caused by SARS- CoV-2 have been reported.[4-6] In addition, arthritis, enthesitis, and dactylitis associated with SARS-CoV-2 infection have also been reported.[7,8] The exact mechanism of musculoskeletal system involvement in patients with COVID-19 remains unclear, however. Various viral pathogens, such as hepatitis C, human immunodeficiency virus, Middle East respiratory syndrome coronavirus, and influenza A and B are known to cause myositis. Furthermore, SARS-CoV-2 has a high affinity for angiotensin-converting enzyme 2 (ACE2), which skeletal muscles express.[9] Thus, direct viral invasion of skeletal muscles by SARS-CoV-2 is possible.

Another mechanism of musculoskeletal system involvement may be the immune-mediated pathway. Viral pathogens are known to cause immune-mediated myositis by triggering or exacerbating autoimmunity.[10] In addition, many inflammatory cells are stimulated, and cytokines are released in patients with COVID-19. This inflammatory response may trigger immune-mediated pathways or may be myotoxic.

In the present case, acquired Brown syndrome was associated with trochlear tendon complex involvement because orbital MRI revealed thickening and enhancement in the distal part of the superior oblique muscle–tendon-trochlea complex. In addition, the onset of ocular findings 3 weeks after COVID-19 infection suggests that this condition may be a reactive response rather than a direct viral invasion.

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Noncongenital juvenile-onset bilateral lamellar cataract in 1p36 deletion syndrome

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We report the case of a 16-year-old girl with 1p36 deletion syndrome, who experienced visual loss in both eyes for 2 months because of lamellar cataracts. Mutations on some 1p36 genes in both experimental models and humans may be associated with cataract. This is the first detailed description of acquired juvenile-onset bilateral cataract with 1p36 deletion.

Monosomy 1p36, affecting 1 in 5,000 newborns, represents the most common terminal deletion syndrome.[1] Deletions, 95% of which are de novo, occur equally in males and females and in all ethnic groups. It is difficult to identify the genes responsible for the phenotypic manifestations, because the distal end of the short arm of the chromosome 1 is very rich in genes.[2] There is no common breakpoint or deletion size in 1p36 monosomy.[1-3] Affected individuals are phenotypically heterogeneous, because the size of the deletion varies widely. The features are not specific for this syndrome, and the cytogenetic identification of the deletion is often difficult. Therefore, some individuals may be misdiagnosed.[3] The systemic findings are summarized in Table 1.[1,2,4] Ocular malformations or functional visual problems are present in more than half the cases. They include strabismus (35%-67%), hyperopia (41%-67%), myopia (17%-40%), astigmatism (23%), nystagmus (13%-23%), unilateral cataract (5.9%), retinal albinism (5.9%), and unilateral optic nerve coloboma (2.9%).[1-4]

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Table 1. Systemic features of 1p36 deletion syndrome

Characteristic facial phenotype
Deeply set eyes
Straight eyebrows
Midface hypoplasia
Broad nasal bridge
Long philtrum
Pointed chin
Global developmental delay (100%)
Severe to profound mental retardation (88%-95%)
Absence or delay in expressive speech (75%-98%)
Behavioral disorders (47%-55%)
Hypotonia (92%)
Seizures, usually improving over time (50%-79%)
Congenital heart defects (71%-75%)
Neurosensorial hearing impairment (>50%)
Skeletal anomalies (41%)
Brain anomalies
Orofacial clefting
Renal abnormalities
Genital abnormalities
Congenital hypothyroidism
Delayed bone age
Higher risk of developing neoplasms (if partial monosomy)

Two cases of patients affected by Duane retraction syndrome that may have been associated with proximal 1p36 deletion have also been reported.[5] There is a single report of bilateral congenital cataract.[6] Visual inattentiveness, that is, the absence of attentive visual behavior with fixation and following movements, is present in 44%-64% of cases.[1,2] Patients usually reach adulthood, experiencing a progressive improvement in behavior, social interactions, and motor abilities.[1]

Case Report

A 16-year-old girl was referred by her ophthalmologist to our clinic at University of Udine for assessment of a cataract in her right eye. She had been experiencing poor visual acuity, worse in the right eye, for the previous 2 months. The patient was the first daughter of nonconsanguineous white parents. Pregnancy and delivery were uneventful. Her family history was unremarkable. (No family member was affected by either 1p36 deletion syndrome or juvenile cataract.) Ten weeks after birth, she developed epileptic seizures, treated with phenobarbital for 1 year. Magnetic resonance imaging showed dilated ventricular cavities and poorly represented corpus callosum. She had global developmental delay and was diagnosed with 1p36 deletion syndrome when she was 4 months old, with cytogenetic analysis and array (comparative genome hybridization). She showed medium intellectual disability as well as difficulty with tests for coordination and fine movements, with walking alterations and general hypotony. The same ophthalmologist had performed regular ophthalmological follow-up examinations since the first years of life, reporting bilateral hyperopia and astigmatism, with normal orthoptic evaluation. At 15 years of age, her best-corrected visual acuity was 20/20 in each eye, with a refraction of +5.00 + 2.75 × 75 in the right eye and +5.50 + 2.00 × 80 in the left eye. No signs of crystalline lens opacities were noted at birth or during her early years. When she started complaining of poor visual acuity, 2 months prior to presenting at our clinic, her best-corrected visual acuity was 20/200 in the right eye and 20/25 in the left eye.

