Strabismus and ptosis tend to be over-represented in reported cases of MH.[3] Although this association between strabismus and MH is not proven, its potential consequences warrant clinical caution.[4] Occult myopathies should be considered in the differential diagnosis of unexplained strabismus as they may confer increased risk of susceptibility to MH and AIR.[5-7] If susceptibility to MH or AIR is suspected, preoperative consultation and testing with a regional MH service should be considered. For MH, in vitro contracture testing has a sensitivity of 97%-99% and genetic testing has a sensitivity of 50%-70%.[8,9] There are currently no means of predicting AIR risk beyond historical association with known susceptible conditions.[10] For strabismus surgery, we suggest that succinylcholine be avoided, because it not only risks triggering MH and AIR, but it also confounds forced duction testing.[2] Perioperative personnel should remain vigilant for early signs of AIR and MH (see Table 1), and if suspected, prompt treatment should be initiated according to guidelines available locally or at http://www.mhaus.org. In both conditions, key early responses are to stop exposure to triggering agents, recruit help, deliver 100% oxygen, administer dantrolene (if MH suspected), cool the patient (if >37°C), treat hyperkalemia, and prepare for resuscitation in the event of a cardiac arrest.

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Glaucoma and degenerative vitreoretinopathy in a girl with Nicolaides-Baraitser syndrome

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We report the case of a 12-year-old girl diagnosed with Nicolaides-Baraitser syndrome with novel ocular features. Diagnosis was based on clinical features, including developmental delay, sparse hair, and craniofacial features along with de novo mutation in *SMARCA2*. Eye findings included bilateral glaucoma, cataracts, and degenerative vitreoretinopathy. Given the absence of an associated recognizable disorder and the low prevalence of these ocular findings in the general population, we suggest that these ocular features may not be chance association.

Case Report

A 12-year-old girl with suspected collagen issues was referred to the Ocular Genetics service at Wills Eye Hospital to evaluate her high myopia, asymmetric cupping, concern for elevated eye pressures attributed to a difficult exam, and degenerative vitreous abnormalities in the setting of Nicolaides-Baraitser syndrome (NCBRS). She was previously diagnosed with NCBRS based on her clinical features and a de novo (parents tested negative) heterozygous c.2267C>T (p.T756I) mutation in *SMARCA2* detected by whole-exome sequencing. This variant was previously reported to be pathogenic in other individuals with NCBRS.[1] Other identified variants occurred in genes inconsistent with the proband's features and maternally or paternally inherited and associated with autosomal

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dominant or X-linked diseases, none of which affected her parents.

Single nucleotide polymorphism (SNP) microarray was performed using NCBI 36(hg18) and the Ilumina HumanQuad610 BeadChip (Ilumina Inc, San Diego, CA) with over 500,000 SNP loci from chromosomes 1-22, >15,000 loci from chromosome X, and >2,000 loci from chromosome Y. There was a 22 SNP, 126kb heterozygous deletion on chromosome 2q13 from base 110,214,532 to 110,340,399. Sequencing of mitochondrial DNA, *POLG1*, and *COL2A1* were normal. Biotinidase enzyme analysis was normal.

The patient has attention deficit disorder with hyperactivity, autism spectrum disorder, and developmental delay. She has thin shiny skin with decreased adipose and muscle mass, ligamentous laxity, prominent interphalangeal joints and finger-tip pads, sparse hair, anhidrosis, scoliosis, and positional posterior plagiocephaly (treated in infancy), and facial dysmorphism (Figure 1). She has generalized convulsive epilepsy, a platelet aggregation disorder, and seasonal/environmental allergies. She was 12th percentile for height and the 17th percentile for weight. Her head circumference was 51.5 cm (50th percentile).

