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Title: Retinal Neuronal Ectopia: a new entity in the differential diagnosis of retinoblastoma.

Running Title: Retinal Neuronal Ectopia

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This case study was conducted at the Royal London Hospital, London, UK

Conflict of Interest Statement:
All authors certify that they have NO affiliations with or involvement in any organization or entity with any financial interest (such as honoraria; educational grants; participation in speakers' bureaus; membership, employment, consultancies, stock ownership, or other equity interest; and expert testimony or patent-licensing arrangements), or non-financial interest (such as personal or professional relationships, affiliations, knowledge or beliefs) in the subject matter or materials discussed in this manuscript.

Abstract:

Background: To present a rare retinal disorder that should be considered in the differential diagnosis of retinoblastoma.

Methods: A 2-year-old male presented with left ocular discomfort, leukocoria and a left divergent squint. Examination of the left eye revealed abnormalities in the anterior segment and fundoscopy showed an irregular white calcified mass with fibrosis and traction towards the lens. As the ocular discomfort worsened, enucleation of the left eye was performed.

Results: Histopathological and immunohistochemical assessment of the enucleated eye established the diagnosis of retinal neuronal ectopia.

Conclusion: We believe that this case is unique in the human retina and highlights the need for specialist differential diagnosis. Although rare, retinal neuronal ectopia should be considered in the differential diagnosis of retinoblastoma.

Keywords: Leukocoria, retinal disorders, retinoblastoma, retinal tumours.

Brief Summary

We present a unique retinal condition called retinal neuronal ectopia that can present with leukocoria and should be considered in the differential diagnosis of retinoblastoma.

This case was presented at the International Congress of Ocular Oncology, Buenos Aires, Argentina, November 2011.

Introduction

Leukocoria and strabismus are the most common presenting features of retinoblastoma, although signs of ocular inflammation have been noted occasionally.[1] Sometimes the clinical features are sufficiently confusing to merit a diagnostic enucleation.[2]

Materials and Methods

A 2-year-old male, presented with left ocular discomfort and photophobia. Born at full term, with normal neonatal history, his parents had noted an abnormal left red reflex at birth and a left divergent squint at 6 months. Visual acuity was 6/5 in the normal right eye and no light perception in the left eye, with a fixed dilated pupil and 15 prism diopters of left exotropia. Examination revealed band keratopathy, iris heterochromia with iris hypoplasia and ectropion uveae, a shallow anterior chamber, early cataract and left intraocular pressure of 32 mmHg. Fundoscopy showed an irregular white 9x7mm calcified mass with fibrosis and traction towards the lens (Figure 1). A thin vascular membrane originating from the mass was adherent to the posterior lens capsule. Retinal pigmentary changes were observed in the superotemporal fundus. On B ultrasound scan the mass had an elevation of 7.1mm with hyper-reflective areas confirming calcification. Fundus fluorescein angiogram showed peripheral abnormal vasculature in the inferonasal fundus with leakage of fluorescein in the late phase. Computed tomography confirmed a calcified mass in the left eye, with normal optic nerve and intracranial appearances. Serum toxocara

antibodies were negative. Although retinoblastoma was in the differential diagnosis, features in the examination, such as the fibrovascular and tractional changes to the posterior lens capsule, did not support this diagnosis. After careful counselling, the child was seen every 4-8 weeks, without any change in the clinical appearance, which would be unusual for a malignant process. After 6 months, the ocular discomfort worsened despite treatment with topical glaucoma and anti-inflammatory agents, and the left eye was enucleated.

Results

Histological examination revealed thickening of the retina anterior to the ganglion cell layer with small neurons, some of which expressed opsin, set in a GFAP-rich background. Similar clusters of neurons were seen anterior to the optic nerve head. More peripherally, abnormal anterior retinal vessels were present and at the far periphery retinal vessels were very sparse. GFAP immunoreactivity was seen on the posterior surface of the cataractous lens and over the ora. No retinoblastoma or retinoma was present. Band keratopathy was confirmed and anterior synechiae were present. The choroid was unremarkable, as was the optic nerve. A diagnosis of retinal neuronal ectopia was made in view of the abnormally positioned opsin- expressing neurons anterior to the ganglion cell layer (Figure 2).

