CASE REPORT

Acute onset of bilateral visual loss during sildenafil therapy in a young infant with congenital heart disease

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SUMMARY

We report a case of posterior non-arteritic ischaemic optic neuropathy (NAION) causing bilateral visual loss in a 7-month-old female infant, after a therapeutic course with sildenafil, a phosphodiesterase type 5 inhibitors (PDE5i). The patient was affected by a complex cyanotic congenital heart defect and had undergone cavopulmonary anastomosis (Glenn operation) 3 months ago. After 2 months of recurring chylothorax, a course of oral sildenafil was administered, with the hypothesis that pulmonary vascular resistances were increased. Approximately 4 weeks later the acute onset of visual worsening and poor pupillary light reflex prompted the diagnosis of posterior NAION. Despite a rapid cessation of PDE5i and systemic treatment with corticosteroids, no visual recovery was noticed at 2-year follow-up. NAION has been associated with PDE5i therapy in adults, but to the best of our knowledge it is almost unheard of in children. We suggest close monitoring of visual function in children undergoing treatment with sildenafil.

BACKGROUND

Phosphodiesterase type 5 (PDE5) inhibitors (PDE5i) are considered standard care in adult patients with arterial pulmonary hypertension (PH), but are also frequently prescribed off-label in children with PH, even though their use remains controversial.[1 2]

Non-arteritic ischaemic optic neuropathy (NAION) may involve the head or the rest of the optic nerve, causing serious visual dysfunction or even blindness.[3] NAION has been described as a potential complication in adults on demand therapy with PDE5i for sexual dysfunction.[4] Clinically, it may manifest as unilateral or bilateral visual loss, which could be either transient or permanent. To the best of our knowledge, this severe adverse event has not been observed in adult cardiopathic patients on PDE5i therapy, while there is just one case described in a 6-year-old girl with multiple congenital cardiac anomalies.[5]

In our patient, NAION was posterior and resulted in complete and persistent bilateral visual loss, strongly believed to be associated with sildenafil treatment.

CASE PRESENTATION

Family history was unremarkable (no ocular problems or autoimmune disease).

The patient had preterm birth for maternal pre-eclampsia (34 weeks gestational age, birth weight 2480 g). At birth an echocardiography confirmed the prenatal diagnosis of double inlet left ventricle, hypoplastic right ventricle, ventricular septal defect and moderate subpulmonary obstruction.

After 3 weeks of uneventful hospital care, the neonate was discharged with satisfactory haemodynamic parameters and about 85% oxygen saturation in room air. Weight at discharge was 2630 g.

Four months after discharge from hospital the patient was becoming tired while feeding. Clinical examination revealed respiratory distress, lower peripheral oxygen saturation in room air (75%) and hepatomegaly. The infant underwent a cardiac catheterisation procedure, which demonstrated she was suitable for cavopulmonary anastomosis: mean pulmonary artery pressure=14 mm Hg, wedge pressure=9 mm Hg, transpulmonary gradient 5 mm Hg and Nakata index 520 mm^2/m^2. On the following day, a Glenn operation was successfully performed.

The postoperative period was, however, characterised by recurrent pleural effusions and chylothorax, treated with multiple drainages, parenteral nutrition, fluid restriction and diuretics, with occasional need for oxygen supplementation. Of note, the weight of the child remained fairly stable before and after the Glenn operation, ranging from 4.2 to 4.5 kg in the following 2 months, suggesting she was not accumulating excessive amount of fluids. Serial echocardiograms performed during her paediatric intensive care unit (PICU) stay showed a patent anastomosis, as well as good function of the left ventricle and atrioventricular valve, with 80% peripheral oxygen saturation. Of note, systemic blood pressure was persistently at 90th–95th centile for age.

After 2 months of constant recurrence of chylothorax, which was refractory to rigid fluid restriction regimen, diuretics and total parenteral nutrition, we began oral sildenafil at 0.2 mg/kg three times a day, with the hypothesis that pulmonary vascular resistances and mean pressure in the Glenn circuit were increased. Although a cardiac catheterisation would have been useful in clarifying this issue, we thought the procedure to be too invasive, given the haemodynamic stability of the child. Thus, we tried sildenafil as an ex juvantibus approach, hoping to promote forward flow into the lungs and reduce any lymphatic 'engorgement'.

