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Case Report

A Report on Children with CEP290 Mutation, Vision Loss, and Developmental Delay

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Abstract

Mutations in CEP290, which encodes a centrosomal protein, cause Joubert syndrome, retinal dystrophy, and several other manifestations. Retinal dystrophy related to CEP290 mutation (Leber's congenital amaurosis type 10) presents with a severe visual impairment from birth, wandering eye movements, and oculodigital reflex. Fundus examination may initially be normal, but varying degrees of retinal pigmentation can be detected over time. This report presents 4 children who were referred to the ophthalmology clinic with a lack of eye contact and the suspicion of low vision. The ophthalmological examination revealed very poor visual function, the vision slightly improved over time, and enophthalmos became evident. There was neuromotor retardation in their history and mutations in the CEP290 gene were revealed in the whole-exome analysis. Both pediatricians and ophthalmologists should be aware of the coincidence between severe vision loss and neuromotor retardation and should refer patients for genetic testing if they suspect it. Genetic diagnosis will enable patients to be followed both neurologically and ophthalmologically and to benefit from rehabilitation opportunities that will contribute to visual and neurological development. It will also allow the family to receive genetic counseling on disease progression and heredity, and to follow ongoing gene therapy studies for mutations in the relevant gene.

Keywords: CEP290 mutation, Joubert syndrome, Leber's congenital amaurosis, low vision

Introduction

Leber's congenital amaurosis (LCA) is hereditary retinal dystrophy that presents with severe visual impairment since birth. It is manifested by the poor pupillary response, roving eye movements, and oculodigital reflex in the early period. Fundus examination can be normal at presentation, then variable fundus findings from salt and pepper changes to the typical appearance of retinitis pigmentosa may develop over time. The annual estimated incidence of the disease is 1 in 30,000 newborns (1). To date, 23 autosomal recessive and 3 autosomal dominant genes associated with LCA have been identified, accounting for 70–80% of all LCA cases (2). Mutation in centrosomal protein (CEP) is one of the most common causes, accounting for 15–20% of all known cases and responsible for causing LCA type 10 (3). The intronic variant c.2991þ1655A>G was reported as the most common pathogenic mutation, especially in Europe and the United States (1).

Joubert syndrome (JS) is a disorder characterized by some clinical findings, including cerebellar ataxia, hypotonia, oculomotor apraxia, and intellectual disability. The specific radiological finding of the disease is the "molar tooth sign" which includes cerebellar vermis hypoplasia or dysplasia, thick and horizontally oriented superior cerebellar peduncles, and an abnormally deep interpeduncular fossa (4). The

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incidence of the disease is estimated to be between 1/80,000 and 1/100,000 live births (5). There are some JS-related disorders, such as occipital encephalocele, polymicrogyria, polydactyly, ocular coloboma, retinal dystrophy, cystic kidney disease, nephronophthisis, and congenital hepatic fibrosis (6). JS has been associated with 135 different genetic mutations, (7) predominantly inherited in an autosomal recessive manner. CEP290 mutation accounts for 7–10% of all known cases and is responsible for causing JS 5 (8-11).

Recently, it has become easier to diagnose the disease with emerging technologies such as whole-exome sequencing. Genetic diagnosis is important in terms of understanding the prognosis of the disease and providing future genetic counseling, as well as following the ongoing gene therapy studies for certain mutations. The purpose of this report is to emphasize the coexistence of LCA and JS in infants with vision loss and developmental delay. Informed consent was taken from all the parents/legal guardians.

