CASE REPORT

Zellweger syndrome with severe malnutrition, immunocompromised state and opportunistic infections

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SUMMARY

Peroxisome biogenesis disorders are related to a spectrum of genetic diseases that range from severe Zellweger syndrome to milder infantile Refsum disease. Zellweger syndrome is characterised by dysmorphic features, severe hypotonia, seizures, failure to thrive, liver dysfunction and skeletal defects. Increased levels of very long chain fatty acids are the biochemical hallmark and the most common mutations found in the PEX1 gene. We report an unusual presentation of Zellweger syndrome in a 2-month-old female infant with severe malnutrition, opportunistic infections, lymphopaenia and a small thymic shadow on chest radiography. With this clinical picture, an initial hypothesis of primary immunodeficiency was considered. It was later confirmed to not be the case. On follow-up, global developmental delay, bilateral optic nerve atrophy and moderate bilateral sensorineural deafness grade II were documented. There were no further infectious complications and we concluded malnutrition was the cause of the infant's immunocompromised state.

BACKGROUND

Peroxisomes play an important role in a number of essential metabolic pathways, including the biosynthesis of phospholipids and bile acids, the α -oxidation and β -oxidation of fatty acids, the detoxification of glyoxylate, and the metabolism of reactive oxygen species such as hydrogen peroxide and superoxide.¹ Peroxisome biogenesis disorders (PBDs; MIM 601539) are inherited in an autosomal recessive manner and have a wide clinical spectrum ranging from the more severe Zellweger syndrome (ZS; MIM 214100) to the milder infantile Refsum disease (MIM 266510).²

Patients with ZS in the neonatal period often present typical dysmorphic features, severe neurological dysfunction with hypotonia and, occasionally, seizures, failure to thrive (FTT), liver dysfunction and skeletal defects. During the first months of life, predominant symptoms may include hepatomegaly, prolonged jaundice and, sometimes, liver failure, but may also manifest as non-specific gastrointestinal problems such as anorexia, vomiting and diarrhoea, leading to FTT and osteoporosis. Survival is rare beyond the first year of life.^{3–4} Estimated prevalence of ZS in North America is around 1:50 000.⁵

FTT is a common sign of several disorders in childhood. It is rarely presented as an isolated symptom in inherited metabolic diseases.⁶ Studies

have shown that atrophy of primary lymphoid organs, particularly the thymus, is correlated with severe protein malnutrition in childhood, leading to a significant state of immunosuppression.⁷

We report a case of ZS, confirmed by clinical, biochemical and molecular findings, diagnosed in the context of dysmorphisms, FTT and opportunistic infections. Primary immunodeficiency was also suspected, but investigation was non-specific.

CASE PRESENTATION

A 2-month-old female infant was admitted to our hospital due to FTT associated with diarrhoea and abdominal distension. She was the first child of non-consanguineous healthy parents. Pregnancy was complicated by maternal hypertension and intrauterine growth restriction. Birth was by vaginal delivery at 38 weeks' gestation, with Apgar scores of 9 at 1 min and 10 at 5 and 10 min. Somatometry at birth was below the third centile (Fenton's curve): weight 2070 g, length 44 cm and head circumference 31 cm. Jaundice on the first day of life led to phototherapy for 48 h. There was a good weight gain up to the first month of life, with regular growth below third centile. After the second month of life, hypotonia and poor weight gain prompted hospitalisation.

On admission, the infant was severely undernourished (weighing 2940 g), with abdominal distension, intermittent stridor and axial hypotonia. Dysmorphic features included a large anterior fontanelle and dehiscence of the interparietal space extending to the posterior fontanelle, broad nasal bridge with orbital hypertelorism, epicanthus, high-arched palate, short neck, rhizomelic shortening of proximal extremities, low-set thumb and overlapping toes (figure 1).

