

Peters Plus Syndrome: Another Way to See a Known Syndrome

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Abstract

Peters Plus Syndrome is a rare autosomal recessive disorder, clinically characterized by abnormal formation of various structures including anterior eye chamber, genitourinary tract, skeletal system and central nervous system. PPS is due to defective B3GALT gene encoding for a glycosyl-transferase that plays a crucial role during embryogenesis. Here we report on a 12-year old boy affected by Peters Plus syndrome who showed peculiar additional features such as absence epilepsy and recurrent bacterial infections.

Keywords: Peters Plus syndrome; Absence epilepsy; B3GALT

Introduction

Peters plus syndrome (PPS) is a rare autosomal recessive disorder mainly characterized by anterior chamber eye abnormalities (Peter's anomaly) and rhizomelic limb shortening. Genitourinary tract and central nervous system (CNS) anomalies are also commonly reported. PPS is due to defective B3GALT gene encoding a glycosyltransferase which plays a crucial role in embryogenesis. Here we report a boy affected by PPS associated with peculiar additional features such as absence seizures and recurrent bacterial meningitis.

Clinical History

First son of a primigravid woman, he was born at 40 weeks. Intrauterine growth restriction was observed during pregnancy. At birth, apgar indices were 8/10^v. Weight, length and head circumference were respectively at the 10th-25th centile, below the 3rd centile and at 25th-50th centile. Physical examination showed dysmorphic features and bilateral corneal leukoma. Genetic and metabolic testing, including karyotyping, urinary organic acids and mucopolisaccharides, were normal. Abdominal ultrasound (US) was normal except for the presence of testes in inguinal canals. Brain US showed a mild enlargement of lateral ventricles with calcifications of small thalamic arteries. Brain MRI imaging revealed widening of the 4th ventricle, enlarged cisterna magna, vermian hypoplasia, enlarged and dysmorphic lateral ventricles, increased signal intensity in the periventricular white matter and small bilateral areas of abnormal hyperintense signal at the level of the corona radiata.

Ophthalmological evaluation showed large bilateral central leukoma associated with residuals of hyaloid artery, colobomatous appearance of right papilla and increased eye pressures.

In infancy, peculiar somatic traits became more evident. The child showed a round face, short upslanting palpebral fissures, thick eyebrows, small and low set ears, micrognathia, maxillary hypoplasia (Figure 1), incomplete cleft lip, scoliosis, rhizomelic shortening of the arms and brachydactyly.

Motor developmental milestones were reached timely while a mild language delay was observed.

On the basis of the physical appearance a diagnosis of Peters Plus Syndrome was formulated, subsequently confirmed by genetic analysis which detected a homozygous mutation c660+1G>A in B3GALT gene. Both parents were found to be heterozygote for that mutation.

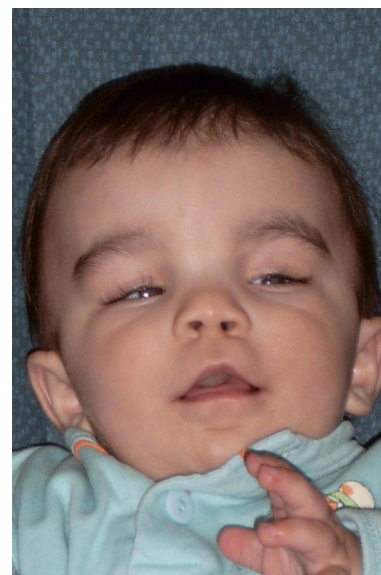


Figure 1: Facial appearance of the patient with round face, short up slanting palpebral fissures, thick eyebrows, small and low set ears, micrognathia and maxillary hypoplasia.

During childhood the patient developed three major infective episodes of CNS complicated by hearing loss with subsequent cochlear device implantation.