Case Report

Case 1 – A 6-month-old girl with a history of abnormal eye movements and inability to make eye contact or follow light and objects from birth was brought to our clinic by her parents. The patient was born full-term to non-consanguineous parents with a birth weight of 2750 g. She had no history of pre-natal or post-natal problems. There was no family history of similar ocular or neurological disorders. There was no history of seizures, and the sleep electroencephalogram (EEG) was identified to be normal. The cranial, orbital, and diffusion magnetic resonance imaging (MRI) had been reported as normal when she was 4 months old. There was no pathology in her metabolic disease investigations. In visual evoked potentials (VEP), P100 wave latencies were prolonged in both eyes (164 ms in the right eye, 162 ms in the left eye). She had head control and was able to sit with support at the hips. She had a response to light but no response to threats or objects on the first ophthalmic examination. The examination also revealed +9.00 D cycloplegic refraction and normal anterior segment findings in both eyes. Fundoscopic examination showed optic disc pallor and slight peripheral pigmentary changes. She was sent to a special education and rehabilitation center for visual rehabilitation. At her 12-month examination, she could follow light horizontally. She was found to have enophthalmos secondary to oculodigital reflex. At age 2, she had a 3 s light fixation and horizontal and vertical light following. Horizontal and vertical object following from a distance of 20 cm was achieved at the 30-month-old exam. Neurological examination revealed motor developmental delay with a history of sitting unsupported at 18 months and walking at 30 months. Cranial nerves were intact, muscle tone and strength were full, and reflexes were normoactive in the neurological assessment. Visual functions remained the same at 36 and 42-month-old examinations and visual acuity could not be measured with the preferential-looking test. The cranial MRI at the age of 3 was also found to be normal. She could reach for objects and follow one-word instructions. Broad-based gait and echolalia were remarkable. Binocular visual acuity was 20/256 with Cardiff cards at the 4-year-old examination. Refractive errors were +6.0 D in both of her eyes. Her visual acuity was measured 20/200 on the Lea chart by matching symbols on the key card at the last visit at the age of 5. The genetic test showed that she had a heterozygous variant of the CEP290 gene, namely c.5344 C>T (p.Arg1782) by new generation DNA sequencing.

Case 2 – A 7-month-old girl with a suspect of brain malformation in the gestational period and diagnosis of JS on MRI at 1-month-old was referred to our clinic with complaints of lack of eye contact and crossing eyes. She was born at term to non-consanguineous parents. At birth, she presented with dyspnea, cyanosis, and signs of respiratory distress. She was admitted to the neonatal intensive care unit and continuous positive airway pressure was administered. There was no history of similar neurological and ocular pathology in the family. She had polydactyly and a renal cyst was detected by ultrasound during the scanning. Sleep EEG response was normal. Motor examination revealed hypotonia with normal tendon reflexes. On the first eye examination, there was only a light response. The cycloplegic retinoscopy revealed +9.00 D in both eyes. Thirty-five prism diopters alternating exotropia and 20 prism diopters hypotropia on the right eye were measured by the Krimsky test. At her 1-year-examination there was still no light fixation and following. The presence of inferior vermis agenesis, partial dysgenesis of the corpus callosum, and the molar tooth sign was confirmed on MRI. When she was 18-month-old, 7 s light fixation and horizontal and vertical light following were reported. Her strabismus persisted at the same angle, and she had mild enophthalmos secondary to oculodigital reflex (Fig. 1). Nystagmus and head shaking were observed. Fundoscopic examination showed optic disc pallor and pigmentary changes in the retina. At the 24-month-old examination, she could follow light and objects horizontally and vertically from a distance of 20 cm. The whole-exome sequencing test report showed that she carried a compound heterozygous variants of the CEP290 gene, namely c.5932 C>T (p.Arg1978Ter) and c.1075 G>T (p.Glu359Ter), the second of which was not reported previously.

