Volume 4 | Issue 1 | 2024 ISSN | 2771-019X

Journal of
Clinical & Medical Images
Case Reports

Open Access |Case Report

Zellweger syndrome in a newborn: A case report

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Abstract

Introduction: Zellweger syndrome, also known as Zellweger Spectrum Disorders (ZSD), is a group of rare genetic disorders affecting peroxisome metabolism. Peroxisomes play a crucial role in the catabolism of very long-chain fatty acids and the metabolism of bile acids, among other essential functions.The aim of this article is to examine the clinical features, genetic aspects, underlying pathological mechanisms and recent advances in the diagnosis and management of Zellweger Syndrome,

Observation: We report the case of a newborn admitted at his first day from a consanguineous marriage, with 3 sibling deaths at the age of 6 months, one of whom was diagnosed with zellweger syndrome. From the outset, there was massive hypotonia, poor reactivity and absence of contact. Micrognatism and large fontanelles were also noted. Generalized convulsions appeared as early as the first week of life. électroencéphalogramme was normal and brain IRM revealed polymicrogyria. The initial fundus was without abnormality and an amino acid and organic chromatography study was performed. The evolution was marked by improvement of the sucking reflex and persistence of profound hypotonia.

Conclusion: This case reminds us of the importance of looking for a disorder of peroxisome biogenesis in hypotonic newborns with facial dysmorphia.

Received: Jan 02, 2024

Accepted: Jan 31, 2024

Published Online: Feb 07, 2024

Keywords: Facial Dysmorphia, Hypotonia, Metabolic Encephalopathy, Zellweger Syndrome.

Cite this article: Mouhdi S, Bennaoui F, Tahiri F, Lalaoui A, Elidrissi N S, et.al., Zellweger syndrome in a newborn: A case report. J Clin Med Images Case Rep. 2024; 4(1): 1622.

Introduction

Zellweger syndrome, also known as cerebrohepatorenal syndrome, is a rare inherited disorder characterized by the absence or reduction of functional peroxisomes. It is an autosomal recessive disease caused by a defect in the PEX gene [1]. It is a rapidly progressive disease with a high mortality rate. In the absence of curative treatment, therapeutic options are limited to supportive care aimed at improving quality of life. This activity describes the assessment and management of Zellweger syndrome, and highlights the role of the interprofessional team in caring for patients with this disease. We report the case of a newborn with Zellweger syndrome with a review of the literature after free and informed consent from the parents [2].

Observation

We report the case of a newborn admitted to our unit at his first day of life, from a 36-year-old mother, 8 gesture, 8Parity, 5 living children and 3 deceased children and a 6-month-old daughter for suspected zellweger syndrome due to cerebro-hepato-renal involvement. The newborn is the result of a 1st degree consanguineous marriage in a well-monitored monofetal pregnancy estimated at 39week of amenorrhea, the infectious anamnesis is positive: greenish, tinted amniotic fluid, Caesarean delivery, imprecise APGAR and delayed cry according to the mother. The patient was admitted to our unit for neonatal respiratory distress due to a neonatal infection with pulmonary localization. Respiratory distress exceeding 4 hours with positive infectious anamnesis and opacity on X-ray, with neonatal convulsion such as eye twitching and chewing. Clinical examination revealed a pink newborn with facial dysmorphia, non-reactive, non-gesticulating, normochardic at 131beat/min, polypneic at 71C/ min and SaO_2 at 88% in free air, weight: 3k700 (75P), height 50cm (50P), CP: 36cm (75P).

Pleuropulmonary examination: Presence of signs of respiratory distress such as moderate chest indrawing, no rales on auscultation.

Neurological examination: Axial and peripheral hypotonia, normotensive anterior fontanel and archaic reflex present but weak, sucking reflex present but weak.

Abdominal examination: Soft abdomen and no hepatomegaly or splenomegaly.

Cardiovascular examination: No murmur on auscultation and peripheral pulses are well perceived and symmetrical. Examination of the external genitalia and no abnormalities.