The first CNS infection episode occurred at the age of 4 years, when he presented pneumococcal meningitis. Immunological tests were normal. In that occasion an electroencephalogram (EEG) was performed which was proved normal. Three years later, he developed a second meningitis

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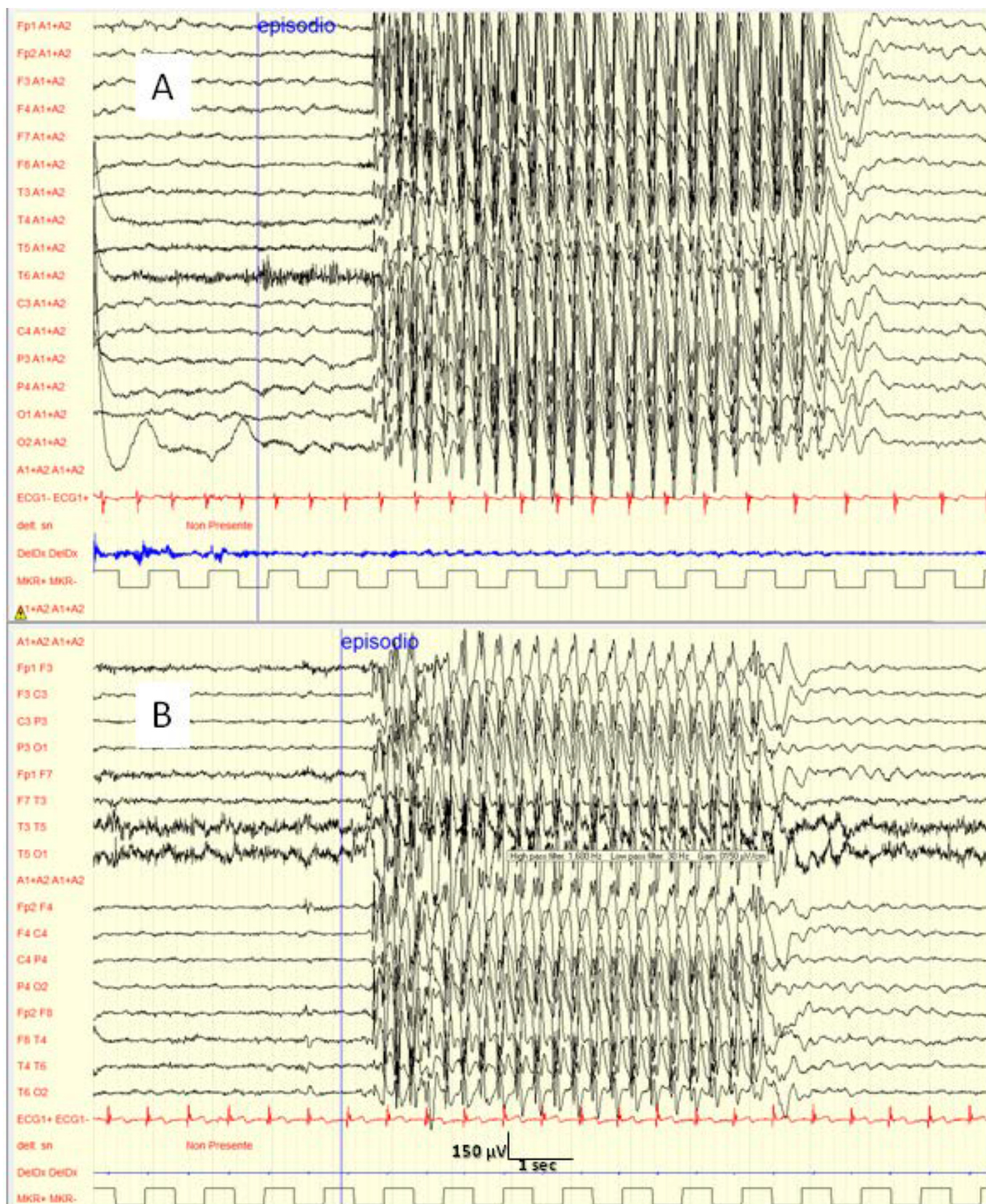