Discussion

In the literature, retinal neuronal ectopia has previously been reported only in a 10-month-old tiger retina.[3] The most important finding was the presence of cells between

the nerve fibre layer and the inner limiting membrane, which exhibited the typical morphology of migrating neuroblasts.[4] It has been suggested that neuronal ectopia could have been due to some unidentified Müller cell disturbance that interfered with their orderly guiding function for migrating neuroblasts. Abnormal placement of photoreceptor cells in neural cells associated with maldevelopment of the retinal vasculature is observed in this developmental disorder where control of retinal maturation has been perturbed. It could be described as a neural hamartoma associated with retinal maldevelopment that presents in infancy. We believe that this case is unique in the human retina and highlights the need for specialist differential diagnosis. Although rare, retinal neuronal ectopia should be considered in the differential diagnosis of retinoblastoma.

Patient consent: The patient's mother has consented to the submission of the case report for submission to the journal.

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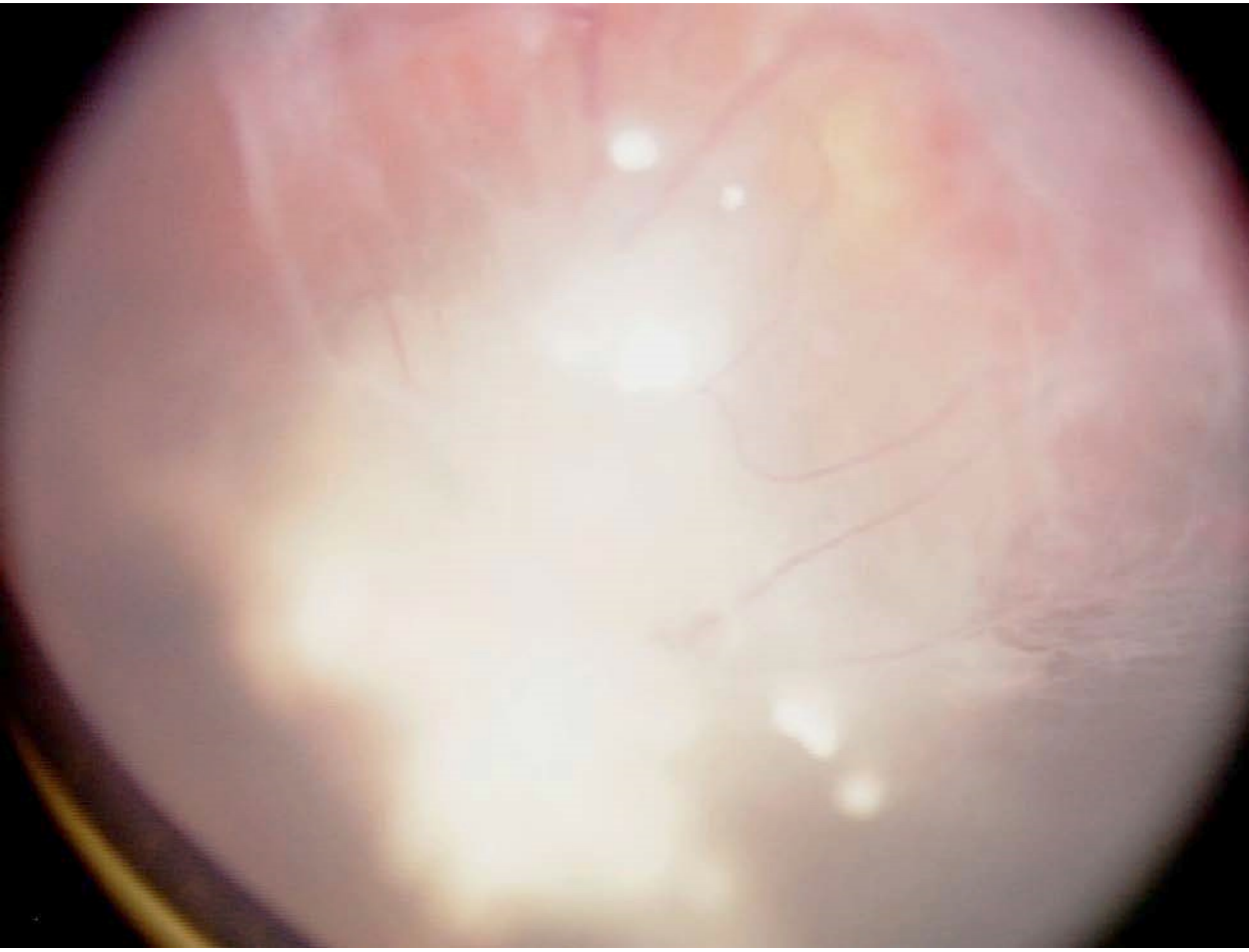
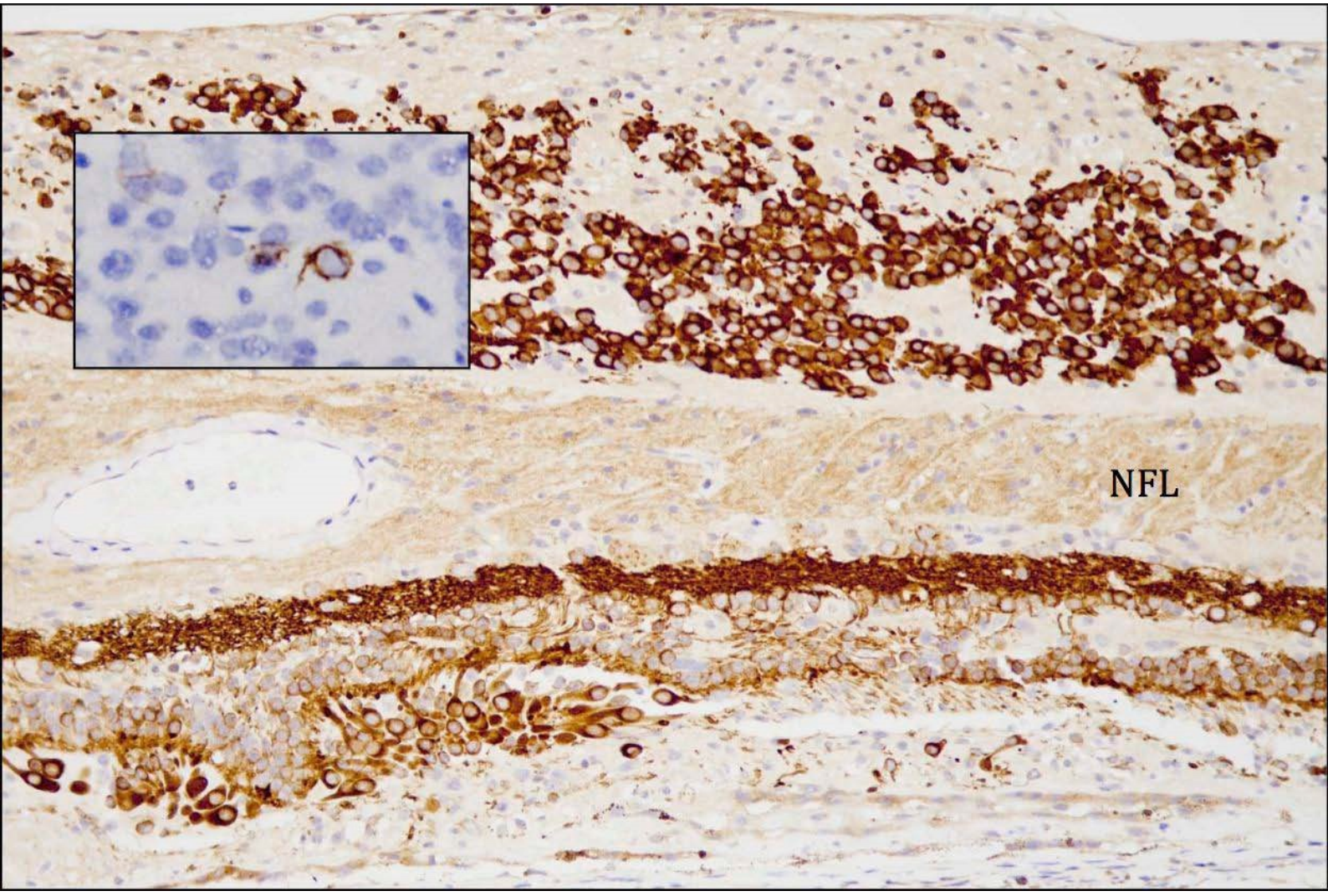
Legends to Figures

Figure 1: Colour fundus photograph showing an irregular white calcified mass with a fibrovascular frond extending through the vitreous to the posterior lens capsule.

Figure 2: Main figure is photomicrograph of posterior retina stained using immunohistochemistry for synaptophysin. Note that anterior to the nerve fibre layer (NFL) there is a layer containing numerous immunoreactive neurons (original magnification x100). The inset shows anterior ectopic neurons with focal immunoreactivity for opsin (original magnification x400).




NFL