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Fulminant bilateral papilloedema during low-dose steroid taper in a child with systemic idiopathic arthritis treated with tocilizumab

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ABSTRACT

Systemic juvenile idiopathic arthritis (SJIA) is one of the most severe forms of arthritis that affects children younger than 16 years of age at onset. SJIA often requires corticosteroids to control the inflammation. However, long-term corticosteroid use may have adverse effects, including intracranial hypertension (IH). Biologic therapies have been used as corticosteroid sparing agents. We report the first case of a child with steroid-dependent SJIA treated with tocilizumab, an IL-6 receptor monoclonal antibody, who developed fulminant IH, bilateral papilloedema and vision loss when oral prednisone was weaned from 2 to 1 mg per day. Despite repeated lumbar punctures and high dose acetazolamide, he required urgent unilateral optic nerve sheath fenestration (ONSF). This endoscopic surgical intervention released the pressure exerted by the cerebrospinal fluid on the optic nerve and stopped the progression of vision loss. Nine weeks after the diagnosis of bilateral papilloedema, his vision was completely restored in one eye and partially recovered in the contralateral one.

Long-term treatment with corticosteroids even at very low dose and tocilizumab may predispose to severe IH, papilloedema and vision loss. The role that tocilizumab might have played in this case in unclear. Early recognition and prompt treatment of papilloedema is crucial in avoiding permanent vision loss. Fulminant papilloedema in an immunocompromised child carries additional significant challenges. Early ONSF is a safe and effective intervention in refractory papilloedema. Children with severe papilledema secondary to IH should be managed by a multidisciplinary team in tertiary centres.

Systemic juvenile idiopathic arthritis (SJIA), the most severe form of chronic inflammatory arthritis of childhood, is diagnosed in children younger than 16 years of age (1). Despite several therapies (2), more than half of treated children have persistent disease (3) that often require chronic corticosteroid treatment. Yet, long-term corticosteroid use may lead to intracranial hypertension (IH) (also known as pseudotumor cerebri). More recently, the use of biologic therapies has revolutionised the treatment of childhood arthritis (4, 5). We report the case of a child with steroid-dependent SJIA treated with the anti-IL-6 receptor monoclonal antibody tocilizumab, who developed fulminant bilateral papilloedema and vision loss fifteen days after the oral prednisone was weaned from 2 mg to 1 mg per day. Written consent to present the case was obtained from parents and child.

A nine-year-old boy was diagnosed with SJIA 30 months prior to development of IH. Since SJIA diagnosis, he has been on oral prednisone. In the past, he failed methotrexate and canakinumab. However, in the last fourteen months, his SJIA has been well-controlled with tocilizumab 8 mg/kg every 2 weeks. Thus, for the past year, prednisone has been slowly weaned by 1 mg every 2–3 months.

Fifteen days after prednisone was reduced from 2 mg to 1 mg, the child developed headache, vomiting, dizziness and blurred vision. His neurologic and musculoskeletal exams were normal. Yet, the uncorrected visual acuity (VA) was count fingers in each eye, although two weeks prior, he had a normal ophthalmologic exam. The child had bilateral, florid disc oedema that was confirmed by optical coherence tomography (Fig. 1A). Cerebral magnetic resonance (MR) imaging with gadolinium showed no mass, hydrocephalus or optic neuritis. There was peri-optic nerve sheath oedema (Fig. 1B). MR venogram ruled out clots, and revealed a hypoplastic left transverse venous sinus. Cerebrospinal fluid (CSF) pressure was above 50 cm H_20. CSF, blood cell count, erythrocyte sedimentation rate and C-reactive protein were normal. Toxoplasmosis, Borellia burgdorferi and Bartonella were ruled out. Insulin-like growth hormone and growth hormone levels were normal. Thus, the child was diagnosed with fulminant (onset less than 14 days) IH and papilloedema possibly due to corticosteroid withdrawal. He was started on oral acetazolamide 36 mg/kg/day (500 mg three times per day) and prednisone was increased back at 2 mg daily.

On day 7 of admission, VA was count fingers in the right eye and 20/400 in the left eye. Repeat CSF opening pressure was still high at 47 cm H_20. Although there was some improvement in macular oedema and the residual macular stars (Fig. 1C), the persistency of IH and severity of visual impairment demanded urgent surgical intervention. On day 11, the child underwent right endoscopic optic nerve sheath fenestration (ONSF) with stereotactic neuronavigation. Two days later, the VA improved to 20/400 in the right and 20/80 in the left eye. The CSF opening pressure was normal (20 cm H_2O). He was discharged home on prednisone 2 mg per day, acetazolamide and tocilizumab 8 mg/kg every 2 weeks. Six weeks later, VA was unchanged in the right eye (20/400) but further improved in the left eye (20/30). There was minimal bilateral disc oedema (Fig. 1D). Nine weeks after admission, VA was 20/200 in the right and 20/25+1 in the left eye. Acetazolamide was discontinued after 3 months. Tocilizumab was decreased to every 4 weeks without return of papilloedema after 1 year of follow-up.