On ophthalmic examination, her best-corrected visual acuity was 20/50 in each eye. Cycloplegic refraction was $-7.50 + 0.50 \times 110$ in the right eye and $-11.50 + 2.50 \times 75$ in the left eye. Examination under anesthesia revealed a normal anterior segment, with the exception of mild posterior subcapsular cataract in the left eye more than the right. The anterior vitreous showed distinct abnormalities, including pigment clumps, thin stranding, and optically empty spaces. After two prior normal examinations, intraocular pressure (IOP) increased to 32-35 mm Hg in the right eye and 39-42 mm Hg in the left eye, with corneal pachymetry of 711 μm in the right eye and 717 μm in the left eye. As clinical techniques to measure IOP are estimates based on a cornea's resistance to deformation, one can infer from her high corneal thicknesses that her IOP readings may be misleadingly high. However, because her prior two examinations were normal, these newly elevated pressures were concerning for a glaucomatous process. Dilated retinal examination was normal, with the exception of peripheral vitreous syneresis with pigmentation of the retina underlying the vitreous base for 360°, being worse in the left eye (Figure 2). A-scan ultrasound by immersion was 25.10 mm in the right eye and 26.79 mm in the left eye. There were no signs of corneal edema, hazy opacities, scarring, or Haab striae.

A diagnosis of glaucoma was made on the basis of glaucomatous optic disk cupping (Figure 2), elevated central corneal thicknesses, and IOPs and she began treatment with timolol-dorzolamide. Later, latanoprost was added to the treatment regimen and her glaucoma has since remained stable over the following 6 months of examinations. During this time, her vitreoretinopathy also appears to be stable and no breaks or tears have been found. Her corneal thickness remained high even after her IOPs stabilized. Her mother and school both describe vision difficulties of reaching off target, holding objects close, and trouble with unfamiliar surfaces or steps, explained by a worsening left cataract. Cataract extraction in her left eye has been recommended. The patient had been followed

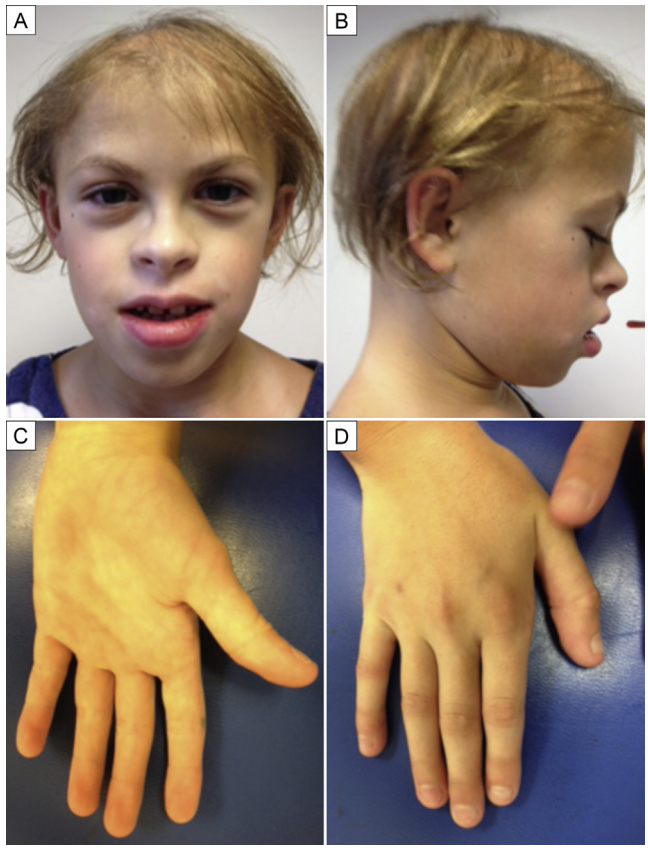

FIG 1. A-B, Clinical photographs showing coarse facial features, sparse hair, sagging periorbital skin, broad nasal tip, upturned nasal tip, thick lower lip, and widely spaced teeth. C-D, Clinical photographs of hands. Note prominent finger pads and interphalangeal joints, marked on physical examination.

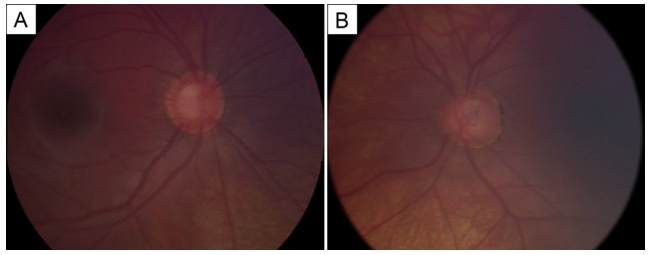

FIG 2. Fundus photographs of the right eye (A) and left eye (B) showing glaucomatous optic nerve cupping. Large optic nerves may contribute to cupped appearance.

by her primary optometrist for myopia since she was 1 year of age. In the following 11 years, the ocular features of her condition were not identified, and it is unclear whether these features were present prior to her referral.

