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Phenotypic Diversity Of North Carolina Syndrome In Ophthalmology: A Case Report

Krichene MA; Mejdoubi K.; Hassina S. ;Akannour Y. ; Serghini L.; Abdallah E.

University Mohamed V de Rabat- Maroc

Abstract:

This case study delves into the unique and intricate realm of North Carolina Syndrome (NCS), a congenital macular degeneration with various clinical manifestations. We examine the exceptional case of a 23-year-old patient, the only child of a consanguineous marriage, who exhibited severe eye asymmetry and a distinct association of NCS with retinal coloboma. Genetic tests pinpointed a mutation in the PRDM13 gene, known to be linked to NCS. This article contributes to our comprehension of NCS by emphasizing its phenotypic diversity and uncommon ocular symptoms.

Introduction:

The North Carolina Syndrome (NCS) is an intriguing issue in ophthalmology characterized by congenital macular degeneration and a wide range of phenotypic variations. Initially identified in North Carolina in 1971, this syndrome has since been observed worldwide, presenting diverse clinical features and genetic expressions. Here, we focus on a specific case: a 23-year-old patient without a family history of NCS, who exhibited significant macular degeneration in the right eye and a peripheral retinal coloboma in the left eye. This case not only underscores the rarity of such a correlation but also highlights the importance of recognizing the various clinical manifestations of NCS.

Case report:

We present the case of a 23-year-old patient who is an only child born to parents in a consanguineous marriage. The patient came to us reporting a reduction in vision in both eyes, more severe in the right eye, where he could only perceive light positively, compared to 5/10 vision in the left eye. Additionally, he presented with convergent strabismus in the right eye.

Upon biomicroscopic examination, we observed a white eye with a clear cornea and normal depth in the front chamber, without any abnormalities in the iris or lens in either eye. The fundus examination showed atrophic macular dystrophy in the right eye, featuring salt-grain pigments and central fibrous scarring, indicative of North Carolina syndrome (NCS).

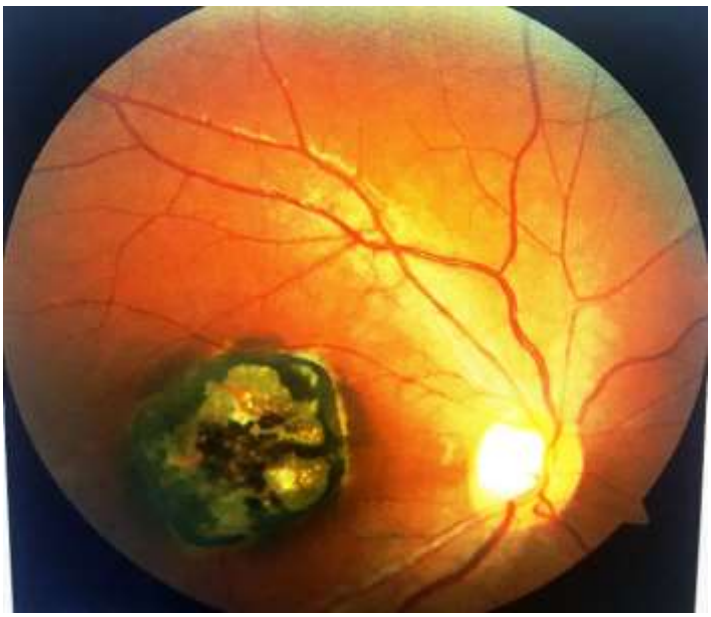

figure 1: macular dystrophy on right eye

On the left eye, there was no macular involvement but a peripheral supertemporal retinal coloboma.

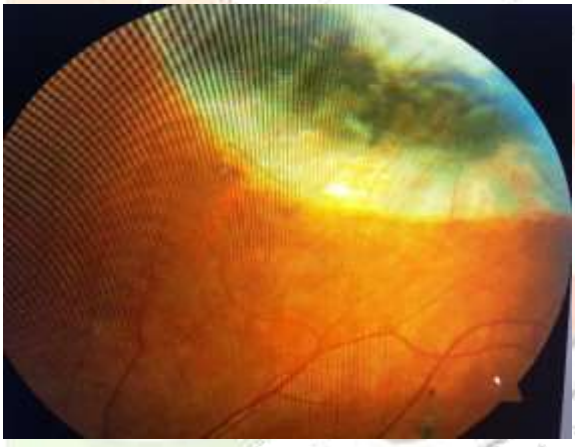

figure 2: peripheral retinal coloboma on left eye

Fluorescein angiography confirmed the absence of choroidal neovascularization.