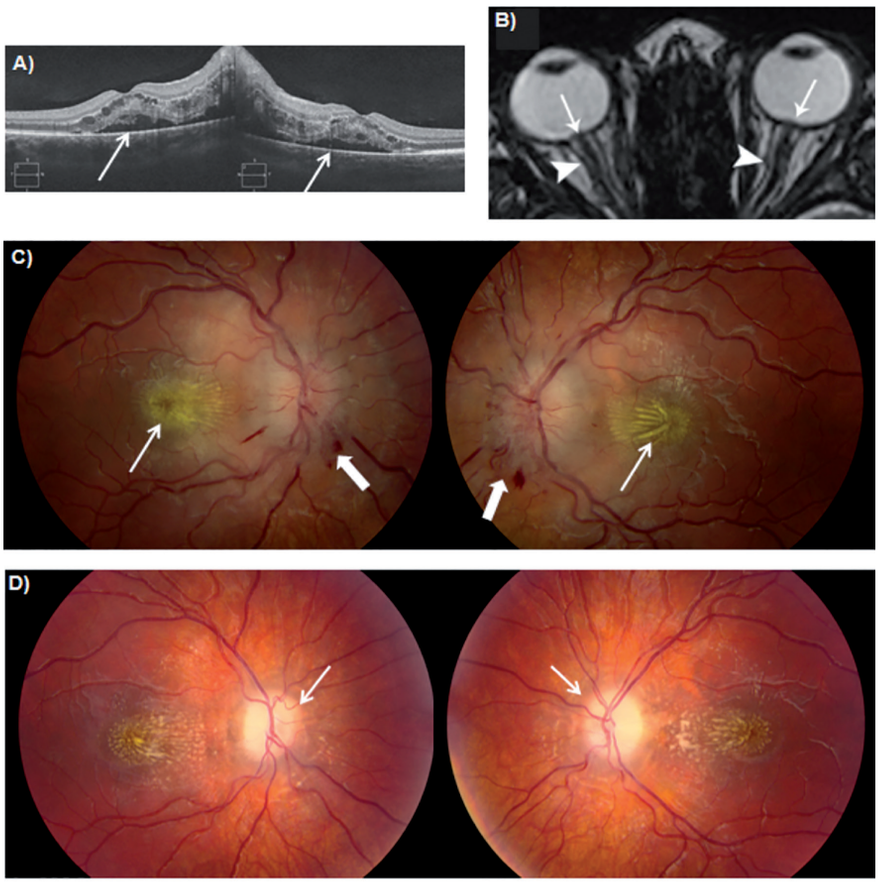

Fig. 1. Optical coherence tomography (OCT) of the retina and MRI of the optic nerves in a child with systemic idiopathic juvenile arthritis and fulminant bilateral papilloedema **A**: OCT demonstrated severe bilateral subretinal and intraretinal oedema (*arrows*); **B**: Axial T2-weighted MRI of the orbits (*arrows*) showed increased cerebrospinal fluid within the optic nerve sheaths (*arrowheads*); **C**: Bilateral macular stars (*arrows*) and papilloedema with disc haemorrhages (*block arrows*) at presentation; **D**: Bilateral disc pallor (*arrows*) after 6 weeks of follow-up.

Discussion and conclusions

This is the first report of a child with steroid-dependent SJIA on long-term tocilizumab who developed fulminant bilateral papilloedema and IH when prednisone was tapered from 2 mg to 1mg. He required urgent ONSF to halt the progression of vision loss.

It was shown that chronic corticosteroid treatment can predispose to IH both at high-dose and during tapering (6), including in SJIA (7). However, IH occurring at very low dose of corticosteroids has not been reported yet.

It is unclear if tocilizumab may have contributed to IH. Yet, IH was reported in a child with polyarticular JIA treated with tocilizumab (8). Tocilizumab blocks IL-6 binding to IL-6R and soluble IL-6. Blockage of IL-6R in a few adults with rheumatoid arthritis and a patient with a novel IL-6-mediated autoinflammatory disease led to IL-6 elevation in serum (9) and CSF, respectively (10). As IL-6 can cross blood-brain barrier (11) and acts on endothelial cells, it may increase the CSF volume.

Moreover, the hypoplastic left transverse venous sinus may have played a role in the development of IH in our child, as intracerebral haemodynamic homeostasis requires dynamic venous adaptation to maintain the CSF volume. Childhood IH is rare. In Canada, the annual incidence of IH is 0.6–0.9 per 100,000 children (12). As the symptoms of IH are non-specific (headache, double vision, nausea and vomiting), other causes of IH need to be excluded, such as cerebral infections, masses and clots, hydrocephalus, excessive weight, certain medications and chronic illnesses. Importantly, males with high grade papilloedema and severe vision loss at presentation have worse visual prognosis (13).

Acetazolamide, topiramate and furosemide have been used to treat IH (14). Although treatment with high dose methylprednisolone has been reported in a few patients with pseudotumour cerebri (15), this was not an option in our child due to risk of rebound IH on subsequent taper of prednisone.