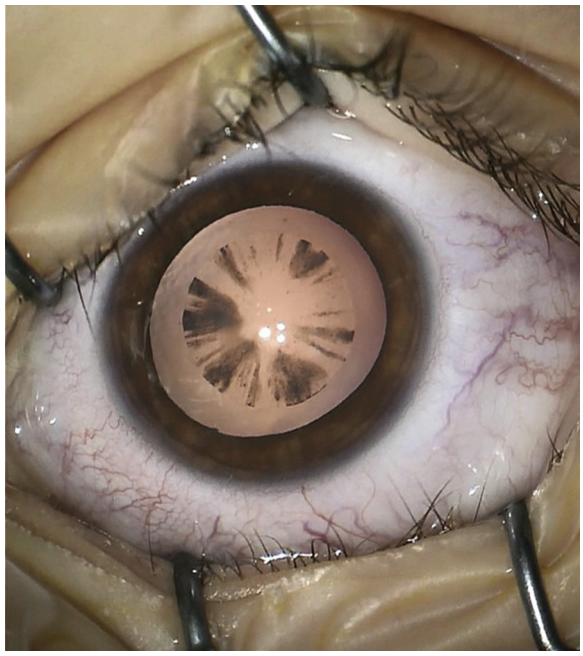

FIG 1. Lamellar cataract in patient's left eye.

On evaluation at our clinic, her visual acuity was still 20/200 in the right eye and had worsened in to 20/32 in the left eye. Intraocular pressure was 15 mm Hg in each eye on rebound tonometry. She had bilateral asymmetrical lamellar cataract (Figure 1), more advanced in the right eye. The remaining ocular findings were normal in both eyes. In particular, the appearance of the optic nerve and of the retina was normal in each eye. The optical biometry showed an axial length of 20.50 mm in in the right eye and of 20.62 mm in the left eye. Corneal keratometry was 41.41/44.35 D in the right eye and 41.87/44.64 D in the left eye.

Cataract surgery was performed uneventfully on both eyes under general anesthesia. The selected refractive target was plano with a +34 D single piece hydrophobic acrylic monofocal intraocular lens (IOL) in each eye. Posterior capsulotomy was performed before IOL implantation. The postoperative course was without complication. Best-corrected visual acuity 1 month after surgery was 20/25 in each eye.

Discussion

Ophthalmological manifestations are present in more than half the cases of monosomy 1p36.[1-4] There are only two reports of cataract in this syndrome: Battaglia and colleagues[1] reported a 5.9% incidence of unilateral cataract in a group of 60 affected patients, without further details on

age of onset, and De and colleagues[6] reported congenital bilateral cataract in a single patient affected by the deletion and β-thalassemia. In both reports, details regarding specific cataract patterns are not provided. The patient described here presented with a bilateral asymmetrical lamellar cataract that was not present at birth and developed in adolescence.

Three reports link congenital cataract to genes at the telomere of the p-arm of chromosome 1.[7-9] Moreover, Jun and colleagues[10] identified Eph receptor A2 (*Epha2*) gene variants, located on chromosome 1p36, that were associated with age-related cortical cataract in 3 different white populations. The same study group[10] demonstrated that Epha2 knockout mice developed progressive cortical cataract. The Epha2 protein is a tyrosine kinase expressed in the cortical lens fiber cells. *Epha2* deletion causes elevated stress responses in the lens, with overexpression of a heat shock protein in an unphosphorylated form, which forms large aggregates with misfolded proteins. This leads to cellular structural damage and eventually to lens opacity.[10]

In conclusion, we report the first case of juvenile-onset bilateral cataract in a patient affected by 1p36 deletion syndrome in the absence of other causative events, such as trauma or medications. It is also the first detailed report regarding cataract pattern, age of onset, and postoperative outcomes. Because some genes on chromosome 1p36 are associated with cataract (congenital, juvenile or age-related), physicians should consider the need for regular eye monitoring in patients with 1p36 deletion syndrome.

Literature Search

PubMed was searched in April 2021 for English-language results using the following terms: *1p36 deletion syndrome*, *1p36 deletion*, *1p36 deletion cataract*, and *1p36 deletion syndrome cataract*.

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Progressive bilateral nuclear cataracts associated with cerebellar-facial-dental syndrome: case report, literature review, and identification of a new genetic variant

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Cerebellar-facial-dental syndrome (CFDS) is a newly described autosomal recessive genetic disorder characterized by mutations in the *BRF1* gene. CFDS is clinically associated with dysmorphic facial features and cerebellar hypoplasia. We report visually significant progressive bilateral nuclear cataracts in a child with CFDS and identify a new causative genetic variant.

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