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Novel retinal observations in a child with DiGeorge (22q11.2 deletion) syndrome

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ABSTRACT

Purpose: DiGeorge (22q11.2 deletion) syndrome is the most common human deletion syndrome with wide range of ocular manifestations. Herein we describe a case with novel retinal observations in this conditions.
Observations: Retinal vascular dysplasia, peripapillary, intraretinal and vitreous hemorrhage were observed in a premature child with DiGeorge syndrome. Vitreous hemorrhage was treated with intravitreal injection of *anti*-angiogenicagents and pars plana vitrectomy surgery. Fundus fluorescein angiography did not confirm leakage of dye from dysplastic retinal vessels.
Conclusions and Importance: Patients with DiGeorge syndrome may develop retinal vascular dysplasia, peripapillary, intraretinal and vitreous hemorrhage.

1. Introduction

Chromosomal microdeletion in 22q11.2 is the most common human deletion syndrome with a prevalence of approximately 1:4000–1:6000 live births.[1] The phenotype of patients with this chromosomal deletion encompasses a number of clinical entities, including DiGeorge syndrome (DGS; MIM#188400) and velocardiofacial (Shprintzen) syndrome (VCFS; MIM#192430). Approximately 90% of patients with features of DiGeorge syndrome have a deletion of chromosome 22.2. The cardinal features of DGS comprise conotruncal heart defects, characteristic dysmorphic facies (unusually shaped ears, long nose with broad bridge, micrognathia and upslanting, short palpebral fissures) and velophryngeal insufficiency or cleft palate. Associated anomalies include absence of thymus, infections and neonatal hypocalcemia. This syndrome is diagnosed using targeted fluorescence in situ hybridization (FISH) testing or by indirect whole-genome studies including high-resolution array-comparative genomic hybridization (CGH) test.[2]

DiGeorge syndrome has a wide range of ocular findings but severe ocular involvement is uncommon. The ocular findings include hypertelorism, telecanthus, eyelid hooding, strabismus, refractive errors and amblyopia, posterior embryotoxon, sclerocornea, autoimmune uveitis, retinal vascular tortuosity.[3–7]

Herein, we report a unique case of a child with DiGeorge syndrome presenting with so far unreported ocular findings including retinal vascular abnormalities with peripapillary, intraretinal and vitreous hemorrhage.

2. Case report

A 27-month-old boy diagnosed with DiGeorge syndrome, born prematurely on week 32, had open heart surgery due to ventriculo-septal defect type I and pulmonary atresia in November 2018. Neonatal fundus examination did not reveal signs of retinopathy of prematurity or retinovascular compromise as a result of his cardiac condition or surgeries. Subsequent computerized tomography scan of his head revealed periventricular leukomalacia and (sub-)cortical atrophy along with calcifications of the basal ganglia with secondary epilepsy. Further neurologic examination revealed pyramidal syndrome, severe encephalopathy with psychomotor delay and swallowing disorder. He suffers from right ventricular failure, bronchopulmonary dysplasia, has gastrostomy and is currently receiving care at medical rehabilitation facility.

He was brought by medical team for ophthalmic evaluation to the Moorfields Eye Hospital Centre in Abu Dhabi, U.A.E in August 2020. Examination took place in supine position to which he is bound. External examination displayed facial dysmorphism including lunar facies, hypertelorism, low-set ears, poor dentation and intermittent exotropia. The eyes slowly followed objects (left eye was slower) and the pressures

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were normal in both eyes. Anterior segment showed presence of tunica vasculosa but clear media and no inflammation. Right eye refraction was −0.50 Sph −3.75 cyl x 10 and left eye was −1.00 Sph −3.50 cyl x 150. Dilated exam showed significant retinal vascular tortuosity in right eye with intraretinal hemorrhage (Fig. 1 upper left). The left eye had dysplastic optic nerve, peripapillary and vitreous hemorrhage precluding more detailed view (Fig. 1 upper right). Ultrasound B-scan of the left eye showed epipapillary structure connecting to the area of vitreous hemorrhage (Fig. 2). Following discussion with Father and signing the consent for off-label use, the patient received an intravitreal injection of ranibizumab in right eye in October 2020. One month later the vitreous hemorrhage was slightly more organized centrally and peripapillary hemorrhage was unchanged. Following second intravitreal injection in November 2020 all retinal hemorrhages disappeared and retinal periphery was now visible (Fig. 1 lower left). For the central vitreous hemorrhage parents wished to proceed with surgical removal. In March 2021, sutureless pars plana vitrectomy with 27-G instrumentation was performed after which clear view to retina has been obtained. The epipapillary structure, presumed a hyaloid artery remnant, was a short fibrotic stalk which did not bleed during removal. This revealed dysplastic optic disc with epipapillary vascularized fibrosis close to distorted retinal vasculature with peripapillary and macular atrophy (Fig. 1 lower right). Following that informed consent was obtained for fundus fluorescein angiography (FFA) to determine the source of prior bleeding. As the peripheral veins were inaccessible, parenteral administration of dye via gastric feeder device was successfully performed (Fig. 3 lower panel). Angiogram showed right vascular tortuosity without leakage and left peripapillary subretinal hyperfluorescent staining and retinal vascular dysplasia without leakage (Fig. 3 upper panels). There is no postoperative cataract or lenticular change, fixation and following of objects have improved following surgery and the patient continues to be monitored.

