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Case Report

Osteogenesis Imperfecta Presented with Aneurysmal Subarachnoid Hemorrhage, Complicated by Vasospasm and Treated with Intravenous Milrinone

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Abstract

Background: Osteogenesis Imperfecta (OI) is a rare inherited collagen disease of variable severity. Our patient was diagnosed with OI prior to aneurysmal Subarachnoid Hemorrhage (aSAH) occurrence. To our knowledge, this is the first case report of an OI patient with SAH associated vasospasm treated with milrinone.

Case Presentation: A 35 year old female - known for OI - was brought to the Neuro-critical care unit after being intubated for generalized tonic-clonic seizure. A CT/CTA of the brain revealed acute aSAH due to basilar artery aneurysmal rupture, with early hydrocephalus. An External Ventricular Drain (EVD) was installed and the aneurysm was coiled the next day. Two days later her Glasgow Comma Scale (GCS) was back to 15/15. Ten Days post aSAH she became obtunded, with right arm weakness. Transcranial Doppler confirmed the diagnosis of vasospasm. She received IV Mi-lrinone and regained her level of consciousness and power. Her modified Rankin Score (mRS) was 1 at time of discharge and 0 three months later. To our knowledge, this is the first case report of OI treated (successfully) using IV milrinone for cerebral vasospasm after aSAH.

Conclusion: Cerebral vasospasm after aSAH has been known to occur in OI. Here we present a patient with OI who developed vasospasm related deficit that responded well to IV Milrinone, with good outcome based on mRS.

Introduction

OI is a rare hereditary collagen disease involving type 1 collagen that can be recognized clinically by skeletal and extra-skeletal manifestations. These include blue sclera, decreased level of hearing and hyper-elasticity of the liga-ments and skin [1]. Clinical manifestations of the disease vary from asymptomatic to multiple fractures and even perinatal death [2]. Aneurysmal SAH (aSAH) in OI has been reported [3].

Case presentation

Our patient is a 35 year old female with genetically proven type I OI: multiple lower extremities fractures - blue-tinged sclera and hyper elastic joints. She collapsed at home, and was brought to hospital where she was intubated because of multiple witnessed seizures and a decreased level of consciousness (7/15 on GCS). She was started on Phenytoin and admitted to the neuro-critical care unit. Computed Tomography (CT) of the brain showed an acute subarachnoid hemorrhage, mainly in the basal cisterns, figure 1. Conventional angiography revealed a basilar artery aneurysm, 13.5 mm x 8 mm x 8.8 mm, with a neck of approximately 5.6mm. As well, there were signs of dysplasia of the basilar artery, figure 2. The aneurysm was coiled, with 90% occlusion achieved, figure 3. Two days later the patient had a normal level of consciousness and neurological exam. On day 10 post aSAH, she developed an acute drop of her level of consciousness (GCS11/15) with right sided weakness. Trans-cranial Doppler Ultrasound (TCD) showed an increased mean peak systolic velocity in the left middle cerebral artery (177 cm/s) and internal carotid artery (39 cm/s) with an abnormal MCA/ICA index (4.53) compared to the baseline (127.1 cm/s, 44.2 cm/s and 2.9 respectively) and to the right ICA/MCA. Intravenous Milrinone was initiated, with a loading dose of 0.05 mg/kg followed by continuous infusion of 75 mcg/kg/min. Over the following 20 minutes she regained her level of consciousness, and the power on the right side recovered to 4+/5 on the Medical Research Council (MRC) scale. Follow up CT/CTA showed no hypo-densities and no

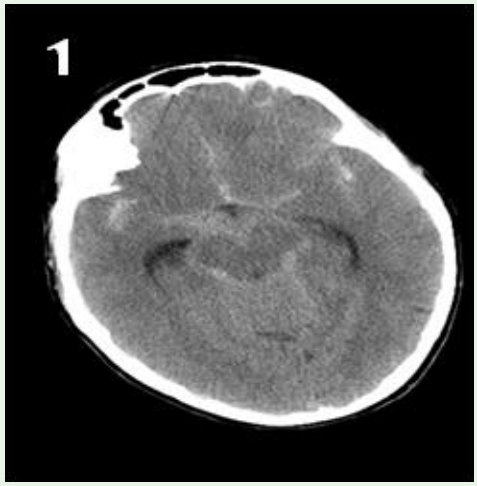

Figure 1: CT Head demonstrating diffuse SAH.

