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Case Report

# Leber congenital amaurosis associated with Chiari I malformation: Two cases and a review of the literature

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## Abstract

**Objective:** Leber congenital amaurosis (LCA) is a rare, clinically and genetically heterogeneous disorder characterized by severe loss of vision in the first year of life, affecting approximately 3000 people in the United States. Some LCA patients manifest developmental abnormalities of the central nervous system (CNS) and neuroradiological studies have revealed a variety of cerebral anomalies in association with LCA; however, Chiari I malformations (CMI) have never been described.

**Case Description:** We report two sisters who were referred to the pediatric neurosurgery clinic for evaluation of CMI. The elder sister presented with convergence nystagmus from 3 months of age and magnetic resonance imaging (MRI) demonstrated evidence of significant CMI. Her younger sister began developing nystagmus at 4 months of age. Both had symptomatic progression and underwent suboccipital decompression. Both were subsequently diagnosed with LCA. Case specifics and imaging findings are presented.

**Conclusions:** CMI have been found in association with several genetic syndromes, but not with LCA. These patients represent the first reported cases of CMI with LCA and suggest an additional potential CNS anomaly. The unique occurrence in siblings and the association with another inherited disorder are suggestive of a genetic basis for CMI.

**Key Words:** Chiari I malformation, children, genetics, Leber congenital amaurosis

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## INTRODUCTION

Leber congenital amaurosis (LCA) is a rare, clinically and genetically heterogeneous, autosomal recessive disorder that affects approximately 3000 people in the United States.[6] First described by Theodor Leber in 1869, patients with LCA usually present before 6 months of age with severe visual impairment, roving eye movements or nystagmus, extinguished or severely reduced scotopic and photopic electroretinogram (ERG), and a near-normal fundus examination.[1,10] LCA is often associated with ocular or systemic abnormalities, and upward of 78% of patients can manifest developmental abnormalities of the central nervous system (CNS).[10]

Chiari I malformation (CMI) is a condition in which part

of the skull is abnormally small or misshapen, resulting in a downward displacement of the cerebellar tonsils through the foramen magnum. Based on analysis of familial aggregation, an underlying genetic basis for CMI has been suggested.[9] CMI has been associated with several genetic syndromes; and while neuroradiological studies have revealed a variety of cerebral anomalies in association with LCA, CMI has never been described. We report two sisters with nystagmus and evidence of CMI on magnetic resonance imaging (MRI), who were subsequently diagnosed with LCA.

## CASE REPORTS

### Case 1

The elder sister initially presented with convergence nystagmus at age 3 months. By 5 months of age, her nystagmus was worsening and an MRI of her head demonstrated CMI. She was referred to the University of Rochester Pediatric Neurosurgery clinic at 1 year of age. The patient still had a prominent nystagmus and had now developed photophobia. She was also was noted to be gagging frequently (four to five times) with every meal. On examination, she was active and playful. She was able to pull to standing and had good motor strength. Her toes were downgoing bilaterally. She appeared to track well in all visual fields, although was noted to be squinting with the lights in the room. A repeat MRI of her head [Figure 1a and b] demonstrated peg-like, cerebellar tonsils displaced 8 mm from the foramen magnum, without evidence of a syrinx.

Due to her worsening symptoms, she underwent a suboccipital decompression. Briefly, the patient was positioned prone on the pediatric horseshoe. A linear skin incision was marked out commensurate with the spinous process of C2 through the inion. A standard sub-periosteal dissection was performed. Using an air drill, a cutting bur, and a diamond bur, the lamina of C1 was thinned out, as was the suboccipital bone adjacent to the foramen magnum. Utilizing a curette as well as small Kerrison and Fulton rongeurs, the C1 arch was removed laterally to the level of the lateral masses. In addition, the suboccipital bone was removed approximately 1.5 cm back from the posterior lip of the foramen magnum and bone removal was carried out to the lateral aspect of the foramen magnum as well. Dense scar tissue was taken off the dura, and while the dura was noted to expand somewhat, it was felt that the dura needed to be opened. The dura was opened in a Y-shape fashion and the arachnoid layer was preserved. A small piece of Gelfoam was placed over the dural defect and arachnoid layer, with no dural patch used. The wound was then closed in layers and the patient tolerated the procedure well. Her symptoms initially improved, but then returned to a lesser degree. Postoperative MRI imaging revealed adequate decompression [Figure 1c and d]. Of note, she also developed symptomatic hydrocephalus and subsequently had a ventriculo-peritoneal shunt placed successfully.