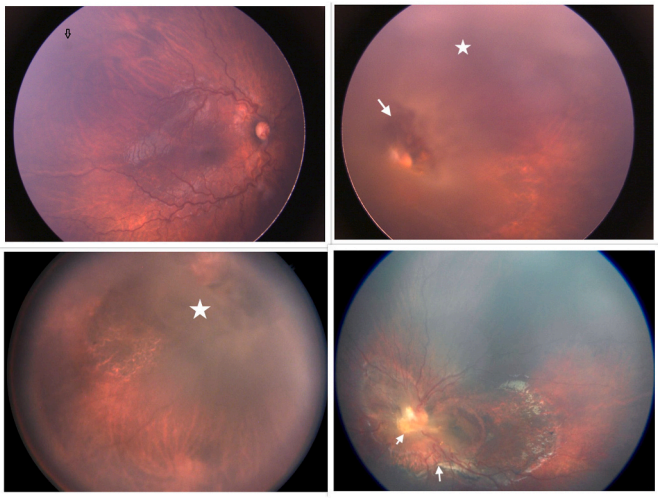

Fig. 1. Upper Left Panel – color fundus photograph of the right eye showing increased retinal vascular tortuosity and an intraretinal hemorrhage (dark arrow). Upper Right Panel - color fundus photograph of the left eye showing diffuse vitreous hemorrhage (white star) and peripapillary hemorrhage (white arrow). Details of the optic nerve head are obscured. Lower Left Panel - color fundus photograph of the left eye following 2 intravitreal injections of ranibizumab showing improved vitreous hemorrhage in the periphery with condensation of hemorrhage centrally (white star). Details of the optic nerve head are obscured. Lower Right Panel - color fundus photograph of the left eye following pars plana vitrectomy showing good retinal view after clearing the vitreous hemorrhage. Optic nerve head shows epipapillary fibrosis (long white arrow). There is distorted retinal vasculature along the inferior arcade and macular and peripapillary atrophy (short white arrow). (For interpretation of the references to color in this figure legend, the reader is referred to the Web version of this article.)

3. Discussion

This reports describes novel observations in DiGeorge syndrome which include retinal vascular dysplasia with peripapillary, intraretinal and vitreous hemorrhage. Intraretinal hemorrhage was bilateral whereas vitreous hemorrhage was unilateral. While DGS can affect various parts of the eye, posterior segment findings have been limited to retinal vessel tortuosity,[3] a case of small optic nerve[7] and another case of optic disc swelling.[8] Bilateral optic disc swelling with transient peripapillary hemorrhage in the latter case was attributed to hypocalcemia.[8]

Retinal vascular tortuosity was previously reported to be present in approximately 24%–75% of patients with velocardiofacial syndrome, and 34%–70% of patients with 22q11.2 deletion syndrome in comparison to much lower prevalence in the general population (6%).[4–7] In a study by Gokturk et al. however, the presence of retinal vascular tortuosity was not correlated with a cardiovascular disease in patients with 22q11.2 deletion syndrome.[6] Our case demonstrated unilateral vascular tortuosity of the retina which does not represent active neovascularization as evidenced by absence of leakage on FFA. Fluorescein angiogram via percutaneous gastric tube is a novel approach in enterically fed bed-bound patient with poor venous access. It seems similar to administration of fluorescein orally with some delay in filling and appearance of early frames but acceptable quality of the images.

It has been suggested that an embryological defect of retinal vessels might be responsible for tortuous retinal vasculature in these patients.[5,7] In experimental studies the absence of the vascular endothelial growth factor $(VEGF)_{164}$ isoform caused birth defects in mice, reminiscent of those found in del22q11 patients (DGS).[9] Moreover, the DGS phenotype was most prominent in mice with severe vascularization defects, possibly indicating that derailed signaling by vascular growth factors may be more important than originally anticipated, and suggesting a vascular etiology underlying DGS.[10] Published data implicate that the $VEGF_{164}$-isoform may represent a candidate disease effector or modifier in the pathogenesis of congenital cardiovascular malformations, and of the del22q11 (DGS) in particular.[9,10] It is, therefore, plausible that this process has taken place in retina of this patient resulting in dysplastic vasculature.

The source of intraretinal bleeding could be defective vasculature due to VEGF dysregulation while the source of vitreous hemorrhage could be the same or the epipapillary vascularized fibrosis or dysplastic vessels visualized following vitrectomy surgery that cleared the media. An additional differential of peripapillary hemorrhage would include presence of choroidal neovascular membrane but this has not has been seen on our FFA examination. Abusive head trauma (shaken baby syndrome) comes to differential but this child has been at rehabilitation facility under care of physician and nursing staff and camera surveillance so this is ruled out. The findings are not typical for sequelae of prematurity or cardiac surgery either. The cause of peripapillary atrophy following resolution of blood remains unclear.

