



Pseudopapilledema in Cockayne syndrome

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ARTICLE INFO

Keywords:

Cockayne syndrome
Pseudopapilledema
Enophthalmos

ABSTRACT

Purpose: This report describes pseudopapilledema in two siblings with Cockayne syndrome and examines a structural mechanism for its development.

Observations: Two siblings with genetically documented Cockayne syndrome, enophthalmos, and hyperopia were found to have pseudopapilledema. Magnetic resonance (MR) imaging disclosed retrodisplacement of the globes, axial foreshortening, posterior scleral flattening, and protrusion of the optic papilla into the vitreous.

Conclusions and importance: In the setting of Cockayne syndrome, pseudopapilledema may arise from retrodisplacement of the globes causing indentation of the posterior sclera by the distal optic nerves. This anatomic aberration may contribute to the development of hyperopia as well.

1. Introduction

Cockayne syndrome is a rare autosomal recessive neurodegenerative disorder that is associated with multiple systemic derangements.^{1–3} Ophthalmologic findings include severe enophthalmos, high hyperopia, cataracts, photophobia, corneal epithelial degeneration, poor pupillary dilation, and a progressive retinal dystrophy.^{4,5} The progressive enophthalmos is classically attributed to loss of orbital fat.⁶ We present two siblings with genetically confirmed Cockayne syndrome in whom pseudopapilledema may have arisen from severe enophthalmos with mechanical compression of the posterior sclera by the distal optic nerves.

2. Case series

Case 1: A 3-year-old boy presented for evaluation of global developmental delay, nystagmus and poor growth. He was born at 38 + 5 weeks gestation following a pregnancy complicated by intrauterine growth retardation. His growth parameters in the nursery were at the 3rd percentile. Developmental Pediatrics was consulted prior to age 2 years due to global developmental delay and hypotonia. He was assessed by Endocrinology for his growth at 3 years of age due to the height and weight being below the 3rd percentile and was noted to have an advanced bone age 5 years. His endocrine and Gastroenterology evaluations did not determine a specific cause for his poor growth. The

alanine aminotransferase was elevated at 86 U/L (normal 7–55 U/L).

Six months later, he had continued to gain skills with the majority of his skills falling in the 18–24 month range. His head circumference was below the 3rd percentile. He had thin blonde hair with decreased subcutaneous tissue in the face. Enamel dysplasia with dental caries were present. Ophthalmologic examination disclosed brisk optokinetic responses, normal pupillary responses to light, no strabismus or nystagmus, severe enophthalmos (Fig. 1), hyperopia (+4.25 + 1.50 × 103 OD, +5.25 + 1.00 × 93 OS), and bilateral pseudopapilledema (Fig. 2).⁷ There were no cataracts or retinal pigmentary abnormalities. His neurological examination was significant for normal tone with tightness at the ankles bilaterally and diffusely decreased deep tendon reflexes.

Magnetic resonance (MR) imaging of the brain demonstrated lack of myelination of the cerebral white matter with normal myelination of the brainstem, cerebellum, corpus callosum, optic radiations and deep cerebral white matter, with thinning of the corpus callosum. Minor mineralization was noted within the deep frontal and parietal white matter. Orbital MR imaging showed retrodisplacement and axial foreshortening of the globes with posterior scleral flattening and protrusion of the optic papilla into the vitreous (Fig. 2). There was no compression of the pituitary gland within the sella (i.e. no empty sella). Lumbar puncture under general anesthesia revealed a normal opening pressure 22.5 cm H₂O. Based on his neuroimaging findings and clinical presentation, molecular testing for Cockayne syndrome was performed which

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<https://doi.org/10.1016/j.ajoc.2021.101035>

Received 23 September 2020; Received in revised form 15 January 2021; Accepted 12 February 2021

Available online 18 February 2021

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Fig. 1. Lateral facial photos showing severe enophthalmos in case 1 (left) and case 2 (right).



Fig. 2. Case 1. Top: Bilateral pseudopapilledema. Bottom left: T2-weighted axial MR image showing retrodisplacement and axial foreshortening of the globes with posterior scleral flattening and protrusion of the optic papilla (arrows) into the vitreous. (Normally, approximately $\frac{1}{4}$ of the globe volume lies anterior to the line connecting the lateral orbital rims on MR imaging).⁷ Bottom right: T2-weighted MR imaging showing bilateral periventricular white matter hyperintensity (arrows).

revealed 2 pathogenic variants in *ERCC6*. His father carried the pathogenic variant c.466 C>T; p.Q156X and his mother carried the pathogenic variant c.1040delG; p.G347DfsX13.

Case 2: His 18-month-old sister was evaluated due to poor growth and mildly delayed gross motor skills. Her examination was significant for diffusely decreased deep tendon reflexes and mild gross motor delay with normal tone. Her history was significant for lack of ability to smell. The ALT was elevated at 84 U/L. Ophthalmological examination showed almost identical findings to the brother, with a greater degree of enophthalmos (Fig. 1), hyperopia (+3.50 + 0.75 × 103 OD, + 4.50 + 1.00 × 092 OS), and bilateral pseudopapilledema (Fig. 3). MR imaging of the brain revealed widespread hypomyelination/dysmyelination (Fig. 3), with apparent absence olfactory bulbs and tracks bilaterally. Orbital MR imaging showed a similar retrodisplacement and axial foreshortening of the globes, and protrusion of the optic papilla (arrows) into the vitreous to that seen in her brother, however, she had vertical tortuosity of the optic nerves producing a kinked appearance with

