

Contribution of Anatomico-pathological findings in diagnosing Zellweger Syndrome in two hypotonic neonates

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INTRODUCTION

Zellweger syndrome (ZS) or cerebro-hepato-renal syndrome is a peroxisome biogenesis disorder. It is a rare condition, inherited in the autosomal recessive mode. It occurs at birth and is characterized by severe neurological impairment associated to other clinical features as specific facies, hepatomegaly and renal cysts [1].

It is lethal in the first year of life in most of cases. The diagnosis is not easy to suspect, given its low incidence and high clinical diversity, especially when there is no index cases in the family [2].

We report the cases of two newborns with ZS, admitted at birth in Neonatology department for neurological distress. The diagnosis was suspected on the clinico-biological features and was confirmed by the autopsy and the neuropathological study. The aim of this study is to recall the clinical and para-clinical characteristics in order to get an early diagnosis, at best antenatally allowing us to carry out in time the genetic counseling.

CASE REPORTS

Case report 1 : AB is a male newborn born to in-bred second-degree consanguineous parents, admitted at birth for acute respiratory and neurological distress. His history revealed a sister who died in the first postnatal days presenting at birth with severe neurological distress, seizures, hemorrhagic syndrome, hepatomegaly and facial dysmorphism (saddle nose, hypertelorism and a high forehead). His mother was 20 years old, gravida 2 para 2. Pregnancy was uneventful (nuchal translucency was 1.8 mm at 13 SA and normal morphological ultrasound). A cesarean section was indicated for late term (42 weeks' gestation (WG)). The newborn was eutrophic with a birth weight of 3300 g and the Apgar score was of 8/9 respectively at 5 and 10 minutes.

Physical examination revealed facial dysmorphism (Fig.1) combining: A triangular face, a big forehead with frontal bossing, a broad anterior fontanel, a flat occiput, a micrognathism and low implanted ears;

limbs distorsion (equinovarus feet and clubhands) and bilateral cryptorchidly.



Figure 1 : Facial dysmorphism (high forehead, nasal hyperthelormism and nasal philtrum) and club feet.

Neurological examination showed axial and peripheral hypotonia with hyporeactivity and a weak sucking reflex. The abdominal exam found hepatomegaly. Transfontanellar ultrasound showed moderate ventriculomegaly. Building upon this, the ZS was highly suspected.

Because of hemodynamic disorder, a severe maternal-fetal infection was suspected and the patient underwent mechanical ventilation and both antibiotic therapy and vaso-active drugs were prescribed. He died after 5 days because of respiratory and hemodynamic failure due to a severe infection. Biochemical tests (measurement of very

long chain fatty acids (VLCFA)) could not be carried out because of the fast progress. Post-mortem histopathological examination confirmed the diagnosis of ZS by showing renal tubular cysts, hepatic fibrosis with bile ducts deformity. Neuropathological examination revealed pachygyria, perisylvian polymicrogyria and periventricular cysts (Fig.2).



Figure 2 : Macroscopic examination showing a pachygyric aspect of the cerebral convolutions, with reduction in the number of tertiary grooves.

Case report 2 : ZB is a female newborn, born to inbred second-degree parents, admitted at birth for neurological distress. Her history showed, two brothers who died in neonatal period suffering from severe neurological impairment, seizures, facial dysmorphism, hepatomegaly jaundice and inter-ventricular communication in one case. The mother was 27 years old gravida 3 para 4, leading a well followed bichorial biamniotic twin pregnancy. Antenatal ultrasounds were normal. Delivery occurred at 36 weeks' gestation per C-section indicated for acute fetal distress. ZB was the 1st twin; she had an Apgar score of 8/9 and an intrauterine growth restriction with a birth weight at 2280 g. Clinical examination objectified: an axial and peripheral hypotonia with a weak sucking reflex, a hepatomegaly and a facial dysmorphism associating: A big forehead with frontal bossing, a broad anterior fontanel, a flat occiput, low implanted ears and a micrognathism. Abdominal ultrasound found a hepatomegaly with two hypertrophic and hyperchogenic kidneys. The Electro-encephalography objectified diffuse brain damage. The diagnosis of ZS was highly suspected.

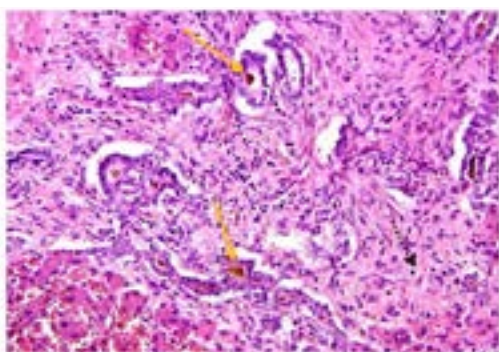


Figure 3 : Hepatic fibrosis with biliary plaque abnormalities and histological cholestasis.

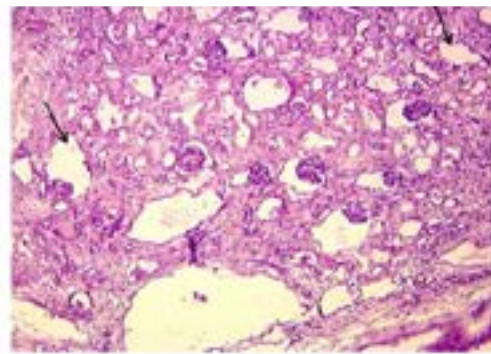


Figure 4 : Sub-cortical cysts of the kidney.