Both central retinal and vitreous hemorrhage are vision threatening conditions. In pediatric age, the presence of central vitreous hemorrhage can be amblyogenic and effort should be made to clear visual axis. Firstly, the hemorrhages are observed for spontaneous resolution. In our case the hemorrhage had no tendency to resolve. We discussed with parents possibility of using intravitreal *anti*-VEGF agent knowing the role of VEGF dysregulation in this condition. Following 2 intravitreal injections the hemorrhage cleared from the periphery but organized centrally in the visual axis precluding detailed view to the posterior pole. Following vitrectomy the structures became clearly visible.

4. Conclusions

Patients with DiGeorge syndrome can develop serious intraocular bleeding complications which can be amenable to treatment. Retinal vascular dysplasia, peripapillary, intraretinal and vitreous hemorrhage are newly described features of DGS. VEGF has been experimentally

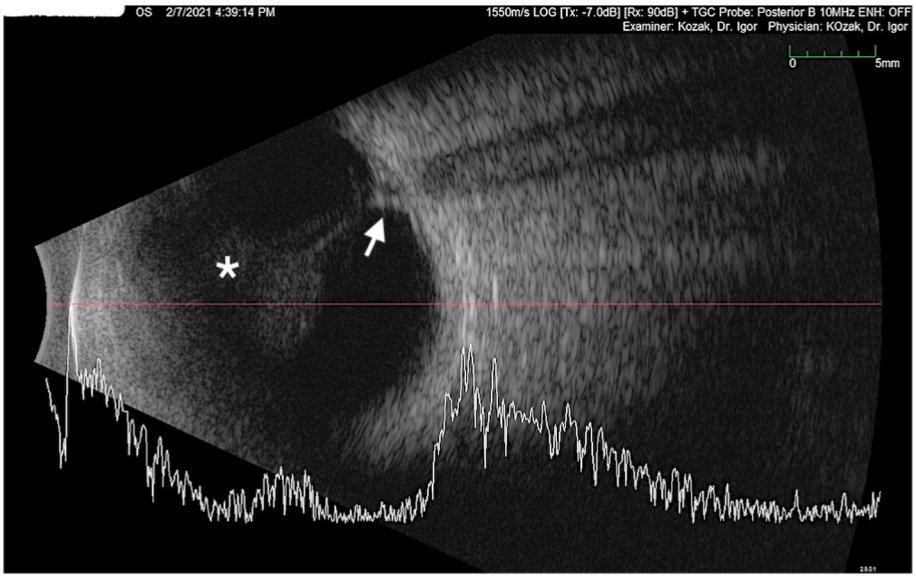

Fig. 2. Ultrasound B-scan of the left eye demonstrates vitreous hemorrhage (white star) and epipapillary structure connected to the vitreous hemorrhage (white arrow).

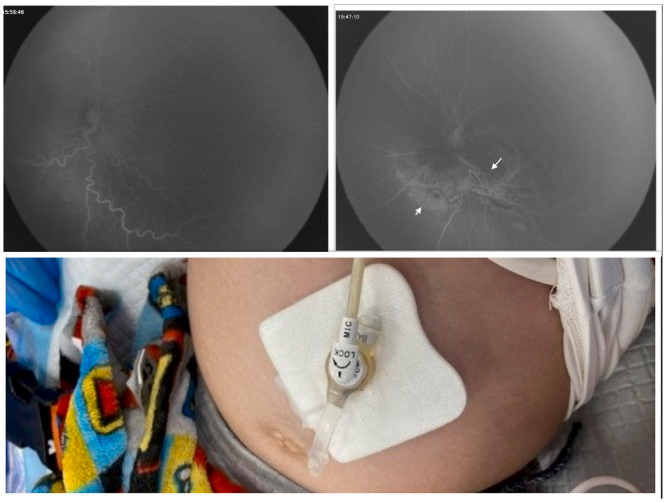

Fig. 3. Upper Left Panel - fundus fluorescein angiogram of the right eye demonstrates severe retinal vascular tortuosity without leakage of dye in late frames. Upper Right Panel - fundus fluorescein angiogram of the left eye demonstrates dysplastic peripapillary vasculature (long white arrow) with subretinal hyperfluorescent staining (short white arrow). There is no leakage of dye in late frames. Lower panel - external photograph showing gastric feeding device through which fluorescein dye was administered for fundus fluorescein angiography.

implicated in various vascular problems in this condition.

Conflicts of interest

None for all authors.

Financial disclosure

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Patient consent

Consent to publish this case report has been obtained from the Father in writing.

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Authorship

All authors attest that they meet the current ICMJE criteria for Authorship.

Declaration of competing interest

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