The patient went on to develop some neurobehavioral symptoms not typical for CMI, such as head banging. She was sent for ophthalmologic examination for her nystagmus, photophobia, and difficulty with learning colors. Dilated retinal examination revealed a normal appearing fundus [Figure 2]. ERG, performed under sedation, was non-recordable under both photopic and scotopic conditions. These findings were diagnostic of LCA. Now 4 years old, her visual acuity is at the level of legal blindness.

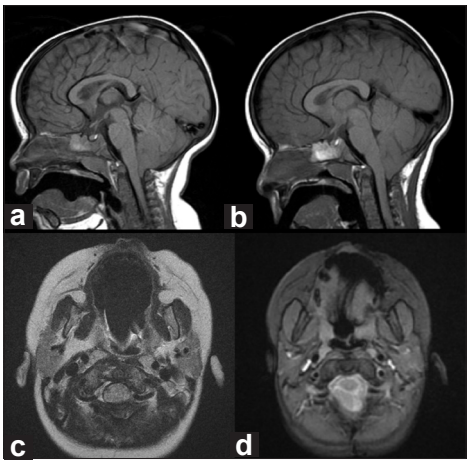


**Figure 1: (a–d) Case 1: Pre- and postoperative MRI images. Preoperative (a) sagittal T1-weighted and (b) axial T2-weighted MRI images demonstrating downward displacement of the cerebellar tonsils by approximately 8 mm, consistent with Chiari Type I malformation. Postoperative (c) sagittal T1-weighted and (d) axial T2-weighted images demonstrating adequate decompression**

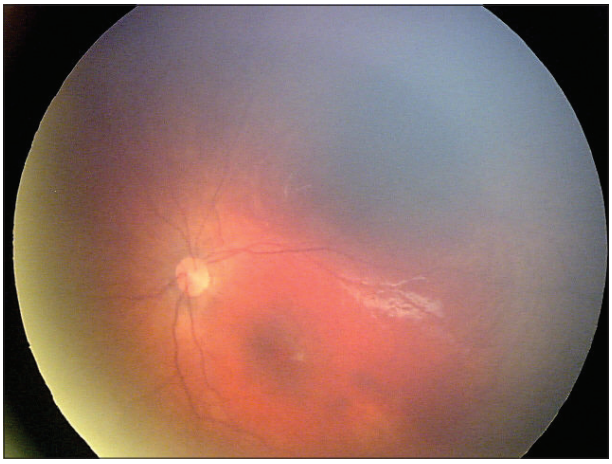

**Figure 2: Dilated fundoscopic examination. Fundus photograph of the left eye, obtained under anesthesia using a retinal camera, shows a healthy appearing optic nerve, macula, and retinal vasculature. Subtle loss of pigmentation was present in the retinal periphery**

### Case 2

The younger sister presented with nystagmus at 4 months of age. Examination revealed swirling, searching nystagmus. She did not exhibit gagging, fussiness, or head banging, but her parents reported poor visual behavior at home. She was seen in consultation with ophthalmology and was determined to have LCA. She was sent for an MRI of her head given her sister's prior medical history and progression. The MRI of her head (not shown) demonstrated evidence of cerebellar ectopia of the tonsils descending down to the level of C1 (approximately 9 mm), although she appeared to have more space at the foramen magnum relative to her sister at 1 year of age. Given her sister's experience and the patient's relatively benign presentation, we elected to clinically observe the patient rather than surgically decompress the CMI.