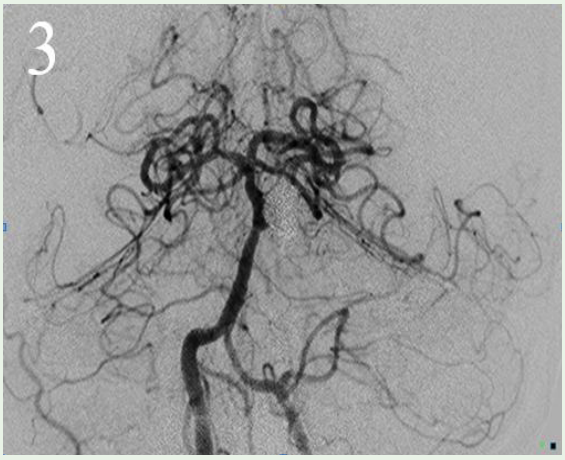

Figure 3: AP view of digital subtracted angiography shows near complete occlusion of the aneurysm.

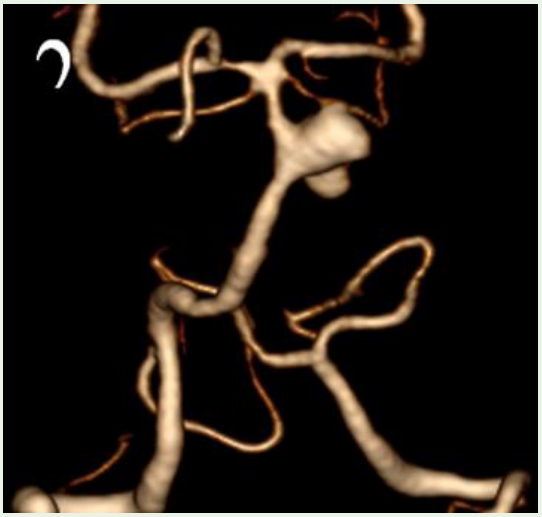

Figure 2: CTA COW demonstrating a 3D reconstructed image of the posterior circulation. The basilar artery is tortuous and dysplastic, on its mid segment there is a broad based multi-lobed aneurysm.

vasospasm respectively. Intravenous Milrinone infusion continued for a total of 7 days with tapering by 0.25 mcg/kg/min every two days according to the Montreal Neurological hospital (MNH) protocol for treatment of vasospasm. The patient spent 18 days in the NICU. Her modified Rankin Scale at time of discharge was 1, and three months later was 0.

Discussion

OI is a group of hereditary diseases affecting the production and quality of type I collagen. A mutated gene encoding a component or modifier of the Type 1 collagen triple helix is responsible for the disease. Although the clinical manifestations may vary, the most common manifestations are bone fractures, growth retardation, blue sclera and hearing abnormalities. Bone fracture can be idiopathic on presentation or due to mild trauma. The Sillence and colleagues classification is widely used, and distinguishes four clinical types of OI, table 1 [4]. In OI type 1, the mutant chain is unable to incorporate itself into the collagen triple helix (probably due to steric hindrance caused by aberrant amino acid interaction) [5]. This unincorporated chain is proteolytically degraded, thereby placing heavy reliance on the non-mutated allele to produce a structurally weaker triple

Table 1: Expanded Sillence classification of osteogenesis imperfecta [Taken with permission].