The initial workup showed : CBC: Hb 13.3g/dl leukocytes 8500 PNN 5770 Pq 317000 - CRP negative at 4. - ASAT/ALAT: 25/70, Staph coagulase-negative blood culture. Urea: 0.15 Creatine: 4, Chest X-ray: opacity of the right middle lobe

Ophthalmological examination: Normal, ENT examination: bilateral deafness, ETT: ostium secondum type CIA and PCA. ETF: dilatation of the 3ème and 4ème ventricle. CFM: type 1 - Carnitine dosage: arachidonic acid deficiency, carintine T: 13.09 / carnitine L: 11.4 / acylcarnitine: 1.7. - Brain IRM: polymicrogyria and bilateral bi-frontal and presylvian cortical thickening, suggesting encephalic involvement in zellweger syndrome. The patient was initially put on oxygen goggles, Double antibiotic therapy (C3G for 10 days and gentamycin for 2 days), Gardenal loading dose, then daily maintenance dose. - Vitamin B6 - priméa baby bio artificial milk (milk with arachidonic acid)

The evolution during hospitalization was marked by the complication at D10 of hospitalization by the nosocomial infection retained before: the appearance of grayish complexion, mottles and ascencion of CRP to 95. A lumbar puncture was performed with the following results: - Leukocyte less than 3 elements - Biochemistry: results not available - Sterile culture The patient was treated for nosocomial infection for 10 days with meropenem and 5 days with amikacin. The evolution was then marked by clinical improvement: - the patient has been weaned off oxygen - The sucking reflex was recovered with spontaneous eye opening and spontaneous gesticulation, but axial and peripheral hypotonia persisted. The patient was discharged after one month's hospitalization with a nasogastric tube and after education of the mother and hypotonia followed in our training to change the gastric tube every week then evolution was marked by improvement of sucking reflex but persistence of hypotonia.

Discussion

Zellweger syndrome (ZS), also known as cerebrohepatorenal syndrome, is a rare autosomal recessive inherited disorder characterized by the absence/reduction of functional peroxisomes in cells, which are essential for the betaoxidation of very long-chain fatty acids [3]. Peroxisomes play an important role in fatty acid oxidation, particularly in the oxidation of very long-chain saturated fatty acids. Among other abnormalities, abnormally high levels of VLCFAs in body tissues and fluids are observed in many patients with peroxisomal disorders. Caused either by a defect in peroxisome formation or maintenance, or by a defect in the function of a single peroxisomal enzyme, peroxisomal diseases lead to central nervous system and systemic damage [4]. Zellweger syndrome (cerebrohepato-rena syndrome1) is the prototype of the group of disorders associated with peroxisome deficiency, also known as disorders of peroxisome biogenesis. Central nervous system malformations are characterized by a disruption of neuronal migration, resulting in microgyria/pachygyria [5], Zellweger syndrome is the most common peroxisomal disease of infancy, with an incidence of 1 in 50,000 live births in the United States, but with regional variations. [The incidence is higher in the Quebec region (1 in 12,000) and lower in Japan (1 in 500,000). The overall incidence of peroxisomal disorders is approximately 1 in 50,000 to 100,000 live births [6].

Zellweger syndrome is caused by mutations in various genes required for peroxisome biogenesis. Mutations in at least 13 different PEX genes have been associated, and PEX genes code for proteins called peroxins (a peroxisome assembly protein). The most common mutations are in the PEX1 or PEX6 genes, found in around 65% of patients. These genes code for ATPases, which are required to import the protein into peroxisomes from the cytosol [1].

The disease affects almost all organ systems, as peroxisomes are present in all organelles. Manifestations include severe craniofacial anomalies, hypotonia, severe neurodevelopmental delay, sensorineural hearing loss, ocular anomalies and enamel abnormalities. Hepatomegaly is present in 80% of cases, with increased liver enzymes and bilirubin levels. Renal cortical cysts are present in 70% of cases [8]. Depending on the age at which they present, ZS patients are divided into three groups [2]:

• Neonatal-infant presentation: Most of these children present with hypotonia, reduced spontaneous movements and a weak cry. They often have feeding difficulties, and seizures may occur early in neonatal life. They often present with facial dysmorphia, a high forehead, large fontanelles, wide sutures, hypoplastic supraorbital ridges and a broad nasal bridge. Ocular anomalies include glaucoma, cataracts and retinopathy, and these patients may present with varying degrees of sensorineural hearing loss.

