Zellweger Syndrome: A Downs Syndrome Mimic

Khadpe T.1, Kondekar A.2, Anand V.3, Ghildiyal R.4

1Dr. Tanmay Khadpe, Post Graduate Resident, 2Dr. Alpana Kondekar, Associate Professor, 3Dr. Varun Anand, Assistant Professor, 4Dr. Radha Ghildiyal, Professor, Department of Pediatrics, All authors are affiliated with TN Medical College and BYL Nair Hospital, Mumbai Central, Mumbai, India.

Corresponding Author: Dr. Tanmay Khadpe, Post Graduate Resident, Department of Pediatrics, TN Medical College and BYL Nair Hospital, Mumbai Central, Mumbai, India. E-mail: tanmay.khadpe@gmail.com

Abstract

The peroxisomal diseases are genetically determined disorders caused either by the failure to form or maintain the peroxisome or by a defect in the function of a single protein that is normally located in this organelle. It is a heterogeneous group of autosomal recessive disorders characterized by a defect in peroxisome formation and are caused by mutations in one of 13 PEX genes. The defect in peroxisome formation or impaired metabolic pathways result in metabolic abnormalities. Typically in Zellweger spectrum disorders (ZSD) patients accumulate very long chain fatty acids (VLCFAs), phytanic and pristanic acid, C27-bile acid intermediates and piperolic acid in plasma and have a deficiency of plasmalogens in erythrocytes. These disorders present with a wider range of phenotype than has been recognized in the past and few of them may phenotypically resemble Downs Syndrome.

Keyword: Peroxisomal diseases, PEX genes, Zellweger spectrum disorders, Very long chain fatty acids, Plasmalogens, Downs Syndrome

Introduction

Zellweger syndrome (ZS) as a cerebro-hepato-renal syndrome was first described in 1964 by Bowen et al [1]. The clinical presentations have clinical overlap in terms of morphological features. Some of the phenotype mimic Downs syndrome [1,2]. Despite of being a cerebro-hepato-renal syndrome in literature, we present a case with predominant neurological involvement without any hepatic or renal manifestations at presentation. The diagnosis was suspected only on basis of clinical phenotype resembling downs syndrome with a normal karyotype.

Case Summary

We report a case of 3-month-old girl presented with fever and vomiting for 3 days with lethargy, refusal to feeds for a day prior admission. There was no significant past history and family history. Perinatal period was uneventful however antenatal ultrasound was suggestive of polyhydramnios. The child presented in status epilepticus, jerky respiration and apneic spells.

On general examination, patient was afebrile, lethargic, with feeble pulses and delayed capillary refill time. Head circumference was 42 cm (Normocephaly). However our patient had marked frontal bossing, dolichocephaly, mongoloid slant, ear lobules bilaterally hypoplastic, depressed broad nasal bridge, lower lid eyelashes sparse, Anterior fontanelle was open (normal size) (Fig1 and 2).

The hand of the patient had simian crease with clinodactyly, absent bilateral proximal interphalangeal flexure lines on index finger, middle finger and no flexure lines on bilateral little finger. No neurocutaneous markers were present. Spine was normal (Fig 3 and 4) On Systemic examination child had marked hypotonia, hyper reflexia, firm hepatomegaly. Fundus examination was normal.
Child required ventilatory support and was stabilised with treatment with antibiotics for 3 days, inotropic support for first 24 hours of admission. Status epilepticus was controlled by Fosphenytoin, Phenobarbitone, Levetiracetam. After initial stabilisation she was further evaluated for dysmorphism mimicking Downs syndrome. Karyotype (46XX) and Thyroid function tests done postnatally were normal.

MRI was suggestive of chronic subdural collections with mild diffuse cortical atrophy in Bilateral Fronto-parieto temporal regions with cystic hygroma in frontal region (Fig 5)

Child was planned for a work up keeping Zell wegers Spectrum disorders owing to a phenotype suggestive of Downs syndrome but a normal karyotype. Hence a Very long chain fatty acid assay was done which reported an elevated C26 and C26/C22. RBC plasmalogen/Fatty acid ratio reported normal C16:0 DMA/C16:0 fatty acid and low C18:0 DMA/C1:0 fatty acid ratios. The report was hence consistent with Zell wegers Syndrome.
Child was discharged on a phytanic free diet, antiepileptics, docosahexaenoic acid (DHA) and multivitamin supplementation. Child was followed up on monthly intervals however patient did not follow up after 6 months of age. The plan for further confirmation of diagnosis in cultured skin fibroblast, DNA sequencing of PEX and related peroxisomal single enzyme defects genes for mutations as mentioned in literature were not feasible due to financial constraints [1].