In the mean time, no episodes of hypoxaemia were observed.

Approximately 4 weeks later, during daily clinical examination in the PICU a lack of visual focus on

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moving objects was observed, with poor pupillary light reflex. According to the nursing report, the baby had been fretful for a few days.

INVESTIGATIONS

Haematocrit was 31% and haemoglobin 9.5 g/dL. Coagulation parameters were normal. C reactive protein was normal, even though the child was on vancomycin and amikacin for a previous infection (sepsis from *Escherichia coli*, with no haemodynamic instability).

EEG, brain ultrasound, CT scan and MRI including eyeballs, optic nerves, retrobulbar adipose tissue, retrobulbar muscle cones and optic chiasma were unremarkable. A complete ophthalmological examination revealed bilaterally: aimless pendular nystagmus, absent pupillary reflex, transparent crystalline lens, light pallor optic disc, arterial venous tortuous vessels, peripapillary retinal haemorrhages and macular exudation. This was the first ocular examination since her birth. Given the sudden onset of visual loss with optic disc pallor, in the absence of any other ocular, neurological and orbital abnormality, the diagnosis of posterior NAION was made.

DIFFERENTIAL DIAGNOSIS

Sudden vision loss is usually caused by a reduction of the arterial blood flow to the eyes, resulting in temporary or permanent damage. Ischaemia is usually the main cause, due to systemic hypotension and hypertension, inflamed and swollen blood vessel in autoimmune giant cell arteritis, peripheral vascular diseases, vasculitis and increased intracranial pressure. Other causes may be tumour compression, infection or trauma. Among the ischaemic forms, posterior ischaemic optic neuropathy involves the posterior part of the optic nerve and is a cause of acute and painless visual loss, mainly in middle-aged or elderly patients. Apart from the postsurgical type, which is usually linked to prolonged arterial hypotension during main surgical procedures, with visual loss detectable as soon as the patient is awake, ischaemic optic neuropathy can be classified in arteritic (due to giant cell arteritis) and non-arteritic types. In its posterior form, NAION seems to have a multifactorial pathogenesis with different risk factors, including arterial hypertension, diabetes mellitus, ischaemic heart disease, cerebrovascular disease, carotid artery and peripheral vascular disease. Aggressive high-dose systemic steroid therapy in the early stage of posterior NAION can improve visual function, but some untreated patients may show spontaneous improvement in visual acuity and visual field.[3]

TREATMENT

The patient was on sildenafil (0.2 mg/kg three times a day, started 4 weeks before), aspirin, hydrochlorothiazide/spironolactone, furosemide and ranitidine.

As soon as the diagnosis of posterior NAION was made, sildenafil was immediately suspended, while methylprednisolone intravenously (0.5 mg/kg, four times a day) was started, as suggested in the literature.[4] In addition, captopril was introduced for a better control of blood pressure, which however persisted at 90th–95th centile levels for age.

OUTCOME AND FOLLOW-UP

A considerable reduction of retinal haemorrhages, macular exudation and arterial venous tortuosity was noted 1 week later.

Unfortunately, there were no visual evoked potentials after 1 Hz (0.72 J) stimulation.

Approximately 3 weeks following ocular diagnosis the patient was discharged on diuretics, aspirin, captopril and methylprednisolone tapering. Ophthalmological examination revealed a complete reabsorption of retinal haemorrhages and macular exudation, bilaterally.

At 1 year follow-up little visual recovery was noticed, while optic disc subatrophy had worsened bilaterally.

DISCUSSION

To the best of our knowledge, this is the first reported case of serious ocular adverse effect caused by posterior NAION associated with the intake of a PDE5i in a young infant.

The pharmacological action of sildenafil consists of a specific inhibition of the enzyme PDE5.[4]

PDE5 acts on the cyclic guanosine monophosphate pathway and its final effect is mainly vasoconstriction due to increased intracellular calcium and potassium concentrations. PDE5 is expressed in different tissues. In the vascular bed its expression is almost selective on the pulmonary vascular side, with minimal concentration in systemic vessels. This enzyme is responsible for the main vascular remodelling in arterial PH, which includes vasoconstriction, smooth-muscle cells proliferation and vascular wall cells apoptosis. In addition, PDE5 decreases right ventricle contractility.[4 6]

In the ocular system, PDE5i act on PDE5 expressed on retinal and choroid vessels and, to a lesser degree, on PDE6 located on retinal rods and cones.

