caloric intake or social difficulties account for most cases, although an organic condition must be ruled out.

The presentation of FTT in association with hepatosplenomegaly and developmental delay, as well as the history, link it to the spectrum of congenital neuro-metabolic disorders.

The current accessibility of genetics made the final diagnosis of Niemann-Pick type C (NPC).

NPC is a rare autosomal recessive disorder characterized by late-endosomal and lysosomal storage of unesterified cholesterol affecting ~ 1: 100,000 live births (1). It is caused by biallelic mutations in either the NPC1 or NPC2 gene, with NPC1 accounting for about 95% of cases and NPC2 for the remaining 5% (2).

These genes code for ubiquitous proteins (3). Lack of their function leads to the accumulation of lipid species such as sphingosine, cholesterol, sphingomyelin, and glycosphingolipids in late endosomes/lysosomes. Typically, the liver, spleen and brain are affected (4).

The clinical presentation and onset of the disease can vary widely (1). The age at which neurological symptoms appear determines the severity and prognosis of the disease (1). Therefore, the classification of NPC is based on the age of onset of neurological symptoms, which can be categorized as early infantile, late infantile, juvenile, and adolescent/adult (1, 2).

In younger patients, systemic signs typically manifest before neurologic signs (5). In the neonatal period, approximately 40% of cases present with hepatosplenomegaly and prolonged cholestatic jaundice (6). A genotype/phenotype correlation has been observed in the literature, and the patient's phenotype corresponds to the identified mutation (5, 7). Figure 3 summarizes the symptoms based on the patient's age. NPC should be considered as a potential diagnosis when the etiology of any of these symptoms remains unclear, such as prolonged neonatal jaundice, splenomegaly, gelastic cataplexia, and supranuclear gaze palsy (2).

Historically, the diagnosis has been made by skin biopsy and Filipin staining for unesterified cholesterol (8). Biochemical markers such as oxysterols, lyso-SM-509 (specific), and lyso-sphingomyelin can be used as screening tools, but genetic sequencing is necessary to confirm the diagnosis (8).

Due to the variability of symptoms and the age of onset, the diagnosis of NPC is often delayed or missed, suggesting that the true prevalence of the disorder may be higher. Early diagnosis is crucial as it can potentially affect the course of the disease. In fact, early initiation of misglustat therapy can slow disease progression and prolong a higher quality of life (6). Misglustat is a competitive inhibitor of glucosylceramide synthase. However, careful patient selection is necessary, as it can only extend good quality of life and not improve poor quality of life. Furthermore, a confirmed diagnosis allows for genetic counseling for future pregnancies.

Treatment options will continue to evolve in the coming years, making earliest possible diagnosis even more important.

Figure 2: Height on the WHO curves from birth to the age of 2 years.