Treatment of refractory papilloedema includes optic nerve sheath fenestration (ONSF), CSF shunting or venous sinus stenting. However, CSF shunting can lead to shunt obstruction and infection. This approach would have posed a high risk in our immunocompromised child. Unilateral ONSF can improve optic disc oedema in both eyes (16) and alleviate other symptoms of IH. This surgical intervention was effective in our child.

To avoid irreversible vision loss due to unrecognised, rapidly progressive papilloedema, we suggest that an urgent eye exam is warranted in children with SJIA on corticosteroids and tocilizumab who developed symptoms of IH. These children should be managed by multidisciplinary teams in tertiary centres.

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References

1. PETTY RE, SOUTHWOOD TR, MANNERS P *et al*.; INTERNATIONAL LEAGUE OF ASSOCIATIONS FOR R: International League of Associations for Rheumatology classification of juvenile idiopathic arthritis: second revision, Edmonton, 2001. *J Rheumatol* 2004; 31: 390-2.
2. KOSTIK MM, GAIDAR EV, HYNNES AY *et al*.: Methotrexate treatment may prevent uveitis onset in patients with juvenile idiopathic arthritis: experiences and subgroup analysis in a cohort with frequent methotrexate use. *Clin Exp Rheumatol* 2016; 34: 714-8.
3. SINGH-GREWAL D, SCHNEIDER R, BAYER N, FELDMAN BM: Predictors of disease course and remission in systemic juvenile idiopathic arthritis: significance of early clinical and laboratory features. *Arthritis Rheum* 2006; 54: 1595-601.
4. DE BENEDETTI F, BRUNNER HI, RUPERTO N *et al*.: Randomized trial of tocilizumab in systemic juvenile idiopathic arthritis. *N Engl J Med* 2012; 367: 2385-95.
5. PASCUAL V, ALLANTAZ F, ARCE E, PUNARO M, BANCHEREAU J: Role of interleukin-1 (IL-1) in the pathogenesis of systemic onset juvenile idiopathic arthritis and clinical response to IL-1 blockade. *J Exp Med* 2005; 201: 1479-86.
6. LEVINE A, WATEMBERG N, HAGER H, BUJANOVER Y, BALLIN A, LERMAN-SAGIE T: Benign intracranial hypertension associated with budesonide treatment in children with Crohn's disease. *J Child Neurol* 2001; 16: 458-61.
7. WANIGASINGH J, LUCAS M N, JAYANETTH S, P LS: Idiopathic intracranial hypertension in a child being treated for systemic onset juvenile idiopathic arthritis. *Sri Lanka Journal of Child Health* 2010; 39: 115-6.
8. BRUNNER HI, RUPERTO N, ZUBER Z *et al*.; PAEDIATRIC RHEUMATOLOGY INTERNATIONAL TRIALS ORGANISATION P, PEDIATRIC RHEUMATOLOGY COLLABORATIVE STUDY G: Efficacy and safety of tocilizumab in patients with polyarticular-course juvenile idiopathic arthritis: results from a phase 3, randomised, double-blind withdrawal trial. *Ann Rheum Dis* 2015; 74: 1110-7.
9. NISHIMOTO N, TERAO K, MIMA T, NAKAHARA H, TAKAGI N, KAKEHI T: Mechanisms and pathologic significances in increase in serum interleukin-6 (IL-6) and soluble IL-6 receptor after administration of an anti-IL-6 receptor antibody, tocilizumab, in patients with rheumatoid arthritis and Castleman disease. *Blood* 2008; 112: 3959-64.
10. SALSANO E, RIZZO A, BEDINI G *et al*.: An autoinflammatory neurological disease due to interleukin 6 hypersecretion. *J Neuroinflammation* 2013; 10: 29.
11. BANKS WA, KASTIN AJ, GUTIERREZ EG: Penetration of interleukin-6 across the murine blood-brain barrier. *Neurosci Lett* 1994; 179: 53-6.
12. BURSZTYN LL, SHARAN S, WALSH L, LAROCHE GR, ROBITAILLE J, DE BECKER I: Has rising pediatric obesity increased the incidence of idiopathic intracranial hypertension in children? *Can J Ophthalmol* 2014; 49: 87-91.
13. WALL M, FALARDEAU J, FLETCHER WA *et al*.; GROUP NIIHS: Risk factors for poor visual outcome in patients with idiopathic intracranial hypertension. *Neurology* 2015; 85: 799-805.
14. KO MW, LIU GT: Pediatric idiopathic intracranial hypertension (pseudotumor cerebri). *Horm Res Paediat*r 2010; 74: 381-9.
15. LIU GT, GLASER JS, SCHATZ NJ: High-dose methylprednisolone and acetazolamide for visual loss in pseudotumor cerebri. *Am J Ophthalmol* 1994; 118: 88-96.
16. ALSUHAIBANI AH, CARTER KD, NERAD JA, LEE AG: Effect of optic nerve sheath fenestration on papilledema of the operated and the contralateral nonoperated eyes in idiopathic intracranial hypertension. *Ophthalmology* 2011; 118: 412-4.