In 1998, the Food and Drug Administration first approved sildenafil for the treatment of erectile dysfunction, thanks to high-PDE5 concentrations located in the corpus cavernosum.[7] Subsequently, in 2005, sildenafil was approved for the treatment of pulmonary arterial hypertension in adults.[8]

Usually PDE5i are well-tolerated drugs. Most frequent side effects observed in the postmarketing phase include headache, facial flushing, epistaxis, nausea and dyspepsia, while changes in lightness and colour perception have been rarely reported.[9] Occasional serious adverse events associated with sildenafil include central retinal vein occlusion, optic atrophy and cilioretinal artery occlusion.[4] Interestingly, also NAION has been indicated as potentially related to sildenafil use.[4 9]

Eye-related side effects are supposed to be due either to an alteration of the ocular vascular autoregulation or due to relative hypotension.[10] To date, most of the reported cases involve adults, using sildenafil on demand and with concomitant risk factors for NAION, such as diabetes, dyslipidemia, coronary and vascular diseases.[4 9] When related to sildenafil use, NAION has been described as mainly anterior, with unilateral and bilateral eye involvement. In some cases visual acuity may recover after PDE5i suspension.[4] Reassuringly, a recent randomised placebo-controlled study, performed in 277 adults in chronic sildenafil therapy for PH, demonstrated a good ocular safety profile and no detrimental effect on mean intraocular pressure, visual acuity, contrast sensitivity, colour vision and visual field.[11]

Despite that PDE5i are not yet formally approved in the paediatric population, these drugs are frequently used as acute or chronic therapy in severe pulmonary diseases with subsequent PH as well as in congenital heart defects with evidence of PH.[2 12 13]

Our report describes an extremely serious adverse event in a 7--month-old female infant treated with sildenafil, causing bilateral visual loss with no evidence of recovery after drug discontinuation.

The only paediatric case of vision loss likely due to sildenafil treatment was reported in a 6-year-old girl, who was on sildenafil therapy for 15 months after cardiac surgery and developed monocular anterior NAION.[5]

In our case, NAION was bilateral and posterior. Visual acuity has not shown any improvement in the 24 months since treatment was discontinued.

Our patient had no previous ophthalmological examination so we cannot exclude if any optic disturbance was already present, but she had no risk factors for NAION and visual function was suddenly lost after 4 weeks of sildenafil therapy. Despite systemic blood pressure was persistently found at upper normal levels for age, it was constantly monitored and no major events, including hypotensive and severe hypertensive episodes, have been registered during her PICU stay.

We also considered whether Glenn operation could have had any role in this serious complication. Indeed, cavopulmonary anastomosis does alter the rheology of upper limb systemic vein drainage, especially in the first period after the operation, thus potentially influencing blood flow regulation also at the ocular level. Nevertheless, after an extensive review of the literature, we could not find any reported case about ocular adverse effects somehow related with Glenn operation.

As NAION has been already associated with PDE5i use in adults, we speculate that a similar phenomenon could have happened also in our young patient, involving the posterior part of the optic nerve.

We believe this quite alarming case needs to open the discussion about the safety of sildenafil in paediatric patients. Further studies will have to better elucidate the role and indication of an ophthalmological evaluation before PDE5i therapy, as well as the need of a strict follow-up schedule in children undergoing prolonged PDE5i treatment.

Learning points

- Sildenafil, a phosphodiesterase type 5 inhibitor, is an off-label drug in patients under 18 years of age. Despite this, sildenafil is frequently used for pulmonary hypertension in paediatric patients.
- Although very few studies have reported serious visual adverse effects associated with sildenafil in children, there could be a potential risk of sildenafil use in this population.
- Ophthalmological examination may be indicated in infants and children before and during sildenafil treatment for pulmonary hypertension.

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Competing interests None.

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