Case 3 – A 17-month-old girl who presented with abnormal eye movements and developmental delay was referred to us with suspicion of LCA. She was born to a non-consan-

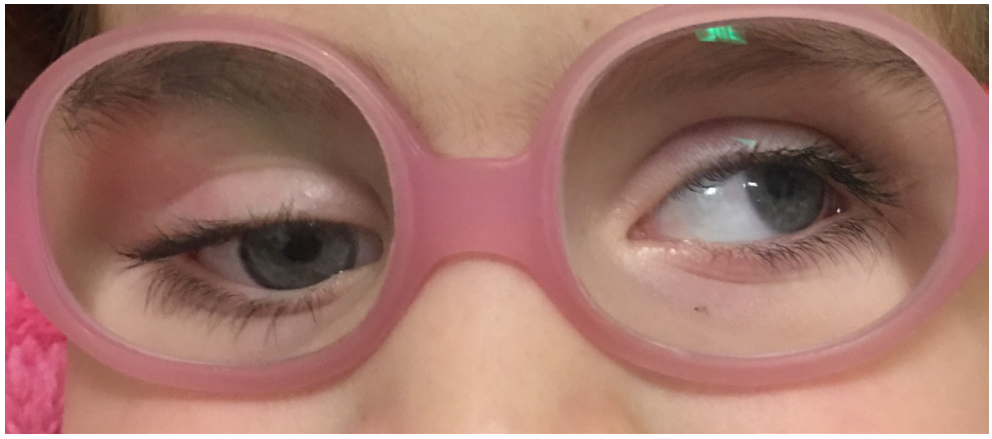

Figure 1. Photograph of the patient with strabismus and enophthalmos.

guineous marriage and a normal full-term pregnancy. There was no history of similar visual or neurological problems in the family. She had a history of hypotonia at birth and head control in the 8th month. She had nystagmus that started shortly after birth and gradually decreased and turned into roving eye movements in time. MRI revealed an elongated bilateral superior cerebellar peduncle giving the "molar tooth" sign (Fig. 2). On eye examination, there was only a response to light but no response to threat or object. The examination revealed the absence of fixation, normal anterior segment appearance, +8.00 D cycloplegic refraction, and punctuated pigmentation in the peripheral retina on fundoscopy. Visual functions remained with the only light response at the follow-up visit 6 months later. She had a global developmental delay in all milestones with an intellectual disability. She walked at 2 years of age with an atactic gait and had no words at that age. The girl was found to harbor compound heterozygous variants of the CEP290 gene, namely c.1225delA on the 14th exon, and c.2218-2A>T on the 22nd exon by the Sanger DNA sequencing method. Both variants were predicted to be pathogenic.

Case 4 – A 14-month-old girl with a history of abnormal eye movements and inability to make eye contact since she was 4 months was referred to our clinic. The patient was born full-term via cesarean section. She presented with hyperpnea-apnea episodes and hypotonia. The family history revealed 3rd consanguinity between the parents. There was no history of similar ocular or neurological disorders in the family. There was no history of seizures and the sleep EEG was identified to be normal. The cranial MRI revealed the diagnosis of JS when she was 5 months old (Fig. 3). The cysts in her kidneys and liver were established afterward in the investigations. VEP showed no response in both eyes. She had head control, and she was able to sit with support at the hips when she was at 12 months. On eye examination,