Transfontanellar, abdominal and renovesical ultrasounds were normal. The skeletal radiograph did not show any calcific stippling of epiphyses. A chest CT with angiography revealed two supra-aortic trunks with preserved permeability (proximal stem yielding to the right brachycephalic trunk and left carotid artery, and distal stem corresponding to the left subclavian artery) and no apparent decrease in the diameter of the trachea, revealing a variant of normal cardiovascular structure. On further investigation, karyotype analysis was normal (46, XX), as were carbohydrate-deficient transferrin, phytanic and pristanic acids, and the erythrocyte plasmalogens. Brain proton MR spectroscopy revealed localised peaks at 0.9

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Figure 1 Dysmorphic features of the patient at 4-months-old, showing large anterior fontanelle communicating with posterior fontanelle, broad nasal bridge with orbital hypertelorism, short neck, rhizomelic shortening of proximal extremities and low-set thumb.

and 1.3 ppm, possibly reflecting the presence of macromolecules and lipids/lactate, without other relevant changes in neuroimaging.

The ZS diagnosis was based on clinical phenotype, increased plasma levels of very long chain fatty acids (VLCFA) (C26:0 2.9 µg/mL (control 0.16–0.57 µg/mL), C26:1 1.58 µg/mL (control 0–0.51), C24:0/C22:0 ratio 1.78 (control 0.63–1.10), and C26:0/C22:0 ratio 0.507 (control 0.004–0.022)) and precursor of bile acids (3α,7α-dihydroxy-5β-cholestan-26-oic acid (DHCA) 1.83 µg/mL (control 0–0.01 µg/mL) and 3α,7α,12α-trihydroxy-5β-cholestan-26-oic acid (THCA) 2.16 µg/mL (control 0–0.03 µg/mL)) and deficient activity of dihydroxyacetonephosphate acyltransferase (DHAPAT) (0.8 mmol/2 h/mg protein (control 3.4–16)) in fibroblasts. Two mutations in the PEX1 gene were found in heterozygosity (c.2528G>A (p.G843D) / c.760dupT (p.S254fs*5)), confirmed by the parent's genetic study.

During hospital stay, investigation identified cytomegalovirus (CMV) colitis and hepatitis (IgM positive), which were treated with gancyclovir; and *Giardia lamblia* and *Clostridium difficile* toxin in stools, treated with metronidazole. Given the severe malnutrition and steatorrhea, nasogastric tube feeding and supplementation with pancreatin was required. A period of total parenteral nutrition was also needed for good weight gain.

During a clinical worsening period with respiratory failure that resulted in invasive ventilation, *Pneumocystis jirovecii*, CMV and *Escherichia coli* were isolated in bronchoalveolar lavage fluid. Meanwhile, a chest radiograph revealed that the thymic shadow was small (figure 2). At this time, the hypothesis of concurrent severe combined immunodeficiency (SCID) was considered. Treatment with cotrimoxazole and cefotaxime was started, as well as prophylaxis with rifampin, isoniazid and fluconazole. Work up for an underlying immunodeficiency was pursued. Immunodeficiency profile revealed a decreased lymphocyte count of 2500/mm³, decreased absolute CD3 (48% (control 65–78%)), CD8 (15% (control 28–38%)) and CD56 counts (3% (control 4–13%)), and normal B cell count and immunoglobulin levels. A mitogen stimulation test showed normal T cell activity following stimulation with phytohemagglutinin (PHA) and pokeweed mitogen (PWM), and decreased response with staphylococcal protein A, not typical of a severe T cell deficiency. ZAP-70 expression in T lymphocytes and

Figure 2 Chest radiograph showing a small thymic shadow and bilateral pneumonia due to *Pneumocystis jirovecii*.

natural killer cells was normal, and HIV-1 and HIV-2 antigen/antibody assays were negative. Study of critical regions for DiGeorge syndrome (MIM 188400, 22q11.2 deletion) was also negative. Owing to the lack of results consistent with primary immunodeficiency syndromes and the subsequent clinical improvement with recovering nutritional status, secondary immunodeficiency due to malnutrition came up as the most likely hypothesis. The patient was discharged at 6 months of age, with a weight of 4195 g.

