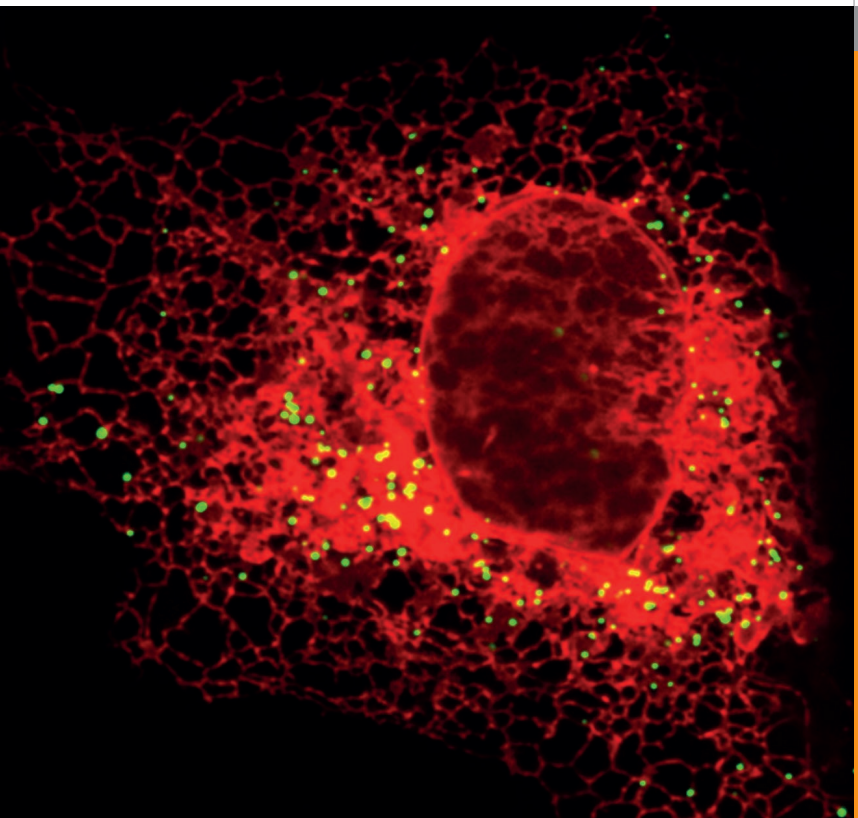
SWISS SOCIETY OF NEONATOLOGY

Zellweger syndrome



July 2012

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INTRODUCTION

The peroxisome biogenesis disorders include three different phenotypes: Zellweger syndrome, neonatal adrenoleukodystrophy and infantile Refsum disease. All of these three disorders are inherited in an autosomal recessive manner. Zellweger syndrome, also known as cerebro-hepato-renal syndrome, is the most severe and the most common peroxisomal disorder to present in early infancy. Its incidence is estimated at 1 in 50'000 to 100'000 live births.

CASE REPORT

This female infant was born to a 23-year-old G1/P1 by spontaneous vaginal delivery at 40 3/7 weeks of gestation following premature rupture of membranes with meconium stained amniotic fluid. Prenatal ultrasound examinations had revealed a number of abnormalities: dilated lateral ventricles, megacystis, left-sided clubfoot, thickened bowel walls and renal cysts.

Following delivery, bag mask ventilation was initiated and continued for about five minutes because of insufficient breathing effort. Apgar scores were 4, 6 and 8 at 1, 5 and 10 minutes, respectively, and umbilical cord pH values were 7.33 (arterial) and 7.37 (venous). She was then transferred to the neonatal intensive care unit on nasal CPAP with an FiO2 of 25%. Two hours later, she had to be intubated because of increasing respiratory distress.

She had a birth weight of 2750 g (P3-5), a head circumference 31.2 cm (P<3) and a body length of 50.5 cm (P25-50). Physical examination on admission showed multiple abnormalities: turribrachycephaly with a very large anterior fontanel, a short neck with redundant skin folds, hepatomegaly, bilateral Simian creases, brachydactyly, fetal fingertips, a left-sided clubfoot, limited extension of the knees, hypotonia, and clitoromegaly.

A chest X-ray showed patchy opacities consistent with aspiration. Echocardiography revealed decreased biventricular function (LV-SF 20%), low cardiac output, a widely open PDA, severe persistent pulmonary hypertension, a perimembranous VSD with a small right-to-left shunt and a PFO with a left-to-right shunt. She was stabilized with dobutamine, norepinephrine, intravenous prostacyclin analogue (iloprost) and inhaled nitric oxide.