• Childhood presentation: Developmental delay, growth retardation, eye and hearing abnormalities, including variable levels of liver dysfunction, adrenal insufficiency and calcium oxalate kidney stones. They may show regression of previously affected neurological milestones, secondary to demyelination (leukodystrophy).

• Presentation from teenager to adult: Developmental delay and neuroregression, cerebellar ataxia, peripheral neuropathy, adrenal insufficiency, leukodystrophy

• The appropriate screening test for an infant suspected of having zellweger syndrome is to measure plasma VLCFA levels [6].

Histological diagnosis is also possible by liver biopsy using the diaminobenzidine staining procedure to study the abundance, size and structure of hepatic peroxisomes [3]. Prenatal diagnosis is also possible by direct analysis of VLCFA levels and bile acid intermediates in amniotic fluid. Another approach is cytochemical staining of peroxisomes in chorionic villus samples. Detailed DNA studies, including immunofluorescence and complementation assays, are now available to confirm and characterize the pathological mutation.

In our case, the diagnosis was not obvious at birth, despite the patient's hypotonia, as the facial dysmorphia was rather non-specific, but the notion of family history in the siblings allowed us to orient ourselves, and the diagnosis was confirmed initially by brain MRI, which revealed images of polymicrogyria, and subsequently by chromatography of amino and organic acids, which revealed a deficiency in arachidonic acid, thus supporting our diagnostic hypothesis.

The various treatment modalities tried were as follows [2]:

• Docosahexaenoic acid - This is a long-chain unsaturated fatty acid, essential for myelination and the development of the brain and eyes. Docosahexaenoic acid levels are low in the plasma of ZS patients. However, its replacement has not been associated with an improvement in neurological symptoms or visual disorders in randomized controlled trials.

• Lorenzo oil - Lorenzo oil is a mixture of glyceryl trioleate and glyceryl trierucate, and its use was initially tried in patients with X-linked adrenoleukodystrophy. It has been shown to reduce plasma VLCFA levels, but not to affect disease progression in ZS patients.

• Cholic acid - This is a 24-carbon bile acid, which contributes to the absorption of fat-soluble vitamins. Due to liver dysfunction and impaired lipoprotein synthesis in patients with ZS, there is a deficiency of fat-soluble vitamins, and the use of cholic acid has been tried in other liver function disorders. The US FDA has approved its use in shingles patients. However, there is little evidence of its efficacy.

Support measures include:

• Hearing aids or cochlear implants for hearing loss

• Referral to an ophthalmologist, cataract extraction and glasses in case of visual impairment Standard antiepileptic drugs for epileptic seizures

• Vitamin K supplementation for coagulopathy

• Vitamin supplementation for low levels of fat-soluble vitamins (A, D, E)

In our case, the patient was put on vitamin supplementation: Vitamin B6 and artificial milk with arachidonic acid with nasogastric feeding. Zellweger syndrome is a rapidly progressive disease with a high mortality rate. In the absence of curative treatment, therapeutic options are limited to supportive care aimed at improving quality of life [3]. In our case, the evolution was marked by clinical improvement with improved sucking reflex, spontaneous eye opening and spontaneous gesticulation, but persistent axial and peripheral hypotonia.

Children who present during the neonatal period have a very poor prognosis, usually dying within the first year of life. Patients who present later in childhood may develop progressive liver disease/insufficiency and have a slightly longer survival after diagnosis compared to the neonatal form. Patients who present in adolescence have a slightly longer survival but generally develop progressive neurological symptoms, including spasticity and peripheral neuropathy, later in life.

Conclusion

Our study highlights the value of brain imaging for rapid confirmation of Zellweger syndrome, enabling early management.

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