OUTCOME AND FOLLOW-UP

During follow-up, the patient had slow but steady growth. Global developmental delay, bilateral optic nerve atrophy and moderate bilateral sensorineural deafness grade II were demonstrated. There were no other major infections reported (apart from nasopharyngitis at 12 months, gastroenteritis at 14 months, roseola at 19 months and gingivostomatitis at 23 months).

Presently she is 30-months-old (figure 3), has a low weight (9360 g, <3rd centile) and height (81.1 cm, <3rd centile) without microcephaly (48.5 cm, 50–85th centile). She has shown some progress in motor development—despite axial hypotonia—but few other advances, in recent assessments. Her best score is in locomotion (15 months). Visual perceptual and fine motor development had the lowest score (6 months). Hearing behaviour, language and communication were at 8–10 months. Current treatment includes pancreatin, multivitamins, physiotherapy, and occupational and speech therapy. A repeated immunological investigation with complete blood count, lymphocyte populations and lymphocyte transformation test was normal. The lymphocyte count was 5500/mm³. The suspected primary immunodeficiency associated with ZS has not been confirmed.

DISCUSSION

This case has some particular features that should be highlighted. The diagnosis of ZS was based on clinical phenotype and specific laboratory and genetic abnormalities. This case showed an unusual evolution with immunocompromised state and severe opportunistic infections, leading to suspicion of primary immunodeficiency.

PBDs are autosomal recessive disorders, with 14 known PEX gene defects. These PEX genes encode peroxisome assembly proteins known as peroxins. These proteins are multifunctional, and responsible for various stages of peroxisome biogenesis and peroxisomal protein import.⁸ In patients with ZS, a mutation in 1 of the 14 PEX genes coding for a peroxin produces

Figure 3 Dysmorphic features of the patient at 30-months-old, showing broad nasal bridge with orbital hypertelorism, epicanthus, short neck, rhizomelic shortening of proximal extremities, low-set thumb and overlapping toes.

functionally incompetent organelles. In typical presented cases, plasma and cultured fibroblasts have increased levels of VLCFA, decreased levels of plasmalogens, and accumulation of phytanic acid and pristanic acid. Phytanic and pristanic acids can be normal until children have contact with phytol in food. Elevated plasmatic levels of precursors of bile acids are also found.^{8,9} Our patient had increased VLCFA and precursor of bile acid levels in plasma, associated with changes in fibroblasts such as elevated VLCFA and deficient activity of DHAPAT, consistent with the diagnosis of ZS.

The most common mutations are in the PEX1 gene, and account for two-thirds of all patients with ZS.^{2,3} PEX1 is located on chromosome 7q21–q22 and encodes peroxin 1, a member of a protein family called ATPases, associated with diverse cellular activities (AAA proteins).³

The most common mutation in PEX1 is the missense mutation c.2528G>A, which replaces a glycine, located at amino acid position 843, by an aspartic acid (G843D; 602136.0001).⁸

In our patient, mutations in PEX1 were detected in compound heterozygosity, c.2528G>A (p.G843D) and c.760dupT (p.S254fs*5), confirmed by genetic study of the parents. The latter mutation has not yet been described, but gives rise to a truncated protein, presumed to be a pathogenic causal mutation.

About 50% of the population in developing countries has severe malnutrition, the most prevalent cause of immunodeficiency worldwide, and this state can affect the functioning of different immune cell types in both innate and adaptive

immunity.^{10,11} Protein malnutrition at an early stage of life, associated with atrophy of the thymus and bone marrow, has serious consequences such as leucopenia, increased circulating immature T cells and decreased CD4/CD8 ratio.⁷

P. jirovecii is a fungus responsible for *Pneumocystis pneumonia* (PCP), one of the opportunistic infections most often found in individuals with severe immunodeficiencies.¹² It is particularly associated with SCID, a group of rare inherited diseases characterised by defects in the function of both, T and B cells.¹³

Thymic atrophy and defective T cell function has been noted in some patients with ZS. There is a published report of two cases of ZS in Swedish siblings, born to consanguineous parents, with distinctive symptoms and pathological findings of ZS.¹⁴ Both children died around the third month of life and were diagnosed with PCP postmortem. At autopsy, an atrophic thymus and small germinal centres in the lymph nodes and spleen were also found. These alterations can be found in malnourished children, also susceptible to infections such as PCP.

