Ophthalmologic and facial abnormalities of Nicolaides-Baraitser syndrome

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ABSTRACT

Background: Nicolaides-Baraitser syndrome (NCBRS), first described in 1993, is a rare autosomal dominant disease caused by pathogenic variants in the SMARCA2 gene located on chromosome 9p24.3 (1). Several disorders causing intellectual disability, including NCBRS and Coffin-Siris syndrome, are caused by variants in the SWI/SNF chromatin remodeling complex, which loosens chromatin and enhances local transcription using ATP hydrolysis (2). The SMARCA2 gene codes for an ATPase subunit of the SWI/SNF chromatin remodeling complex (3). Missense mutations are the most common cause of NCBRS, though several pathogenic deletions have been reported (4,5). Likewise, pathogenic variations are nearly ubiquitously due to de novo events, but one case of paternal mosaicism inheritance has been reported (6). Features that are now associated with NCBRS were first reported by Nicolaides and Baraitser in 1993 in a 16-year-old patient with severe intellectual disability, sparse hair, and facial and digital dysmorphologies (7). In 1996, Krajewska-Walasek et al. reported the case of a 19-year-old patient with similar symptoms and later in 2003, Morin et al. reported an additional two patients and supported the classification of NCBRS as a new distinct disease (8,9). Over 100 cases of the disorder have now been reported in literature. NCBRS is recognized by a collection of distinct features including sparse scalp hair, microcephaly, course facies, prominent interphalangeal joints, thick distal phalanges, seizures, intellectual disability, and developmental delay (10).

Ophthalmologic features of NCBRS have not been thoroughly described in literature. We report the case of a 4-year-old male patient with a confirmed SMARCA2 missense mutation and clinical features common to NCBRS. His eye features include myopia, down slanting palpebral fissures, sagging inferior periorbital skin, hypertelorism, and long eyelashes. In addition, we present a summary of the common ocular, ocular adnexa, and facial features of NCBRS from a systematic review of literature.

Case report

At the time of most recent exam, the patient is a 4-year-old boy born at 39-weeks’ gestation to a 35-year-old G2P2 mother. The pregnancy was complicated by placenta previa that self-
resolved, otherwise the pregnancy and delivery were routine. Family history was notable for the patient’s father and two paternal uncles having the autosomal recessive condition primary hypertrophic osteoarthropathy type 2.

The patient has a history of seizures beginning at 1–2 months old when the parents noted episodes of staring. At 5 months old, the patient demonstrated his first episode of unresponsiveness with irregular breathing, no eye deviation, and limpness. These episodes were also associated with difficulty breathing and desaturation.

The patient was admitted at 10 months old due to failure to thrive and was noted to have iron deficiency anemia, which was treated with iron supplementation. He was again admitted 3 months later following an episode of difficulty breathing possibly due to choking/aspiration while eating. Hypercalcemia was noted during inpatient admission. Calcium was noted to be persistently elevated during follow-up appointments and renal ultrasound revealed nonobstructive right renal calcium. Both the hypercalcemia and nephrolithiasis resolved without intervention.

The patient first presented for genetic evaluation at 15 months old due to dysmorphic features, failure to thrive, and seizures. Upon examination his dysmorphic features included down slanting palpebral fissures, sagging inferior periorbital skin, hypertelorism, long eyelashes, depressed/flat nasal bridge, long philtrum, micronathia, broad forehead, sparse scalp hair, thin upper lip, everted lower lip, wide mouth, and prominent interpahpebral joints. In addition to feeding difficulties, the patient continued to demonstrate motor and speech delay. Speech, feeding, and ABA therapies were initiated and the patient was able to achieve the ability to walk by himself.

Coffin-Siris Syndrome sequencing and deletion/duplication analysis performed via GeneDx revealed a heterozygous missense c.3485 G>A p.Arg162His variant in the SMARCA2 gene. This p.Arg162His missense variant has been associated with other individuals with NCBRS reported in the literature (1). In-silico analysis of this variant supports a deleterious effect; thus, this variant was interpreted as pathogenic in our patient.

A head MRI performed at 2 years old found small bilateral choroidal fissure cysts, generalized prominence of the perivascular spaces, and symmetric faint T2 signal hypointensity and restricted diffusion along the anticipated courses of the central segmental tracts. With drug therapy, the patient’s last reported seizure was nearly 2 years before the most recent patient encounter.

