Instructive Case:

Acute Bilateral Myopia Caused by Lamotrigine Induced Uveal Effusions

A 14 year old girl presented to the Emergency Department with blurred vision two months after commencing Lamotrigine due to a new diagnosis of Juvenile Absence Epilepsy. She had no other significant active or past medical history. An MRI brain performed electively two weeks prior to presentation for investigation of headaches and seizures was normal with normal orbital views.

She initially complained of blurred vision in her left eye that did not impede her evening activities. The following morning she woke with bilateral blurred vision. On presentation to the emergency department her visual acuity was 6/60 on right with pinhole improvement to 6/9 and she was limited to counting fingers on left, again with an improvement using a pin hole to 6/12. There was no relative afferent pupillary defect and colour vision testing was normal, with Ishihara fifteen plates correct. Her eye movements were normal and corneas were clear with no keratoconus, anterior chambers appeared equally deep and non-inflamed. Intraocular pressures were right 21mmHg left 19mmHg (iCare tonometry) and healthy normal ocular media bilaterally. Her central retina and optic discs were all healthy and there was no evidence of papilloedema. Following cycloplegia with cyclopentolate 1% retinoscopy revealed myopia right -2.50 DS and left -3.00 DS.

On general examination there was significant painless, hard lymphadenopathy in the posterior cervical chains that the teenager had reported being present for one month. There was no further lymphadenopathy or hepatosplenomegaly.

Due to the temporal relationship to the commencement of lamotrigine, a drug reaction was suspected. Lamotrigine was ceased and valproate was commenced in its place.

Within 48 hours of lamotrigine cessation her visual acuity returned to unaided 6/6 bilaterally. The significant cervical lymphadenopathy also rapidly resolved. An eye ultrasound performed one month after her initial presentation and once her vision had returned to normal, was normal. The expected mechanism was a sudden induced myopia secondary to lamotrigine causing uveal effusions.

Discussion:

Lamotrigine is a sodium channel blocker that interacts with the alpha pore-forming subunit of voltage-sensitive sodium channels and inhibits glutamate release¹. It is a frequently used broad-spectrum AED that is effective in the treatment of both focal and generalised epilepsies². In young women lamotrigine is often the first-line medication due to the known teratogenicity of sodium valproate³. Well recognised side effects of lamotrigine include a skin rash and hypersensitivity syndrome that can be severe and in some cases life threatening⁴. Blurred vision and diplopia have also previously been reported as a rare adverse effect of lamotrigine use⁴. Acute onset myopia as a result of uveal effusions has not previously been reported with lamotrigine use. Localised lymphadenopathy, a likely hypersensitivity reaction, has previously been reported as an adverse effect of lamotrigine use in a case reports.⁵ The presence of the lymphadenopathy in this case could suggest the presence of a more systemic hypersensitivity reaction, of which the visual loss is a consequence.

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The presumed mechanism of visual loss in this case was uveal effusions. Unfortunately, uveal ultrasound was not performed during the acute presentation and so the exact mechanism cannot be confirmed.

Hydrostatic uveal effusions are recognised to be caused by some medications and indeed some AEDs. Several case reports have shown that topiramate use is associated with an increased risk of developing ocular adverse effects such as uveal effusions^{6,7}. However, lamotrigine is not known to be associated. Uveal effusions consist of a transudative fluid that has leaked into the choroid from the choriocapillaris. This transudate can cause engorgement of the choroid. It can be associated with serous retinal detachments due to sub-retinal fluid build-up⁸. The exact mechanism by which the medications cause the effusion is not known, but failure of the physiological mechanisms to reabsorb the excess protein is a likely causative process. This may be due to vortex vein compression. Alternatively, if there is interruption of the transscleral hydrostatic water movement and albumin diffusion or the bulk flow around the scleral emissaria the usual physiological reabsorption is unlikely to occur effectively⁸. Several theories have suggested the causation of uveal effusions and these include: a reduction in the permeability of the sclera to proteins; compression of the vortex veins; alterations to the hydraulic conductivity of the sclera; inflammatory changes in the choroid; or increased blood vessel permeability within the choroid⁸. In the context of lymphadenopathy an inflammatory process has to be considered to be high amongst the potential pathophysiological mechanisms.

Uveal effusions have the effect of causing swelling and anterior rotation of the ciliary body. This shallows the anterior chamber and forward displaces the lens-iris diaphragm⁷. This causes myopia and in some cases is sufficient to obstruct aqueous access to the anterior chamber angle and cause acute angle closure glaucoma. Removal of topiramate therapy has been shown to result in resolution of the ocular symptoms⁷.

In our patient with acute myopia after withdrawal of lamotrigine, her visual acuity returned to normal within 48 hours. It is therefore likely that the mechanism of the acute onset myopia in our patient had a similar causative mechanism as those hypothesised for topiramate. The lack of raised intraocular pressure, corneal oedema and the painless nature of the case exclude angle closure as the cause of the visual change. Accommodative spasm could also present in a similar way, but a lack of resolution of blur after cycloplegia excludes this differential diagnosis.

This case represents to our knowledge the first known report of suspected uveal effusions causing acute reversible myopia as a result of lamotrigine use. Due to the apparent reversibility if recognised early, prescribers should be aware of this very rare adverse effect of a commonly prescribed AED.

Multiple Choice Questions:

1. Which anti-epileptic medication would routinely be considered to be the first line therapy for a 16 year old female with an idiopathic generalized epilepsy?
 - a. Carbamazepine
 - b. Sodium Valproate
 - c. Lamotrigine
 - d. Topiramate
 - e. Levetiracetam

Answer: c. Lamotrigine. Although an argument could be made by many that low doses of sodium valproate would be the most effective anti-epileptic medication to control seizures in the context of idiopathic generalized epilepsy, the concerns regarding risks of teratogenicity has put many clinicians prescribing valproate in this context. It is now widely recognized that Lamotrigine would be considered to be first line therapy in this context.

2. What is thought to be the pathophysiology causing the well-recognised phenomenon of topiramate induced reversible myopia?
- Accommodative spasm
 - Papilloedema secondary to raised intracranial hypertension
 - Acute angle glaucoma
 - Uveal Effusions
 - None of the above

Answer: d. Topiramate use is associated with an increased risk of developing uveal effusions

3. In the context of a suspected unwanted drug-induced reaction, what should the treating clinician do?
- Reassure the patient and take no further action
 - Stop the medication and take no further action
 - Stop the medication, review the patient in a few days and depending upon severity of the reaction consider trial of restarting medications to see if recurrence of symptoms
 - Refer to a colleague for a second opinion.

Answer: c. In the context of a suspected unwanted drug-induced reaction, the medication should be stopped and the patient reviewed a few days later. It could then be re-introduced at a lower dose with slower increments if deemed safe to do so. (Riedl et al. *Adverse Drug Reactions: Types and Treatment options. Am Fam Physician* 2003;68(9):1781-91)

Learning Points:

- Acute myopia is a reasonably common cause for presentation to the Emergency Department and common differentials would include acute angle glaucoma and accommodative spasm.
- Drug-induced myopia has been described with topiramate use before.
- Lamotrigine-induced acute myopia has not previously been described
- This case illustrates that it is lamotrigine induced myopia should be considered as a rare cause of drug induced myopia
- In patients presenting with acute symptoms, even in those not previously linked to medication use, drug-induced side effects should be on the list of potential differential diagnoses.

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