Type	Clinical severity	Typical features	Typically associated mutations*
I	Mild non-defonning osteogenesis imperfecta	Normal height or mild short stature; blue sclera; no dentinogenesis imperfecta	Premature stop colon in COL1A1
II	Perinatal lethal	Multiple rib and long-bone fractures at birth; pronounced deformities; broad long bones; low density of skull bones on radiographs; dark sclera	Glycine substitutions in COL1A1 or COL1A2
III	Severely deforming	Very short; triangular face; severe scoliosis; greyish sclera; dentinogenesis imperfecta	Glycine substitutions in COL1A1 or COL1A2
IV	Moderately deforming	Moderately short; mild to moderate scoliosis; greyish or white sclera; dentinogenesis imperfecta	Glycine substitutions in COL1A1 or COL1A2
V	Moderately deforming	Mild to moderate short stature; dislocation of radial head; mineralized interosseous membrane; hyperplastic callus; white sclera; no dentinogenesis imperfecta	IFITM5
VI	Moderately to severely deforming	Moderately short; scoliosis, accumulation of osteoid in bone tissue, fish-scale pattern of bone lamellation; white sclera; no dentinogenesis imperfecta	SERPINF1
VII	Moderately deforming	VII Mild short stature; short humeri and femora; coxa vara; white sclera; no dentinogenesis imperfecta	CRTAP

*May or may not be detectable in a given patient.

helix. The result is type I collagen that is structurally correct but in much smaller quantities. Extra-skeletal manifestations in type 1 OI include blue-tinged sclera, progressive hearing loss due to damage of the ossicle of the middle ear, hyper-elasticity of the skin and joints and dentinogenesis imperfecta (opalescent teeth). These patients are also often of short stature. The neurologic complications mostly concern skeletal disorders, and the most striking finding is basilar invagination. Intracranial hemorrhage caused by mirror trauma can also occur. OI is associated with type I collagen abnormalities: marked decrease in collagen levels can cause vascular complications such as aortic and cervical artery dissection, carotid cavernous fistula, and ulnar and coronary artery aneurysms. Unlike other connective tissue diseases, the cerebrovascular system is less frequently involved in OI.1 Subarachnoid hemorrhage secondary to ruptured cerebral aneurysm is reported in only 3 cases [6,7,8]. Yet type I collagen is the major extracellular component of the cerebral arterial wall, with a structural role, and is mainly expressed in the adventitia. It would therefore seem reasonable that increased vessel fragility would lead to aneurysm formation and rupture. Milrinone is part of the MNH protocol for the treatment of Delayed Ischemic Neurologic Deficit (DIND) due to vasospasm, which consists of euvolemia, normo tension and IV Milrinone [9]. Milrinone is a selective phosphodiesterase type 3 (PDE-3) inhibitor, inhibiting cAMP-Dependent Phosphodiesterase (PDE). In the heart, increasing the intracellular concentration of c-AMP increases both myocardial contractility and heart rate. In smooth muscle, Milrinone increases cAMP and inhibits the enzyme myosin light chain kinase, responsible for phosphorylation of smooth muscle myosin. Smooth muscle myosin is responsible for smooth muscle contraction, and the administration of Milrinone is thought to result in smooth muscle relaxation and vasodilatation. As mentioned, collagen type I is the most abundant of the collagen fibrils and is found in all three tunicae and especially around the smooth muscle cells of the media, where they provide the scaffold necessary for mechanical strength and contractility [10]. We postulated that Milrinone would still work in OI type DIND because the collagen that is still present is normal, even though the amounts are decreased. Also, the usual mutation in these cases is within the COL1A1 gene, and not the COL1A2 involved in the more lethal types. To our knowledge this is the first case report of a patient with type 1 OI presenting with aSAH complicated by vasospasm, and successfully treated with IV milrinone.

Conclusion

Despite a decrease in the amount of collagen type 1 found in type 1 OI, the collagen present in the cerebral vessels is normal, and the latter seem to have responded to Milrinone, a phosphodiesterase 3 inhibitor, during aSAH-related symptomatic vasospasm. This is the first report of vasospasm treated with milrinone in an OI patient. Treatment in this case was successful.

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