An ophthalmic examination at 3 years old was notable for bilateral myopia, mildly sagging inferior periorbital skin, and mildly down slanting palpebral fissures with otherwise normal appearing anterior and posterior ocular segments. The patient’s additional medical issues included chronic atopic dermatitis, duodenal ulcer, dysphagia, recurrent ear infections, gastric reflux, and rhinitis. He underwent adenoidectomy at 3 years old that improved breathing, swallowing, and speech.

Only articles describing unique Nicolaides-Baraitser syndrome cases with molecularly confirmed SMARCA2 gene variants and a thorough clinical description were included. Two articles were excluded due to non-English language presentation. One article was excluded because the authors did not delineate between the novel cases and the previously published cases. No articles were excluded due to publication year. References were reviewed to identify articles that did not appear in the initial search. Unique cases of Nicolaides-Baraitser were identified from the articles and the frequencies of abnormal eye, ocular adnexa, and facial features were determined.

Discussion

Our systematic review yielded 17 articles describing 79 unique molecularly confirmed cases of NCBRS, for 80 total cases including our patient (1,4,5,10–23). The male to female ratio skewsl slightly male at 47:33. The Supplemental Table demonstrates the total clinical features and SMARCA2 variant information of the individual reported cases.

The most common eye and ocular adnexa findings reported in these cases are prominent/long eyelashes (n = 53, 66.3%), thick eyebrows (n = 49, 62.8%), sagging periorbital skin (n = 41, 53.9%), down slanting palpebral fissures (n = 35, 46.7%), ptosis (n = 17, 22.1%), synophrys (n = 14, 18.9%), myopia (n = 12, 15.0%), narrow palpebral fissures (n = 9, 11.8%), astigmatism (n = 5, 6.3%), and hypertelorism (n = 2, 2.5%) (Table 1). The true frequency of refractive errors among patients with NCBRS may be higher in reality than what is presented in this paper due to underreporting within the literature. Less common but notable clinical findings include degenerative vitreoretinopathy (n = 1, 1.3%), cataracts (n = 1, 1.3%), and glaucoma (n = 2, 2.5%) described in a 12-year-old girl by Sethi et al. in 2019 (11). Upon ophthalmologic examination this patient demonstrated high myopia with astigmatism and best corrected visual acuity of 20/50 bilaterally, bilateral mild posterior subcapsular cataracts, bilateral peripheral vitreous syneresis with retinal pigmentation, and optic disk cupping, elevated central corneal thickness, and increased intraocular pressure that led to a diagnosis of bilateral glaucoma. Sethi et al. (11) argues that due to the rarity of these ocular findings among the general pediatric population, it is likely that these abnormalities are associated with NCBRS. Additionally, in 2021 Foley et al. (5) report a case of a neonate with NCBRS with congenital glaucoma.

Table 1. Common eye and ocular adnexa abnormalities reported in 80 confirmed cases of Nicolaides-Baraitser syndrome.

| Clinical Feature                  | Frequency |
|----------------------------------|-----------|
| Prominent/Long Eyelashes         | 53/80 (66.3%) |
| Thick Eyebrows                   | 49/78 (62.8%) |
| Sagging Periorbital Skin         | 41/76 (53.9%) |
| Down Slanting Palpebral Fissures | 35/75 (46.7%) |
| Ptosis                           | 17/77 (22.1%) |
| Synophrys                        | 14/74 (18.9%) |
| Myopia                           | 12/80 (15.0%) |
| Narrow Palpebral Fissures        | 9/76 (11.8%) |
| Astigmatism                      | 5/80 (6.3%) |
| Glaucoma                         | 2/80 (2.5%) |
| Hypertelorism                     | 2/80 (2.5%) |

Methods

A systematic review of literature was performed to summarize the eye, ocular adnexa, and facial features of Nicolaides-Baraitser syndrome. A Pub-Med search of “Nicolaides-Baraitser syndrome” yielded 55 articles on November 2021.
The SWI/SNF remodeling complex is implicated in eye development. Brm, the product of SMARCA2, is essential for retinal ganglion cell differentiation through promotion of Brn3b, a retinal ganglion cell regulator, and Notch signaling inhibition (24). It thus may be expected to observe vitreoretinal abnormalities among NCBRS patients at an increased frequency. Brg1 (SMARCA4) and Snfh2 (SMARCA5) are additional SWI/SNF ATPase subunits that are shown to be independently necessary for embryonic lens differentiation and lens nuclear degradation (25,26). It is possible that Brm also has a role in the crystalline lens differentiation process or that Brm variants can negatively interact with Brg1 or Snfh2, thereby leading to increased incidence of cataracts and refractive errors among NCBRS patients. The potential effect of SMARCA2/Brm variants on the development and differentiation of the crystalline lens provides an avenue of future investigation to better understand the effect of NCBRS on ocular phenotype.