Optical coherence tomography (OCT) showed loss of retinal pigment epithelium and photoreceptors in the macula of the right eye and normality in the left eye.

figure 3: Macular dystrophy: loss of retinal pigment and photoreceptors

Genetic testing identified a mutation in the PRDM13 gene, responsible for NCS.

Discussion:

The NCS is a congenital macular dystrophy that is inherited and does not advance. It is caused by a mutation in a non-coding region of chromosome 6, near the PRDM13 gene (1). This gene codes for a transcription factor involved in the differentiation of retinoblastoma cells (2). The NCS is distinguished by intra- and interfamilial phenotypic variability ranging from macular drusenodes to colobomatous lesions with varying visual acuity (1) (3). NCS is a rare condition with unknown prevalence. It was initially observed in patients from the northern state of Caroline in the United States in 1971 (6). Since then, cases have been documented in France, Brazil, Canada, Australia, India, Japan, China, Saudi Arabia, and Morocco, among others. In 2016, Brown et al. (6) discovered the causal mutation, which was a 7.4 kb tandem duplication in the 6q16.3 region, approximately 40 kb downstream of the PRDM13 gene. This duplication increases PRDM13 gene expression in the retina, disrupting amacrin differentiation and affecting macular function (2).

Phenotypic variability is common in NCMD but is poorly understood (4). The NCS appears as a bilateral macular asymmetry that can be discovered at birth or during childhood (1) (3). According to Small (3) (5), the macular phenotype differs between people and families and can be divided into three types:

• Type 1: yellow or gray macular drusenodes with normal or slightly reduced visual acuity.

• Type 2: atrophic or colobomatous macular lesions with substantially impaired visual acuity.

• Type 3: presence of mixed macular lesions with varied visual acuity, including drusenoides and atrophic or colobomal zones.

Green and al. study revealed the existence of three benign cases that were asymptomatic and initially diagnosed incorrectly as having a kind of early macular erythmopathy in adulthood. The macular elevations were non-typical drusen, and genetic testing revealed that the lesions were congenital (7).

Other ocular anomalies such as nystagmus, myopia, glaucoma, ptosis, anisocoria, iritis heterochromia, microcornea, cataract, retinal detachment or Duane syndrome may be linked to NCS (8) (9). Choroidal neovascularization is a rare but sight-threatening complication of NCMD and can occur in both children and adults (10). Multiple drusen-like spots in the peripheral retina have been described on wide-field retinal imaging. Although this feature is not pathognomonic, it has prompted targeted genetic testing.

There are several aspects of our case worth considering. Firstly, this is an isolated case with no known family history of NCS. Secondly, he presents with marked asymmetry between the two eyes, with severe macular damage in the right eye and a peripheral retinal coloboma in the left eye, with no macular abnormalities. Only a few cases of this association between NCS and retinal coloboma have been described in the literature. Finally, he has convergent strabismus of the right eye, which may be associated with secondary amblyopia and reduced visual acuity.

When choroidal neovascularization is ruled out, it might help identify other possible diagnoses or complications related to NCS. OCT can be employed to evaluate retinal anatomy when retinal pigment epithelium and photoreceptors are lost in the macula and retinal thickness decreases (1) (3).

The main therapy for NCS is symptomatic, with the intention of improving the patient's eyesight and preventing complications.

NCS is a rare retinal disease with a wide phenotypic variability and a complex genetic expression. The identification of the causative mutation and the underlying gene has improved understanding, but questions remain about the molecular and cellular mechanisms that underpin the variety of clinical presentations. Additional research is required to understand the factors that influence the expression of the PRDM13 gene, as well as to investigate potential therapeutic avenues such as genetic therapy or the transplantation of stem cells from the retina.

Conclusion:

Our case report adds information on the phenotypic variability of North Carolina Syndrome, highlighting its complex presentations beyond conventional macular involvement. The specific relationship with retinal coloboma in this case emphasizes the importance of a full assessment when dealing with NCS. Our findings, which revealed a mutation in the PRDM13 gene, contribute to a better understanding of the genetic basis of NCS. Moving forward, further research is needed to understand the molecular complexities and cellular mechanisms that underpin the many clinical manifestations of NCS. This instance illustrates the importance of a sophisticated approach to diagnosis and the need for continued research into potential therapeutic options in the management of this rare retinal condition.

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