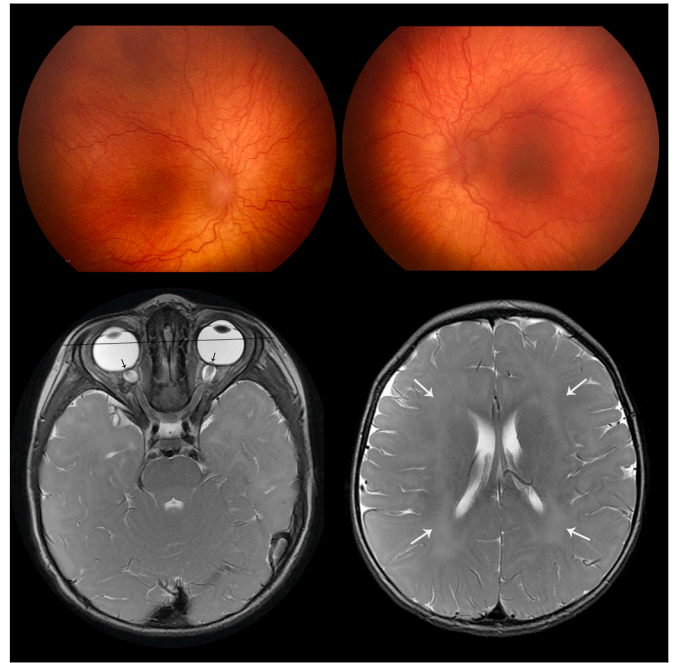


Fig. 3. Case 2. Top: Bilateral pseudopapilledema similar to that seen in case 1. Bottom left: T2-weighted axial MR image showing retrodisplacement and axial foreshortening of the globes, and protrusion of the optic papilla (arrows) into the vitreous. Note vertical tortuosity of the optic nerves producing a kinked appearance with entrapment of perioptic CSF within the distal optic nerve sheaths. Bottom right: T2-weighted MR images showing bilateral periventricular white matter hyperintensity (arrows).

apparent entrapment of perioptic CSF within the distal optic nerve sheaths. There was no compression of the pituitary gland within the sella (i.e. no empty sella). Lumbar puncture under general anesthesia revealed a normal opening pressure of 24.2 cm H₂O. Molecular testing revealed the same *ERCC6* mutation as in her brother.

3. Discussion

First described as “dwarfism with retinal atrophy and deafness” in 1936,¹ Cockayne syndrome is a rare, autosomal recessive disorder with a multitude of clinical features that include growth failure, microcephaly, developmental delay, persistently cold hands and feet, bilateral hearing loss, dermal photosensitivity, tremor, joint contractures, progressive loss of body fat and typical facial features, and progressive neurologic dysfunction.^{2,3} Ophthalmologic findings include severe enophthalmos, high hyperopia, cataracts, photophobia, corneal epithelial degeneration, poor pupillary dilation, and a progressive retinal dystrophy.³⁻⁵ Typical neuroimaging findings include white matter changes consistent with hypomyelination or dysmyelination, calcifications/mineralization, cerebellar hypoplasia or atrophy, enlarged cerebral ventricles and thinning of the corpus callosum.⁸ It is associated with mutations in either the excision repair cross-complementing 6 *ERCC6* gene (known also as the *CSB* gene) gene on chromosome 10 q11.23, or the *ERCC8* gene on chromosome 5 q12.1 (known also as the *CSA* gene).^{2,5}

To our knowledge, pseudopapilledema has not been described as a component of Cockayne syndrome. However, the unusual neuroimaging findings in these two siblings suggest a possible anatomical mechanism for its development. MR imaging showed severe retrodisplacement with axial foreshortening of both eyes (manifesting clinically as enophthalmos), raising the possibility that anterior pressure from the optic nerves against the retrodisplaced globes may be contributing to the axial foreshortening of the eyes while causing the papilla to mechanically protrude into the vitreous. This mechanical effect would differ from the

classic mechanism of pseudopapilledema, which is usually attributed to small narrow scleral canal causing prelaminar axoplasmic stasis.^{9–11}

In pseudopapilledema, CT scanning often shows calcification within the optic nerve heads, but MR imaging usually shows no abnormalities. In elevated intracranial pressure with papilledema, however, distended perioptic CSF within the optic nerve sheath can push forward against the globes to cause flattening of the posterior sclera, vertical tortuosity of the optic nerves, and anterior protrusion of the optic discs into the vitreous is commonly seen on MR imaging.¹² In our cases, however, these overlapping findings may have been attributable to posterior pressure of the enophthalmic globes on the optic nerve head. It is unlikely that these patients had low-grade papilledema given that 1) the ophthalmoscopic features of the optic disc elevation corresponded to those of pseudopapilledema; 2) the CSF pressures were documented to be normal (well below the accepted threshold of 28 cm H₂O for producing papilledema); and 3) neither patient had associated pituitary compression giving rise to an empty sella on MR imaging (a neuroimaging sign of elevated intracranial pressure that reflects downward CSF pressure upon the pituitary gland).¹²

These cases raise the intriguing possibility that severe degrees of congenital enophthalmos can give rise to pseudopapilledema by pushing the globes against the distal optic nerves, causing focal compression of the posterior sclera and anterior protrusion of the optic discs. Further study will be necessary to clarify this potential mechanism.

Patient consent

Consent to publish this case report has been obtained from the patient(s) in writing. The patient's legal guardian consented to publication of the case. This report does not contain any personal information that could lead to identification of the patients.

Funding/support

Supported in part by a grant from the Knights Templar Eye Foundation, Inc., Flower Mound, TX and the Mayo Foundation, Rochester, MN.

Other acknowledgments

None.

Role of the sponsors

None.

Authorship

All authors attest that they meet the current ICMJE criteria for Authorship.

Declaration of competing interest

The following authors have no financial disclosures: Michael C. Brodsky, and Deborah L. Renaud.

Acknowledgements

None.

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