Cranial ultrasound revealed slightly enlarged and irregular lateral ventricles, a limited number of gyri in the perisylvian area, an apparently reduced white matter mass and a small subependymal hemorrhage (Fig. 1). The abdominal ultrasound examination demonstrated megacystis, hepatomegaly, and edema of the gallbladder; the kidneys showed significantly increased echogenicity and several, subcapsular, thin-walled cysts (Fig. 2). The examination of the eyes revealed hyper-

telorism, lagophthalmus, no pupillary reaction, ocular hypertension and Brushfield spots.

These findings were felt to be compatible with a peroxisomal disorder, most likely Zellweger syndrome (cerebro-hepato-renal syndrome). The diagnosis was confirmed by the presence of very long chain fatty acids (VLCFA) and increased plasma ratios of C26 (hexacosanoic acid) to C22 (docosanoic acid), as well as C24 (tetracosanoic acid) to C22 fatty acids.

The patient continued to require mechanical ventilatory support with high FiO2 and pulmonary vasodilators. In view of the very poor prognosis and the persistence of severe pulmonary arterial hypertension a decision was made together with the parents to redirect care.

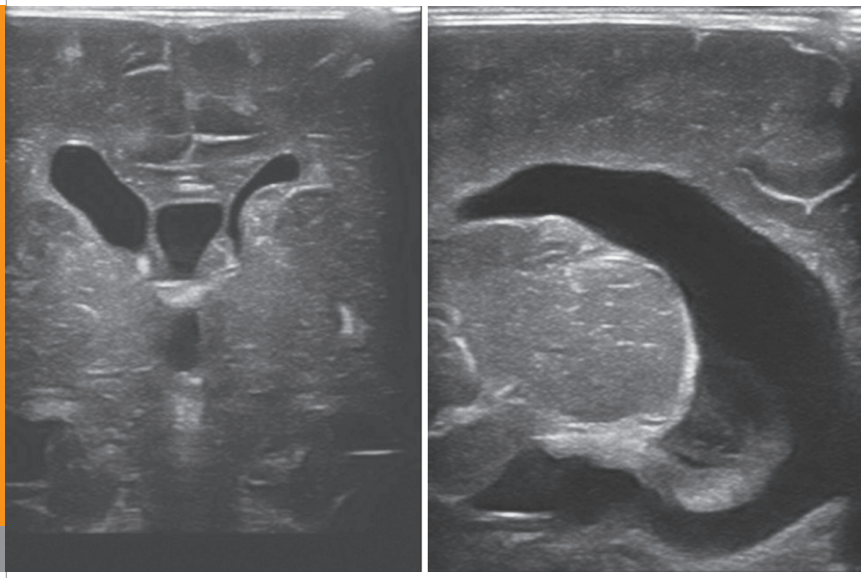

Fig. 1

Cerebral ultrasound examination: irregular and slightly enlarged lateral ventricles, large cavum septi pellucidi and cavum vergae, small bilateral subependymal hemorrhages.

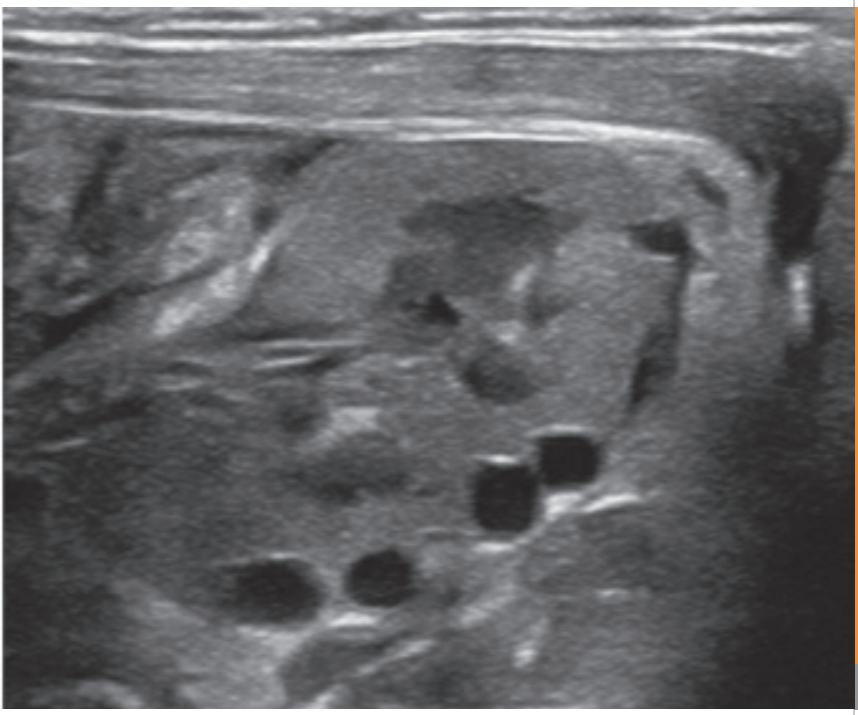

Fig. 2

Renal ultrasound examination: multiple, thin-walled subcapsular cysts with diameters ranging from a few millimeters to a maximum of just under one cm.