**Discussion**

Peroxisome biogenesis disorders, Zellweger syndrome spectrum (PBD, ZSS) is a continuum comprising three phenotypes:

1. Zellweger syndrome (ZS), the most severe
2. Neonatal adrenoleukodystrophy (NALD);
3. Infantile Refsum disease (IRD), the least severe

Children with the severe phenotype (neonatal-infantile presentation with severe clinical symptoms) have a poor prognosis and these patients usually die within the first year of life.

Patients that present in childhood or adolescence usually have a better prognosis, but can develop progressive liver disease or leukodystrophy and gradually deteriorate. Despite early presentation with ZS our patient did not have any liver involvement. Progressive liver disease or leukodystrophy are poor prognostic indicators.

The remaining milder individuals can reach adulthood without progression or with long periods of stabilization. When progression occurs, it is mainly related to peripheral neuropathy and pyramidal signs, while cognition remains stable. Most patients with ZS succumb in first year of life. The incidence is variable worldwide with highest in Quebec (1 in 12) and lowest in Japan (1 in 5,00,000)[2].

We reviewed other Downs Mimic Syndromes

a) 49, XXXXY chromosome and other high-order multiple X chromosome disorders
b) Congenital hypothyroidism
c) Mosaic trisomy 21 syndromePartial trisomy 21 (or 21q duplication)
d) Robertsonian Translocation
e) Zellweger spectrum disorders

We could narrow down our differentials by karyotype and a normal thyroid function test. The final diagnosis was established based on Very long chain fatty acid and RBC plasmalogen/Fatty acid ratio done as our patient had a Downs phenotype.

MRI was done to look for CNS migration defects. Very long chain fatty acid and RBC plasmalogen/Fatty acid ratio were consistent with Zellwegers Spectrum disorder.

Like any other syndromes, Zellwegers spectrum disorders too have a variation in phenotypes from case to case, we enlist few features in the Table 1 based on earlier reported case reports [3-6].

The treatment modalities at present dovetail clofibrate, glycerol and the oral administration of DHA in an attempt to achieve postnatal correction of the biochemical abnormalities [4].

However, in view of the multiplicity and severity of the defects only supportive care is recommended. The supportive care would be supplementing cortisone for adrenal insufficiency, Vitamin K supplementation for Coagulopathy, use of antiepileptic drugs for seizure control, oral citrate treatment for hyperoxaluria, Supplementation of fat soluble vitamins (A,D,E), appropriate visual and hearing aids for respective impairment.

Surgical interventions like cataract removal or gastrostomy may be needed as and when warranted.
**Table 1: Clinical Features in ZSD.**

| Morphological Features | Features present in our case | Systemic involvement in our case |
|------------------------|-----------------------------|---------------------------------|
| Head and neck          |                             | Cardiac                         |
| High forehead          | +                           | Ventricular septal defects      |
| Large fontanelles*     | -                           | Aortic abnormalities            |
| Flat occiput           | +                           | Patent ductus                   |
| Redundant neck skin    | -                           | arteriosum                      |
| Dolichocephaly         | +                           | Endocrine                       |
| Metopic suture         | -                           | Impaired adrenal function        |
| Micrognathia           | -                           | Fibrotic pancreas               |
| Eyes, ears, nose, mouth| +                           | Islet cell hyperplasia          |
| Epicanthus*            | +                           | Pyloric hypertrophy/stenosis     |
| Hypertelorism          | -                           | Hepatic                         |
| Cataract/Corneal clouding | -                       | Hepatomegaly*                   |
| Brushfield spots       | -                           | Jaundice                        |
| Optic disc palor       | -                           | Cryptorchidism                  |
| Retinitis pigmentosa   | -                           | Hypospadiasis                   |
| Glaucoma               | -                           | Clitoromegaly                   |
| Abnormal retinal       | +                           | Musculoskeletal                 |
| pigmentation*          | +                           | Chondrodysplasia punctata*       |
| Shallow orbital        | -                           | Shortened proximal limbs*       |
| ridges*                | +                           | Delayed bone age                |
| ocular medulloepithelioma | -                      | Myopathy                        |
| External ear           | +                           | Encephalopathy*                 |
| deformity              | +                           | Developmental                   |
| Low/broad nasal bridge*| -                           | arrest/delay*                   |
| Anteverted nares*      | -                           | Abnormal Moro’s reflex*          |
| Micrognathia           | -                           | Severe hypotonia                |
| High arched palate     | -                           | Hyporeflexia/areflexia          |
| Limb anomalies         | -                           | Poor sucking/gavage feeding      |
| Varus deformity        | -                           | Seizures                        |
| Club feet              | +                           | Nystagmus                       |
| Club deformity         | -                           | Impaired vision*                |
| Clinodactyly           | -                           | Impaired hearing*               |
| Brachydactyly          | +/-                          | Renal                           |
| Simian crease          |                             | Hyperoxaluria                    |

*Clinical features noted in .50% of patients with ZS and when present together are clinical criteria highly suggestive of a diagnosis of a peroxisomal disorder. The diet in form of phytanic free diet plays an important role for further reducing metabolic stress. Table 2 illustrates the recommend able and avoidable food items in ZS[7,8, 9].