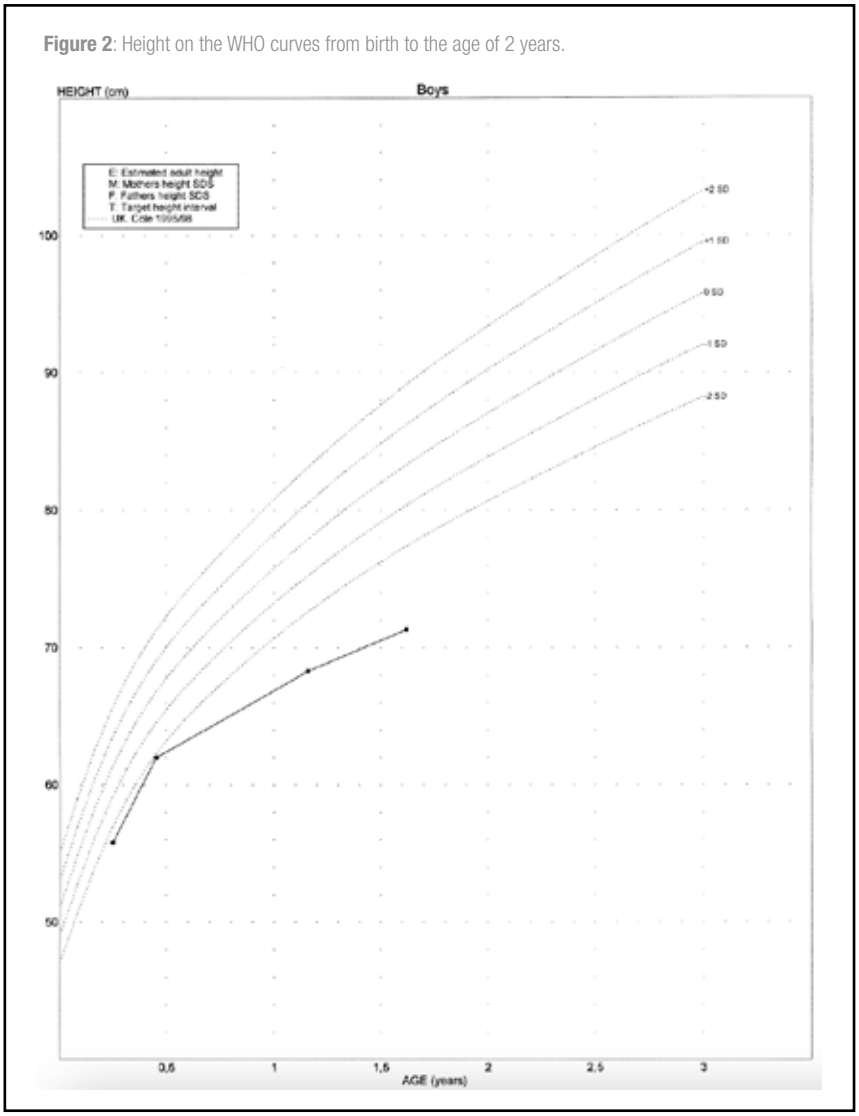
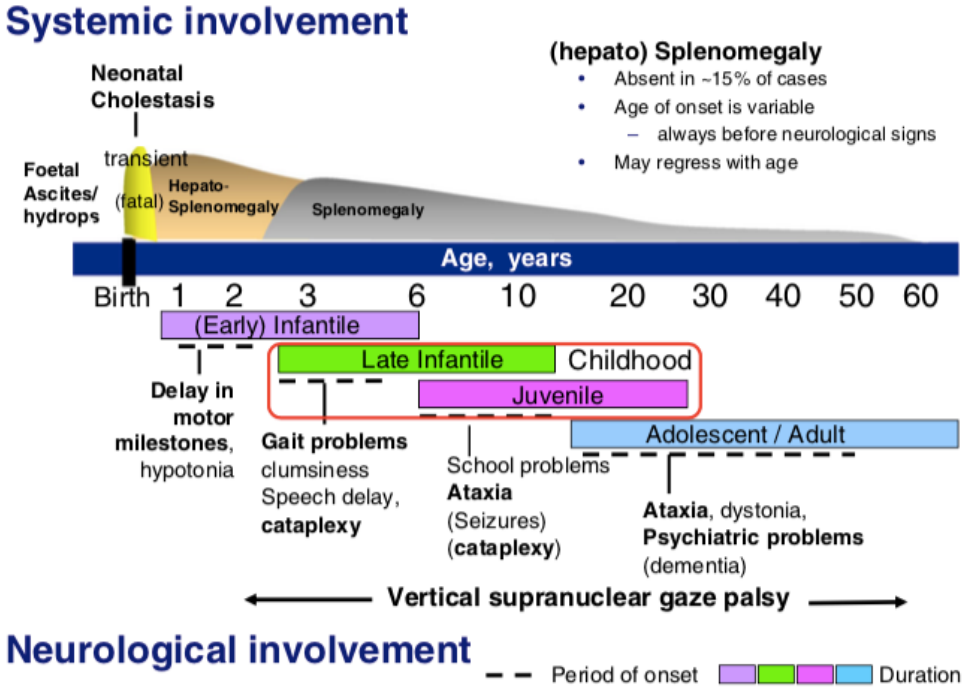


Figure 3: Schematic representation of the clinical aspects of Niemann-Pick C disease. Emphasis is given to the main initial neuro- logical manifestations (published with permission of M.T Vanier and Springer Nature) (9)



Conclusion

This case illustrates the need for long-term follow-up of patients, especially when clinical symptoms persist. Our patient was discharged from the hospital with an incomplete diagnosis and without a good follow-up, his diagnosis could have been missed. We also want to highlight the impact of the genetic testing, which can be useful in such situations.

Finally, neurometabolic diseases are rare and pediatricians should be able to recognize red flag symptoms in order to refer to a multidisciplinary pediatric center.

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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