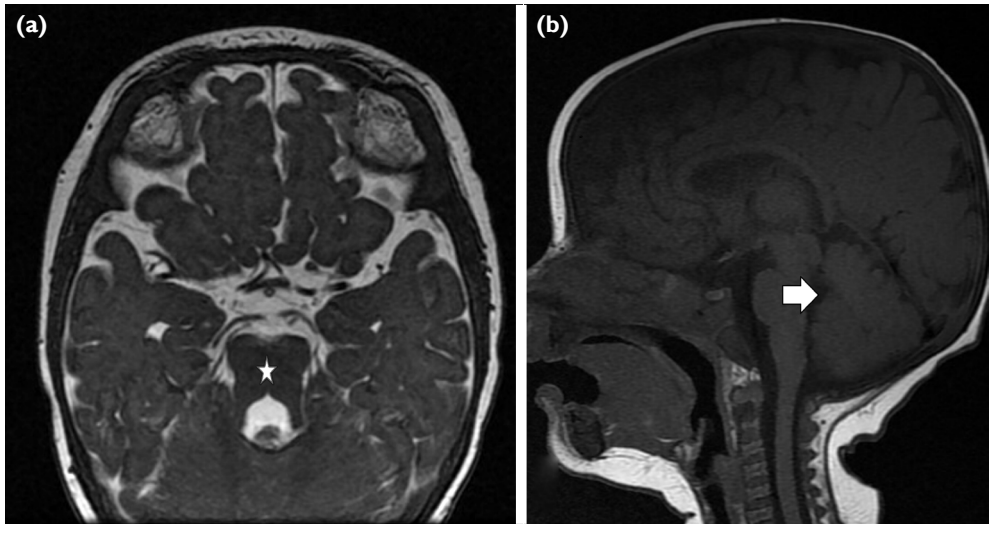

Figure 2. Magnetic resonance imaging of the axial T2-weighted image showing molar tooth appearance of the mid-brain (white star) **(a)**, and the sagittal T1-weighted image showing vermis hypoplasia of the case 3 **(b).**

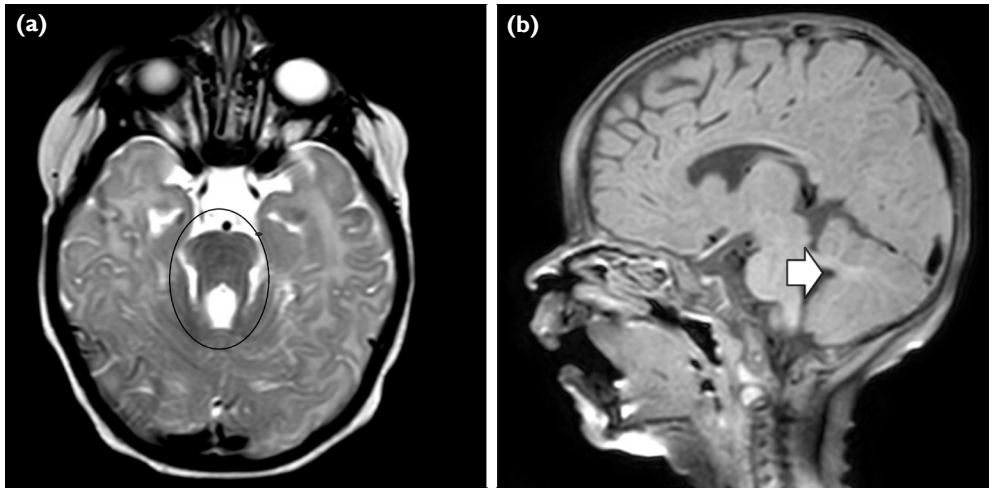

Figure 3. Magnetic resonance imaging of the axial T2-weighted image showing molar tooth appearance (encircled) **(a)**, and the sagittal T1-weighted image showing vermis hypoplasia of case 4 (white arrow) **(b)**.

the light response was suspicious and there was no response to threat or object. The examination revealed the absence of fixation and follow, and normal anterior segment appearance. Refractive errors were found +8.50 D by cycloplegic retinoscopy at both eyes. Fundoscopic examination showed diffuse pigmentation in the retina (Fig. 4). Visual functions were found similar at the follow-up visit 6 months later. On neurological examination, she had generalized hypotonia and normal deep tendon reflexes. The clinical exome sequencing test report showed that she carried a homozygous variant of the CEP290 gene, namely c.4148_4149dup:p.R1384Nfs*36 on 32nd exon.

Discussion

These case reports provide clinical and genetic findings of children with LCA and JS related to CEP290 mutation. These findings may help understand the disease phenotypes better and estimate the prognosis. With this report, our goal is to help pediatricians identify LCA-related neuromotor retardation and visual impairment cases easily; and help ophthalmologists consider JS when they examine patients with LCA findings and additional delayed milestones and keep the CEP290 mutation in mind.