Figure 2: EEG during absence seizures. Ictal rhythm consisting with generalized spike-and-wave complexes of 3-3.5 Hz in both referential (A) and bipolar montages (B).

episode caused by non-capsulated haemophilus. Two years after this event, a new episode of meningitis occurred. The child was immediately placed under massive antibiotics therapy. Although cultural tests did not show bacterial growth, CSF was markedly turbid with increased protein concentration, very high cellularity, and reduced glucose levels.

The latest neuropsychiatric evaluation underlined a mild delay in performance subtests with better speech abilities, which could be considered within reference range.

At the age of 11 years he started to present with episodes characterized by abrupt loss of consciousness, with interruption of the ongoing activity and unresponsiveness, sometimes associated with mild clonic jerks of the eyelids, lasting 5-10 s and occurring several times per day.

A prolonged video-electroencephalogram recording was performed. Several episodes of typical absences were observed. Ictal EEG showed regular and symmetrical generalized discharges of 3-3.5 Hz spike-and-slow wave complexes which were congruent with a diagnosis of absence seizures (Figure 2). The interictal EEG demonstrated a substantially normal background with functional spikes and spike-and-slow waves in the frontal-central-temporal areas.

The patient was therefore placed under therapy with Valproate (VPA), which gave an incomplete control of absences. A combined therapy with Ethosuximide (ETS) resulted in a complete seizure control. The occurrence of side effects such as headache, gastritis and sleep disturbances led us to introduce Lamotrigine (LMT) in place of ETS. The patient is still seizure-free after two years of follow-up.

Discussion and Conclusion

PPS is a rare disease characterized by the association of Peters anomalies, represented by the triad of central corneal opacity, defects in the posterior layers of the cornea and lenticulo-corneal and/or irido-corneal adhesions, with systemic features such as short stature, short broad hands with fifth finger clinodactyly, distinctive facial features, cleft lip and/or cleft palate, hearing loss, abnormal ears, heart defects, genitourinary anomalies, mental retardation and CNS abnormalities [1-3].

PPS is a congenital disorder of glycosylation caused by a defect in a 1,3-glucosyltransferase whose function is to complete the synthesis of a rare O-linked Glc-Fuc disaccharide on thrombospondin type 1 repeats (TSRs) domains found in extracellular signaling proteins. TSRs plays a key role in development, including angiogenesis and neurogenesis [4].

The patient we report showed the classical clinical phenotype of PPS. Diagnosis was confirmed by molecular analysis which detected the most common mutation found in that disorder. However, he presented with additional findings such as absence seizures and recurrent bacterial meningitis.

Epilepsy has not been commonly reported in PPS. Hannekam et al. [5] described a patient with PPS presenting with febrile seizures. No further information is available on that issue. The International League against Epilepsy (ILAE) Commission of 1981 described typical absence seizure as "of sudden onset, interruption of ongoing activities, staring, possible upwards version of eyes with few seconds duration, associated to symmetrical 2-4 Hz, mainly 3 Hz, spike-and-wave complexes, and normal background activity" [6].

Clinical and electrographic findings observed in our patient were congruent with a diagnosis of typical absence seizures. The prompt

clinical response to ETS and to the combined polytherapy VPA/LMT further corroborates that hypothesis. Such a diagnosis may be hampered by the presence of a "neurological disorder" which makes absence seizures not "primary" in our patient. Of course, an association by chance between PPS and absence seizures may be an explanation. However, TSRs which is defective in PPS, plays a key role in the regulation of neuronal plasticity, neuronal metabolism, and in the formation of new neuronal networks with consequent abnormal neuronal signaling and increased excitability [7]. Therefore, the hypothesis that epilepsy may be part of the clinical picture of PPS, cannot be ruled out *a priori*.