By 9 months of age, however, she began to experience gagging with meals and the patient was evaluated by a pediatric neurosurgeon at another institution closer to their home. An MRI of her head was repeated and demonstrated further cerebellar displacement, now measuring approximately 14 mm. She underwent surgical decompression for her CMI and has done well postoperatively thus far regarding those symptoms; however, her vision has continued to deteriorate.

## DISCUSSION

LCA is the earliest and most severe form of all inherited retinal dystrophies, responsible for 10–18% of cases of congenital blindness.[2] Its incidence is about 1 per 80,000–100,000 births, with only approximately 3000 people affected in the United States.[6] While no universally agreed-upon standard diagnostic criteria exist, the following features are highly suggestive: blindness/severe visual impairment, extinguished or severely reduced ERG testing, an oculo-digital sign (poking, rubbing, pressing of the eyes), and family history.[1] Other patients can frequently also exhibit sluggish pupillary reactions, nystagmus (which can be pendular or roving), or photophobia. Infants typically present with a normal fundoscopic exam and only occasionally with subtle retinal pigment granularity.[3,7,8]

At least 14 genes have been associated with LCA, with mutations in the most common 9 genes accounting for approximately 70% of cases, and with 30% of cases whose causative genes are as yet undiscovered.[6] Association between neurological and neurodevelopmental (mental retardation) features and LCA has been well documented. CNS abnormalities are also common in patients with LCA, and several neuroradiological studies have revealed a series of cerebral anomalies in association with LCA such as microgyria, polygyria, porencephaly, and ventricular dilatation; the only consistent finding has been hypoplasia of the cerebellar vermis, seen in 10% of infants with LCA.[2,8] LCA has been observed in association with Joubert syndrome as well; however, the relationship is unclear.[10] The variable presentation of the disease and its associated anomalies may be a manifestation of the lack of understanding regarding the specific underlying genetics and disease process.

CMI is a congenital abnormality of the brain, resulting in the displacement of the cerebellar tonsils through the foramen magnum. The condition can cause obstruction of CSF flow (resulting in a non-communicating hydrocephalus), as well as headaches, fatigue, nystagmus, difficulty swallowing, dizziness, nausea, impaired coordination, and in severe cases, paralysis. Visual symptoms have been described in CMI as well.[4] CMI has been described in association with many different genetic disorders of established inheritance patterns, including Klippel–Feil syndrome, Carpenter syndrome, and Hadju–Cheney syndrome, but has never before been described with LCA. Syndromic CMI only accounts for <1% of CMI prevalence, with most occurring as isolated phenomena.[5] There have been several investigations into the etiology of CMI. Several studies have pointed toward a genetic basis of CMI, referring to familial aggregation patterns exhibited by the affected families.[9] Although no extensive twin cohort studies have been published, there have been reported cases of monozygotic triplets concordant for tonsillar ectopia and CMI, as well as female monozygotic twins with an affected mother, and each with an affected daughter as well.[5] Pedigree analysis of various family clusters has suggested Mendelian inheritance patterns (autosomal dominant, X-linked, or recessive inheritance), and these data are further supported by co-segregation studies of CMI with known genetic disorders and relative risk analyses of relatives of CMI affected individuals in comparison to the general population.[5,9]

We have reported here two sisters who presented to our clinic with symptoms concerning for symptomatic CMI but not dissimilar from those observed in some patients with LCA. Both patients were finally diagnosed with LCA as their vision deteriorated and formal ophthalmologic examinations were pursued. While CNS abnormalities are known to be associated with LCA, these patients represent the first reported cases of CMI in LCA and suggest an additional potential CNS anomaly. The association further suggests a genetic etiology of CMI. While a sporadic occurrence of CMI in these two sisters is possible, the previously reported familial aggregation pattern of CMI and its unique occurrence in these siblings with a known rare inherited disorder further supports the notion of a genetic basis for some forms of CMI. This observation is clearly limited by the number of patients in this report. However, the findings are intriguing nonetheless and the potential overlap that may exist between these two conditions necessitates further investigation.

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