Due to the frequency of opthalmologic abnormalities among NCBRS patients, rapid referral for ophthalmology evaluation should be made following diagnosis. It may be beneficial to regularly screen NCBRS patients for refractive errors, ptosis, glaucoma, cataracts, and vitreoretinal disorders. If left untreated, NCBRS related eye pathologies could lead to permanent loss of vision, such as with glaucoma or vitreoretinal disease. Severe untreated ptosis may lead to amblyopia and interfere with vision, thus surgical intervention may be required.

NCBRS often presents with a very distinctive set of facial features. The most commonly reported facial findings include thick/everted lower lip (n = 69, 83.5%), coarse facial features (n = 58, 77.3%), wide/large mouth (n = 59, 74.7%), thin upper lip (n = 59, 74.7%), thick/anteverted alae nasi (n = 57, 73.1%), low frontal hairline (n = 47, 62.7%), upturned nasal tip (n = 49, 62.0%), broad philtrum (n = 47, 59.5%), long philtrum (n = 44, 56.4%), broad nasal base (n = 42, 55.3%), and broad nasal tip (n = 39, 52.0%) (Table 2). Other common findings include sparse scalp hair (n = 76, 95.0%) and microcephaly (n = 37, 52.1%). Some less common features may have been underreported in past literature. Broad nose was reported in 31.6% (6/19) of cases and depressed nasal bridge was reported in 26.3% (5/19) of cases since 2015, whereas neither were reported in the prior 61 cases.

Our patient possesses several clinical features that commonly present with NCBRS including myopia, sagging periorbital skin, long eyelashes, down slanting palpebral fissures, sparse hair, wide mouth, long philtrum, thin upper lip, and everted lower lip. Clinical findings less commonly associated with NCBRS present in our case are micrognathia, hypertelorism, and depressed/flattened nasal bridge.

The p.Arg1162His missense variant of the SMARCA2 gene seen in our patient is also reported in two NCBRS cases by van Houdt et al (1). In comparison, thin upper lip, thick lower lip, long philtrum, and sparse hair are reported in all three cases. The features of our patient that match one of the other cases but not both include prominent eyelashes, down slanting palpebral fissures, and wide mouth. Features absent in our patient and reported in both the other two cases are widely spaced teeth, narrow nasal bridge, upturned nasal tip, thin alae nasi, low frontal hairline, and broad philtrum. This overlap in features may be explained by the high frequency of these features in the general NCBRS population. Our patient’s features that are not reported among the other p.Arg1162His cases are myopia, sagging periorbital skin, hypertelorism, micrognathia, broad forehead, and depressed/flattened nasal bridge. The differing phenotypes between identical SMARCA2 variants provides an additional direction for future investigation.

Dental anomalies are frequently reported among NCBRS patients. 45.8% (33/72) of published cases reported widely spaced teeth, 12.9% (8/62) reported hypodontia/oligodontia, 4.9% (3/61) reported abnormal enamel, and 1.3% (1/80) reported hypodontia. Referral for dental examination may be recommended for NCBRS patients shortly following diagnosis.

In summary, this article reports on the abnormal ocular, ocular adnexa, and facial features of NCBRS and helps to elucidate the ophthalmologic and facial presentations of NCBRS. As eye manifestations and distinctive facial features appear highly associated with the phenotype, this report highlights these entities and may benefit patients affected with the syndrome by allowing for more rapid recognition, management, and referral to appropriate services. This article may also alert providers to more carefully access NCBRS patients for potentially serious ocular abnormalities such as glaucoma that may be associated with the phenotype. Further investigations into the role of SMARCA2 on eye development could enhance our understanding of the pathophysiology of ophthalmologic manifestations of NCBRS.

### Disclosure statement

Natario L. Couser, MD, MS:
1. Retrophic, Inc./Travere Therapeutics, Inc. (Clinical Trial)
2. National Cancer Institute/Children’s Oncology Group (Clinical Trial)
3. Elsevier (Book editor)
4. Patient-Centered Outcomes Research Institute (PCORI; Advisory Panel on Rare Disease)

### Consent

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