Discussion

NCBRS (OMIM # 601358) is an autosomal dominant disorder caused by mutations in *SMARCA2*.[1] Characteristic findings include developmental delays, sparse hair or alopecia, short stature, seizures, brachydactyly, and prominent finger joints.[2] Fewer than 75 cases have been reported worldwide. Previously reported ophthalmological details noted no unusual findings aside from refractive errors, including myopia in 10 cases and astigmatism in 4 cases.[2]

Our patient was found to have bilateral glaucoma, cataracts, and vitreoretinopathy. In a population study in Olmstead County, Minnesota, the incidence of pediatric glaucoma in all forms was reported to be approximately 2.29 per 100,000 patients <20 years of age.[3] The global incidence of childhood cataracts is 1.8 to 3.6 in 10,000 children.[4] Although the incidence of juvenile vitreoretinopathies is unknown, they are certainly rare, and this child did not have features that could be attributed to a specific recognizable vitreoretinopathy. We suggest that our patient's ocular findings are not chance association.

NCBRS is caused by heterozygous dominant-negative missense mutations in *SMARCA2*. *SMARCA2* encodes for Brm, a highly conserved subunit of the switch/sucrose nonfermenting (SWI/SNF) protein complex.[1] This complex is a chromatin remodeling enzyme that has been implicated in the regulation of gene expression and cell cycle control (OMIM #600014). The SWI/SNF complex regulates cell differentiation in a number of cell lineages.[5] In the eye, the SWI/SNF subunits Brg1 (*SMARCA4*) and Snf2h (*SMARCA5*) have been identified as critical components of crystalline lens cell differentiation and denucleation.[6] Brg1 and Brm both encode for an ATPase subunit of the SWI/SNF complex. Mutations in *SMARCA2* may result in a Brm that interferes with Snf2h function, a potential mechanism for cataract development.

Brm also plays an important role in regulating the differentiation of retinal progenitor cells into retinal ganglion cells by facilitating cell cycle exit, promoting the expression of a retinal ganglion cell regulator, and inhibiting Notch signaling to enable cell commitment.[7] Brm deficiency has also been associated with increased cell proliferation and an increase in mass of connective tissue in adult mice.[8] These data suggests a pathway for vitreoretinal abnormalities.

Unlike other ATP-dependent chromatin remodeling complexes, the SWI/SNF complex regulates a homolog of mammalian ATR (Mec1in *S. cerevisiae*).[9] Biallelic mutations in ATR cause Seckel syndrome 1, typically characterized by intrauterine growth retardation, dwarfism, developmental delay and a "bird-headed" facial appearance (OMIM #210600). Childhood glaucoma has been reported in Seckel syndrome and has been suggested to be due to the critical role of ATR in response to DNA damage.[10]

Mutations in *SMARCA2* have also been reported in studies identifying Coffin-Siris syndrome (CSS) by clinical features.[11] CSS shares many features with NCBRS and may be clinically distinguished by excessive hair growth and small thumbs. Holsten and colleagues[11] presented 4 patients with CSS and *SMARCA2* mutations who were eventually reclassified as having NCBRS. A number of ophthalmic findings have been reported in CSS, including myopia, astigmatism, strabismus, amblyopia, microspherophakia, optic disk coloboma, and optic nerve atrophy.

Our patient's genetic findings include a 126kb microdeletion on chromosome 2q13. The genes in this region are *NPHP1* (OMIM #607100) and a portion of *MALL* (OMIM #602022). *NPHP1* is phenotypically associated with isolated nephronophthisis, Joubert syndrome 4, and Senior-Loken syndrome, whereas *MALL* has little evidence of a phenotypic association. The patient's deletion has been reported in unaffected carriers for these disorders and has not been associated with glaucoma, vitreoretinopathy, cataracts, or myopia. Therefore, it likely does not explain the specific ocular manifestations in our patient.

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