Nicorandil induced ophthalmoplegic migraine

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DECLARATIONS

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This report describes a patient who developed an ophthalmoplegic 'migraine' with an isolated sixth nerve palsy after commencing nicorandil for exertional angina, with complete resolution on cessation of nicorandil.

Case Presentation

A previously healthy 45-year-old male patient seen in the Chest Pain Clinic giving a classical history for angina having developed exertional central chest/left arm discomfort while training for a marathon. He had a past history of infrequent migraines but nil else of note. He had a family history of ischaemic heart disease in first degree relatives and was an ex-smoker, he was just on aspirin.

Physical examination showed no clinical abnormality, with a BMI of 24, BP was 135/60 mmHg and HR 58 bpm. Resting ECG showed sinus rhythm and an exercise stress test was stopped prematurely because of ST depression in anterior leads, achieving Bruce protocol of 10.4 mets before experiencing exertional chest pain. A diagnosis of exertional angina was made and an outpatient coronary angiogram was requested. Given his good history of angina, he was prescribed simvastatin 40 mg nocte (with initial pretreatment total cholesterol of 4.7 mmol/L and LDL 3.0 mmol/L) and nicorandil 10 mg twice daily, which he started 4 days later.

The patient developed a headache immediately on starting nicorandil, which at times was extremely severe, having some 'thunderclap' elements. This resulted in him being admitted 6 days after starting his nicorandil. The headache was bilateral in nature, no preceding aura or flashing lights and no abdominal symptoms, however he did have double vision for 2 days preceding the admission. Clinical examination showed a total left 6th nerve palsy and no other abnormal findings (Figures 1, 2 and 3). Blood pressure on admission was 138/70 mmHg. Investigations for his headache showed a normal CT head, MRI brain and MRA head/neck (including post-gadolinium). Lumbar puncture was performed to exclude a subarrachnoid haemorrhage, opening pressure was 9 cm H2O and there was no xathochromia. An autoimmune profile to exclude vasculitidies was also normal (Rheumatoid factor negative, ANA negative and ANCA negative). Clinical review by consultant ophthalmologists and neurologists confirmed a severe isolated sixth nerve palsy (Figure 1).

His nicorandil was stopped whilst he was an inpatient, simvastatin was continued as it was not felt to be causal in his symptoms. The sixth nerve palsy fully resolved within 6 weeks with no further ophthalmoplegic symptoms and the patient has had no further headache. He went on to have a successful coronary angioplasty for a very tight stenosis to his proximal LAD and was commenced on dual anti-platelet therapy.

Discussion

This case demonstrates that a severe headache associated with a 6th nerve palsy can be related to nicorandil therapy, as our patient developed these symptoms immediately on the commencement of nicorandil. The International Headache Classification describes ophthalmoplegic migraine as 'recurrent attacks of headache with migrainous characteristics associated with paresis of one or

Figure 1
Full patient consent is documented in the patient case notes. Primary position

Figure 3
Full patient consent is documented in the patient case notes. Looking right

more ocular cranial nerves in the absence of any demonstrable intracranial lesion other than MRI changes within the affected nerve'.[1] Our patient has had a single episode with many uncharacteristic headache features for migraine but occurring in a patient with a background history of mild migraine.

Ophthalmoplegic migraine is more commonly seen in children – having two or more episodes of migraine associated with an isolated nerve palsy. In children, the most common nerve to be affected is the oculomotor (3rd) nerve in the majority of cases, whereas in adults, the most commonly affected nerve is the 6th nerve, causing 35% of isolated nerve palsies with migraine.[2,3] There are a few published case reports of drug-induced isolated sixth nerve palsies, induced by vincristine therapy,[4] influenza vaccine,[5] and bevacizumab,[6] demonstrating that pharmacological agents can precipitate this syndrome.

Figure 2
Full patient consent is documented in the patient case notes. Looking left

The potential mechanism for nicorandil, a potassium channel activator, to cause a 6th nerve palsy may be its' arterial or venous dilation action.[7] The vasodilatation action could have caused a temporary compression or ischaemia of the sixth nerve in the region of the internal carotid artery and the cavernous sinus, which resulted in a temporary lateral rectus palsy. A further possibility is that nicorandil caused micro-inflammatory nodules within the tract of the 6th nerve. Nicorandil causes isolated anal ulceration[8] due to micro-inflammatory nodules which resolve on cessation of nicorandil therapy. Whether this process is a systemic manifestation of inflammation related to nicroandil would need histology. The delay of four days between commencing treatment and developing neurological problems may reflect a cellular response of perhaps a certain fluctuating intensity in the headache which resulted in the development of the palsy.

In summary this case for the first time illustrates that nicorandil, a widely prescribed anti-anginal medication, with a well known side effect of causing headache can be associated with 6th nerve cranial palsy which in our patient had a benign outcome.

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