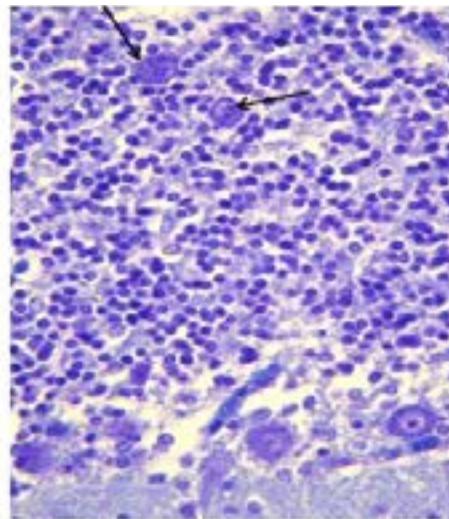


Figure 5 : Luxol blue x 400: Presence of neuronal heterotopia in the cerebellum.

The determination of VLCFA in fibroblast culture showed an increase in C26 to 3.34 mg/l (normal rate: 1.03 mg/l) and C26:0 / C22:0 to 0.516 (normal rate: 0.069 mg/l).

On day 2, the neonate presented with seizures, followed by coma. Death happened at one month age, after repeated episodes of bradycardia and desaturation, probably due to central apnea.

Post-mortem examination showed histopathological findings including bile ducts and renal cysts. Neuropathological examination confirmed neuronal migration disorder, associated with pseudo-cystic subependymal injuries and diffuse white matter gliosis. Those abnormalities led to ZS diagnosis.

DISCUSSION

Peroxisomes are cellular organelles involved in many biochemical processes, such as β -oxidation of very long chain fatty acids, α -oxidation of phytanic acid, and plasma gene synthesis. Peroxisomes are plentiful in 2 particular tissues: the nervous system and the liver.

Peroxisome biogenesis abnormalities (PBA) are a group of metabolic disorders, divided into 2 distinct spectra [3]: the Zellweger spectrum and the Rhizomelic Chondrodysplasia spectrum. These diseases are due to a mutation of one of the PEX genes. These genes code for proteins called peroxins involved in

the transport of matrix and membrane enzymes to the peroxysome [4]. The Zellweger spectrum has 3 phenotypic entities: Zellweger syndrome (ZS), neonatal adrenoleukodystrophy (NALD) and infantile Refsum disease (IRD) [5]. Zellweger syndrome (ZS) or cerebro-hepato-renal syndrome is the most critical prototype compared to NALD and IRD. In 70% of cases, it is due to the mutation of the PEX1 gene [6]. In the other cases, it involves a mutation of other PEX genes (2, 6, 10 or 26) [7].

It is a rare congenital condition with an estimated incidence of 1 per 100,000 births [8].

The diagnosis of ZS is difficult to establish in the antenatal period, especially if there's no index cases, because of its non specific clinical presentation. Fetal hypokinesia, hydramnios, IUGR, and sub-ependymal cerebral pseudo-cysts [9] or nuchal translucency greater than 6 mm can be detected by antenatal ultrasound [10].

The most consistent clinical signs in ZS are severe hypotonia, seizures, a typical facial dysmorphism with a big high forehead and broad fontanel, and hepatomegaly. Other disorders may include kidney cysts, jaundice, severe developmental disorders, heart defects or skeletal abnormalities [1].

Generally, the clinical picture is incomplete and individual variability does exist. None of those signs is pathognomonic but their association is so relevant especially in case of inbreeding or history of neonatal deaths in the family. Those features can lead to the diagnosis of a peroxisomal disease, particularly ZS.

Regarding the two newborns reported in our study, diagnosis was suspected based on: inbreeding, the history of sibling death as newborns suffering from neurological distress and facial dysmorphism, and the clinical picture combining facial dysmorphism, neurological distress and hepatomegaly.

ZS is confirmed by : peroxisomal functions exploration , VLCFA accumulation, plasmalogen-rate drop and significant decrease in catalase and DHAP-AT (Dihydroxyacetone-phosphate-acyltransferase enzymatic activities), which can be performed by skin-fibroblast culture; Accurate genotyping and identifying exact PEX genes mutations and/or a neuropathological examination [11] which shows abnormal gyration, maturation interruption pictured as neuronal migration defect and diffuse white-matter demyelination with secondary gliosis [12].

However, the diagnosis of ZS has benefited from medical advances in magnetic resonance imaging (MRI), which can reveal brain abnormalities, particularly white matter abnormalities and gyration [13]. In the first case, the diagnosis was confirmed, despite the lack of specific biochemical testing and enzymatic markers and/or molecular genetics study. It was based on the neuropathological examination, which found multiple characteristic disorders such as: germinolysis pseudo-cystic damages in the caudothalamic area, sylvian valley polymicrogyria, parietal pachygyricgyrus and sub-cortical and cerebellar heterotopia. In addition, other findings such as renal

microcysts and bile duct disorders, also pointed to the diagnosis of ZS.

In the second case, the diagnosis of ZS was based on neuropathological examination and VLCFA assay measurement by skin-fibroblast culture. It showed an increase in C26: 0 rate (3 times greater) and an increase in the C26:0/C22:0 ratio (7 times greater). In general, ZS is lethal in the first year, due to respiratory and/or neurological failure, often caused by infection.

CONCLUSION

ZS diagnosis is often underestimated and many cases are unnoticed, as it requires biochemical tests, detailed neuropathological examination and/or precise genotyping. Genetic counseling is crucial because of the autosomal recessive inheritance pattern and the lack of curative therapy. In fact, it allows us to start a family pedigree chart , assess the risk transmission and to offer a prenatal diagnosis to the family. It is based on antenatal ultrasound scan which may show suggestive signs of ZS [14, 15]. An additional investigation by MRI may be requested between 28 and 30 weeks of gestation, in order to detect the gyration abnormalities, grey matter demyelination and heterotopia. Amniocentesis is the key of prenatal diagnosis by allowing peroxisomal functions exploration through aminocytes or fibroblasts culture [16].

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