DISCUSSION

Zellweger syndrome was first described in 1964 by the Swiss pediatrician Hans Ulrich Zellweger as a lethal, multiple malformation syndrome of infancy (1, 2). In 1973, Goldfischer et al. noted the absence of peroxisomes in the kidney and liver cells of a child with Zellweger syndrome (3).

Peroxisomes are ubiquitous components of the cytoplasm in all human cells except erythrocytes (Fig. 3) They catalyze several anabolic and catabolic functions in cell metabolism such as beta-oxidation of VLCFA, oxidation of phytanic, pristanic, pipecolic and other dicarboxylic acids. The peroxisomes are also involved in the synthesis of bile acids and plasmalogens. The latter are part of myelin and cell membranes (4).

Zellweger syndrome is caused by a mutation in one of at least 12 different genes: PEX1, PEX2, PEX3, PEX5, PEX6, PEX10, PEX12, PEX13, PEX14, PEX16, PEX19, PEX26 (5). The majority of patients has either a mutation in PEX1 or PEX6 (6).

The characteristic clinical features of Zellweger syndrome that were present in our patient are turribrachycephaly, large fontanels, white matter abnormalities, microgyria, hypertelorism, Brushfield spots, redundant skin folds of the neck, VSD, PDA, hepatomegaly, clitoromegaly, renal cortical cysts, Simian creases, club foot, and hypotonia.

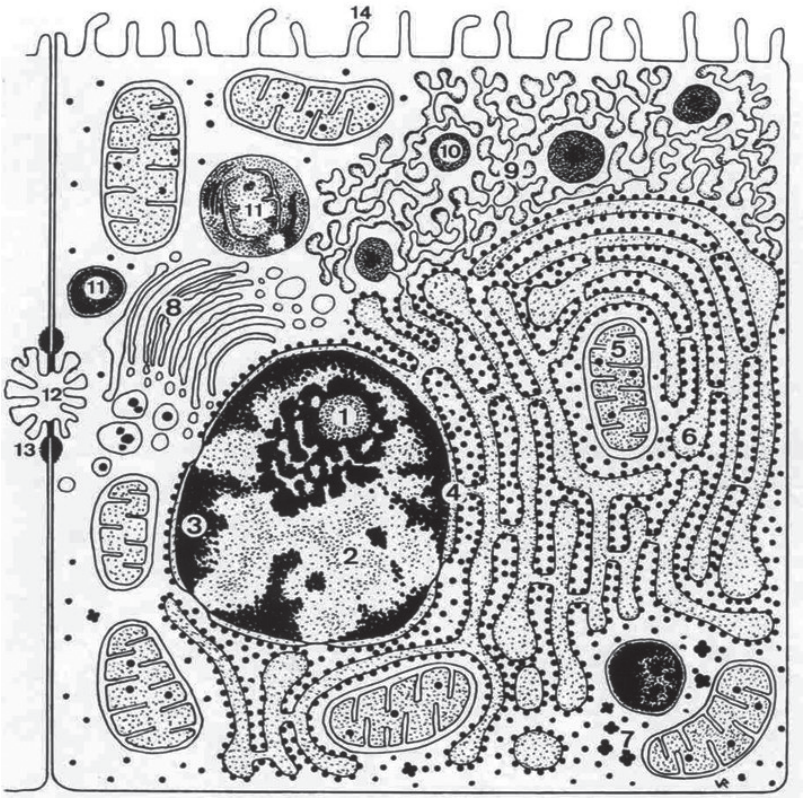

Fig.3

Cell organelles: 1:nucleolus; 2:chromatin; 3:dense chromatin; 4:nuclear pores; 5:mitochondria; 6:rough endoplasmic reticulum; 7:ribosomes; 8:golgi apparatus; 9:smooth endoplasmic reticulum; 10:peroxisomes; 11:Lysosomes; 12:bile capillary; 13:desmosomes; 14:microvilli.

The most reliable test to confirm the diagnosis of peroxisomal biogenesis disorders is the measurement of VLCFA concentrations in plasma. Patients with Zellweger syndrome have elevated plasma concentrations of VLCFA and elevated ratios of C26 to C22 and C24 to C22 fatty acids (5). In addition, sequence analysis is available for the twelve genes to identify the gene defect. Most affected children die within the first year of life (5). Longer term survivors are rare, fail to thrive and have severe mental retardation.

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