As in our case, FTT and diarrhoea, usually described in ZS, resembling a malabsorption syndrome, could have led to a state of protein malnutrition, favouring secondary immunosuppression. After the treatment of infections and malnutrition, the patient had no more serious infections, and her immunological changes reverted. We have not found published reports of the association of recurrent infections or severe immunodeficiency with ZS.

Despite the many existing problems, our patient has been faring reasonably well, with a slow improvement in psychomotor milestones, contrarily to what is classically described.

Learning points

- We report the unusual presentation of a patient with Zellweger syndrome with severe malnutrition, opportunistic infections, lymphopaenia and small thymic shadow.
- Malnutrition was the cause of this infant's immunocompromised state, and must be considered in the differential diagnosis of severely malnourished children with immunocompromised states and opportunistic infections.
- The patient progressed favourably, unlike what is classically described for Zellweger syndrome.

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REFERENCES

- 1 Wanders RJ, Waterham HR. Biochemistry of mammalian peroxisomes revisited. *Annu Rev Biochem* 2006;75:295–332.
- 2 Steinberg SJ, Dodt G, Raymond GV, et al. Peroxisome biogenesis disorders. *Biochim Biophys Acta* 2006;1763:1733–48.
- 3 Rosewich H, Ohlenbusch A, Gärtner J. Genetic and clinical aspects of Zellweger spectrum patients with PEX1 mutations. *J Med Genet* 2005;42:e58.
- 4 Lee PR, Raymond GV. Child neurology: Zellweger syndrome. *Neurology* 2013;80: e207–10.

- 5 Orphanet (FR). *Zellweger syndrome*. Paris, France: Orphanet (FR), 2012 (cited 30 November 2015). http://www.orpha.net/consor/cgi-bin/OC_Exp.php?Lng=PT&Expert=912
- 6 Fidicioglu C, An Haack K. Failure to thrive: when to suspect inborn errors of metabolism. *Pediatrics* 2009;124:972–9.
- 7 França T, Ishikawa L, Zorzella-Pezavento S, *et al*. Impact of malnutrition on immunity and infection. *J Venom Anim Toxins Incl Trop Dis* 2009;15:374–90.
- 8 Waterham HR, Ebberink MS. Genetics and molecular basis of human peroxisome biogenesis disorders. *Biochim Biophys Acta* 2012;1822:1430–41.
- 9 Steinberg SJ, Snowden A, Braverman NE, *et al*. A PEX10 defect in a patient with no detectable defect in peroxisome assembly or metabolism in cultured fibroblasts. *J Inherit Metab Dis* 2009;32:109–19.
- 10 Schaible UE, Kaufmann SHE. Malnutrition and infection: complex mechanisms and global impacts. *PLoS Med* 2007;4:e115.
- 11 Stapleton PP, Fujita J, Murphy EM, *et al*. The influence of restricted calorie intake on peritoneal macrophage function. *Nutrition* 2001;17:41–5.
- 12 Centers for Disease Control and Prevention (US). *DPDx—laboratory identification of parasitic diseases of public health concern—Pneumocystis*. Atlanta, USA: Centers for Disease Control and Prevention (US), 2013. (cited 30 November 2015). <http://www.cdc.gov/dpdx/pneumocystis/index.html>
- 13 National Human Genome Research Institute (US). *Learning about severe combined immunodeficiency (SCID)*. Bethesda, USA: National Human Genome Research Institute (US), 2014. (cited 30 November 2015). <http://www.genome.gov/13014325>
- 14 Brun A, Gilboa M, Meeuwisse GW, *et al*. The Zellweger syndrome: subcellular pathology, neuropathology, and the demonstration of *Pneumocystis carinii* pneumonitis in two siblings. *Eur J Pediatr* 1978;127:229–45.

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