CEP290 mutations produce a phenotype of LCA, which results in blindness in the 1st year of life. The severity and prognosis vary over a wide spectrum. No clear genotype-phenotype correlation was shown (12). There are studies that reported the patient homozygous for the most common intronic mutation had either better or worse final visual outcomes (13-15). Perrault et al. (16) reported 47 subjects with CEP290 mutations and discovered that all patients displayed severe cone-rod dystrophy with profound and early reduction in vision, high hyperopia, and macular degeneration in the first decade of life. Having 2 non-sense CEP290 mutations was found to be associated with worse final VA and the presence of non-ocular features in a retrospective study with 40 patients with CEP290 mutation (17). CEP290 variants have been described in a few atypical LCA cases with early-onset severe retinal degeneration but without nystagmus and oculodigital signs (18). A patient who had a relatively mild phenotype with a better-preserved visual acuity and minimal measurable scotopic response to the ERG

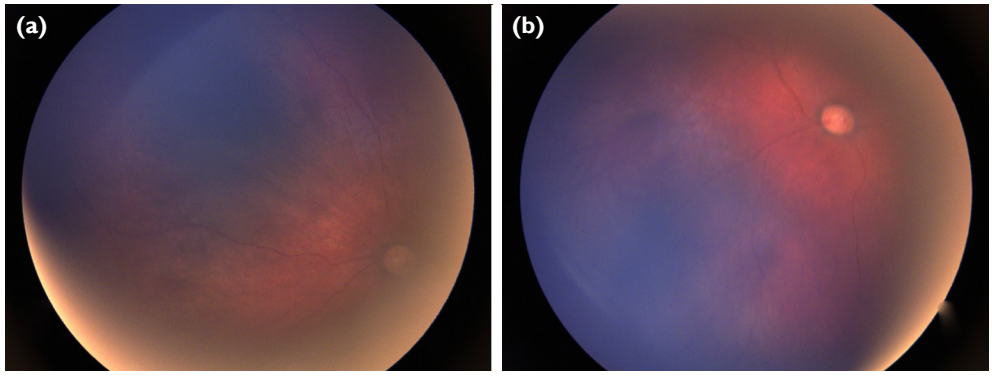

Figure 4. (a, b) Color fundus photographs of the right and left eye show pigmentary changes of the retina.

has also been reported (19). A retrospective analysis of 40 patients with mutations in CEP290 showed that all the cases had undetectable photopic ERGs consistent with severe maculopathy despite relative preservation of foveal architecture on OCT (17). It has been suggested that the underlying pathology of severe vision loss despite anatomically spared central cones may be a putative intersegmental trafficking defect and impaired phototransduction efficiency (20). CEP290 encodes a protein that localizes to the transition zone of the connecting cilium of photoreceptors. When the microtubule-binding domain of the protein disrupts, significant deficits in cilium formation occur. This pathology leads to retinal degeneration (21).

The diagnostic criteria for classical JS were defined as molar tooth sign on cranial MRI, hypotonia in infancy, developmental/intellectual delay, and one or both criteria of irregular breathing in infancy and abnormal eye movements (22). The interpretation of the typical image on MRI can be subjective, and if this finding is not evaluated correctly, the diagnosis may be missed. JS is also categorized among the ciliopathies because its responsible genes produce proteins that are important in the function of primary cilia. Twenty-eight identified genes, including CEP290, are known to play a role in the pathogenesis of JS. CEP290 mutations account for approximately 50% of patients with oculorenal JS who suffer from both retinal dystrophy and renal defects (23). Further, these data provide insight into the mechanism of both LCA and the other CEP290-related ciliopathies, including JS, and suggest innovative strategies for therapeutic intervention.