**Table 2: Food items recommended and avoidable in ZS.**

| No phytanic- Safely recommended foods | High Phytanic- Not recommended foods |
|--------------------------------------|--------------------------------------|
| Fruits, Cereals and vegetables       | Fish                                 |
| sunflower and safflower oils         | All milk products                    |
| poultry or pig meats                 | beef, rabbit meats, sheep and goat products |
| Breast milk (especially of fish consuming mothers for DHA) | |

Most patients succumb in infancy. Antenatal diagnosis is hence needed. There is are port on the successful application of Preim plantation genetic diagnosis (PGD) in a family affected with Zellweger syndrome (ZS) caused by a mutation in PEX26 gene. This was the first successful report of PGD for ZS, with the subsequent delivery of a homozygous normal baby after delivering 4 children with ZS and therapeutic abortion may hence not be needed in future[10].
Conclusion

We emphasize the importance of a clinical suspicion of Zellweger Spectrum Disorders based on the typical phenotype and appropriate metabolic work up for early diagnosis and timely intervention. Supportive management and dietary modification help in improving the quality of life as well as modifying the disease process.

Acknowledgement: The authors thank Dr. Ramesh Bharmal, Dean, T.N. Medical College & BYL Nair Hospital for granting permission to publish this manuscript.

Funding: Nil, Conflict of interest: None initiated, Permission from IRB: Yes

References

1. Ledesma-medina J. The Cerebro-Hepato-Renal (Zellweger’s) Syndrome: Report of Four Cases. 1978;741–5. Available from: http://dx.doi.org/10.1148/127.3.741

2. Klouwer FCC, Berendse K, Ferdinandusse S, Wanders RJA, Engelen M, Poll-The BT. Zellweger spectrum disorders: Clinical overview and management approach Inherited metabolic diseases. Orphanet J Rare Dis. 2015;10(1):1–11. Available from: http://dx.doi.org/10.1186/s13023-015-0368-9

3. Braverman NE, Raymond GV, Rizzo WB, et al. Peroxisome biogenesis disorders in the Zellweger spectrum: An overview of current diagnosis, clinical manifestations, and treatment guidelines. Mol Genet Metab. 2016 Mar;117(3):313-21.doi:10.1016/j.ymgme.2015.12.009. Epub 2015 Dec 23.

4. Patil A, M RH, Udani VP, Colaco MP, Prabhu S. Case Reports Zellweger’s Syndrome. 34. Available from: https://indianpediatrics.net/feb1997/149.pdf.

5. Galvez-Ruiz A, Galindo-Ferreiro A, Alkatan H. A clinical case of Zellweger syndrome in a patient with a previous history of ocular medulloepithelioma. Saudi J Ophthalmol. 2018;32(3):241–5. Available from: https://doi.org/10.1016/j.sjopt.2017.09.004.

6. Kale Y, Celik IH, Kulali F, Yilmaz O, Bas AY, Demirel N. A case of zellweger syndrome accompanied by hypertrophic cardiomyopathy. Med Sci Discov. 2016;3(5):242. Available from: http://dergipark.gov.tr/doi/10.17546/msd.72829.

7. Brown PJ, Mei G, Gibberd FB, Burston D, Mayne PD, McClincy JE, et al. Diet and Refsum’s disease. The determination of phytanic acid and phytol in certain foods and the application of this knowledge to the choice of suitable convenience foods for patients with Refsum’s disease. J Hum Nutr Diet. 1993;6(4):295–305. Available from: https://doi.org/10.1111/j.1365-277X.1993.tb00375.x

8. Egge H, Murawski U, Györény P, et al. Minor constituents of human milk (I) identification of cyclohexanoundecanoic acid and phytanic acid in human milk fat by a combination gas chromatograph-mass spectrometer. FEBS Lett. 1969 Feb; 2(4): 255-258.

9. Aumeistere L, Ciproviča I, Zavadska D, et al. Fish intake reflects on DHA level in breast milk among lactating women in Latvia. Int Breastfeed J. 2018 Jul 20;13:33. doi: 10.1186/s13006-018-0175-8. eCollection 2018.

10. Al-Sayed M, Al-Hassan S, Rashed M, et al. Preimplantation genetic diagnosis for Zellweger syndrome. FertilSteril. 2007 Jun;87(6):1468.e1-3. Epub 2007 Mar 6.

How to cite this article?

Khadpe T, Kondekar A, Anand V, Ghildiyal R. Zellweger Syndrome: A Down’s Syndrome Mimic. Int J Pediatr Res. 2019;6(02):76-80. doi:10.17511/ijpr.2019.i02.05