The patient also showed major episodes of CNS infections in the context of a recurrent bacterial meningitis condition, defined as two or more episodes of pyogenic meningitis separated by a period of convalescence and the complete resolution of all signs, symptoms and laboratory findings [8] were proved normal and no other symptoms/signs of immunodeficiency were present. Among the several etiologies, structural deficiencies at the base of skull, congenital or acquired, were also considered. However, CT scan and several brain MRI resulted normal. Of course, that investigation might not be sufficient while finding the cause of recurrent bacterial meningitis in an immunocompetent host. Alternatively, functional alterations of properdin observed in patients carrying B3GALT mutations [9], may have caused a latent immunodepression in our patient. Unfortunately, no investigations were made in that direction to validate that hypothesis.

Brain MRI imaging studies, performed both in the neonatal period before the occurrence of meningitis episodes and later in life, showed a supratentorial multifocal encephalopathy combined with a Dandy-Walker-like abnormality. Our observation further supports the association between PPS and Dandy-Walker-like anomaly, which was previously reported in only one PPS patient [10].

In conclusion we report on a patient affected by PPS in whom peculiar additional findings such as absence seizures and recurrent bacterial meningitis were described. Further studies on PPS patients are necessary to validate our observations and to extend the syndrome clinical phenotype.

References

1. Lesnik Oberstein SA, Kriek M, White SJ, Kalf ME, Szuhai K, et al. (2006) Peters Plus syndrome is caused by mutations in B3GALT1, a putative glucosyltransferase. *Am J Hum Genet* 79: 562-566.
2. Sato T, Sato M, Kiyohara K, Sogabe M, Shikanai T, et al. (2006) Molecular cloning and characterization of a novel human beta1,3-glucosyltransferase, which is localized at the endoplasmic reticulum and glucosylates O-linked fucosylglycan on thrombospondin type 1 repeat domain. *Glycobiology* 16: 1194-1206.
3. Lesnik Oberstein SAJ, van Belzen M, Hennekam R (2007) Peters Plus Syndrome. *Gene Reviews*, Seattle (WA), University of Washington, Seattle.
4. Heinonen TY, Maki M (2009) Peters'-plus syndrome is a congenital disorder of glycosylation caused by a defect in the beta1, 3-glucosyltransferase that modifies thrombospondin type 1 repeats. *Ann Med* 41: 2-10.
5. Hennekam RC, Van Schooneveld MJ, Ardinger HH, Van Den Boogaard MJ, Friedburg D, et al. (1993) The Peters'-Plus syndrome: Description of 16 patients and review of the literature. *Clin Dysmorphol* 2: 283-300.
6. Commission on Classification and Terminology of the International League against Epilepsy (1981) Proposal for revised clinical and electroencephalographic classification of epileptic seizures. *Epilepsia* 22: 489-501.
7. Risher WC, Eroglu C (2012) Thrombospondins as key regulators of synaptogenesis in the central nervous system. *Matrix Biol* 31: 170-177.
8. Ghosh A, Sharma S, Halder PP, Bhattacharya A, Mukherjee S (2017) Diagnostic dilemma in a 15 year old boy with recurrent pneumococcal meningitis. *J Clin Diagn Res* 11: SD03-SD04.

9. Hess D, Keusch JJ, Oberstein SA, Hennekam RC, Hofsteenge J (2008) Peters Plus syndrome is a new congenital disorder of glycosylation and involves defective Omicron-glycosylation of thrombospondin type 1 repeats. J Biol Chem 283: 7354-7360.
10. Schoner K, Kohlhase J, Müller AM, Schramm T, Plassmann M, et al. (2013) Hydrocephalus, agenesis of the corpus callosum and cleft lip/palate represent frequent associations in fetuses with Peters' plus syndrome and B3GALT1 mutations. Fetal PPS phenotypes, expanded by Dandy Walker cyst and encephalocele. Prenat Diagn 33: 75-80.