Currently, the most extensive work on genome surgery in the retina has focused on mutations in the CEP290 gene. Because of its large size, CEP290 is beyond the packaging capability of AAV vectors that are used in gene therapies (24). Novel approaches using a functional truncated version called miniCEP290, proved effective at significantly improving photoreceptor survival after subretinal injection in a mouse model of human LCA10 (25). Today, CRISPR-Cas systems are used to regulate the CEP290 mutation precisely. In this method, the de novo splice donor site can be removed using SpCas9 and a pair of gRNAs flanking the new splice site. After non-homologous splice repair of the cleavage site, this encrypted splice donor can be deleted, and normal mRNA processing is restored (26).

All the 3 cases we reported here were referred for severe vision loss. All the patients were sporadic cases, and all had severe vision loss and motor retardation from birth. Although ERG could not be performed for the differential diagnosis of the cause of vision loss in the patients because of their young age, their clinical findings were typical for LCA. Insufficient fixation capacity due to severe visual impairment and poor cooperation due to their young age, and additional neurological findings prevented multimodal retinal imaging. The digital fundus image could be taken in the supine position with the RetCam Digital Retinal Camera (Massie Research Laboratories Inc., Pleasanton, CA). Only one of the cases had additional polydactyly and renal pathology. The visual functions of these children, whose vision was very poor at initial examinations, increased a little with the visual stimulation program.

Developmental retardation seen in patients with the typical LCA phenotype and also being followed up by pediatric clinics due to mental and motor retardation is thought to be related to vision loss and may even be confused with autism spectrum disorders. Although developmental retardation due to visual stimulus deficiency is expected in LCA, the history of hypotonia in the newborn period of the baby or the presence of delay in developmental milestones such as head control and sitting without support should make the ophthalmologist and pediatrist suspect about a neurological pathology.

Similarly, low vision findings in children with motor developmental delay may be confused with cerebral visual impairment by ophthalmologists. LCA may be missed because the fundus examination may be normal in the early period. In clinical practice, LCA is a typical disease characterized by severe vision loss from birth, oculodigital reflex, and subsequent enophthalmos. Although walking may start later than peers due to low vision, no delay is expected in other gross motor developmental milestones. It is critical to take a detailed history of children who apply to an ophthalmologist due to low vision and refer them to the pediatric neurology clinic in case of doubt.

On cranial MRI, molar tooth signs can be seen in most patients, and this sign can be regarded as relatively subjective. The most accurate diagnosis can be made by genetic analysis. Genetic diagnosis will allow patients to be followed up in ophthalmology as well as neurology clinics and benefit from rehabilitation opportunities that will contribute to visual and neurological development. In addition, it will help the family receive genetic counseling about the progression and the inheritance of the disease, and closely monitor the ongoing gene therapy studies for the mutations in the relevant gene.

Although there are many case reports about JS and LCA in the literature, detailed information about the clinical findings of the patients is not given in case of the coexistence of these two diseases. The aim of this report, which includes 4 patients, is to remind physicians of the association of LCA in patients with JS, a syndrome they are very familiar with, and suspected of having low vision.

Conclusion

These case reports provide clinical and genetic findings of children with LCA and JS related to CEP290 mutation. These findings may help understand the disease phenotypes better and estimate the prognosis. With this report, our goal is to help pediatricians identify LCA-related neuromotor retardation and visual impairment cases easily; and help ophthalmologists consider JS when they examine patients with LCA findings and additional delayed milestones and keep the CEP290 mutation in mind.

Disclosures

Informed consent: Written informed consent was obtained from the patient for the publication of the case report and the accompanying images.

Peer-review: Externally peer-reviewed.

Conflict of Interest: None declared.

Authorship Contributions: Concept – E.S.; Design – E.S., P.B.K.; Supervision – A.I.; Materials – E.S., P.B.K.; Data collection and/or processing – E.S.; Analysis and/or interpretation – E.S., P.B.K.; Literature search – E.S.; Writing – E.S.; Critical review – A.I.

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