Rare disease

Osteogenesis imperfecta presenting as aneurysmal subarachnoid haemorrhage in a 53-year-old man

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Summary

The authors describe a case of aneurysmal subarachnoid haemorrhage in a 53-year-old man with background of osteogenesis imperfecta (OI). CT brain revealed diffuse subarachnoid haemorrhage (SAH) and cerebral angiogram subsequently confirmed vertebral artery aneurysm rupture leading to SAH. To the authors knowledge this is the first case of vertebral artery aneurysmal SAH described in OI. A previously undiagnosed OI was confirmed by genetic analysis (COL1A1 gene mutation). This aneurysm was successfully treated by endovascular route. Post interventional treatment patient developed stroke secondary to vasospasm. Communicating hydrocephalus, which developed in the process of management, was successfully treated with ventriculo-peritoneal shunt. The aetio-pathogenesis and management of this condition is described. The authors have reviewed the literature and genetic basis of this disease.

BACKGROUND

Aneurysmal subarachnoid haemorrhage (SAH) is known to occur in osteogenesis imperfecta (OI). Our patient had a vertebral artery fusiform aneurysm that ruptured leading to SAH. To our knowledge this is the first case of vertebral artery aneurysmal rupture leading to SAH in OI type 1. The patient had blue sclera on physical examination associated with deformed long bones. An otherwise undiagnosed OI was brought to light with the SAH. Genetic analysis confirmed COL1A1 gene mutation conforming the diagnosis of OI. This rare condition was managed by endovascular route successfully.

CASE PRESENTATION

We describe the case of a 53-year-old man who was admitted to his local hospital after an episode of collapse. He had no known background medical illnesses. His Glasgow Coma Scale (GCS) was 8/15 at admission, which improved to 15/15. His neurological examination was normal. CT scan of brain revealed a Fisher grade 4 SAH with early hydrocephalus (figure 1). CT angiogram performed subsequently showed a right V4 segment fusiform aneurysm distal to the origin of posterior inferior cerebellar artery (figure 2).

A technically difficult stent assisted coiling of the vertebral aneurysm was performed the following day (figure 3). Post coiling he developed acute onset left sided hemiplegia. MRI brain showed multiple punctate cerebellar and occipital lobe infarcts that were deemed to have most likely occurred secondary to an embolic shower originating within the aneurysm.

Aspirin was increased to 300 mg from 150 mg following this episode and was commenced on Clopidogrel 75 mg once daily. The patient deteriorated further 2 days after the coiling with new onset of aphasia and right-sided hemiplegia. Clinically this was thought to represent

vasospasm. MRI/magnetic resonance angiogram (MRA) was performed again following the new neurological deficits, which confirmed severe vasospasm with a new infarct in the left middle cerebral artery territory (figure 4). Ventriculomegaly was also noted in the MRI and it was noted to have worsened relative to the previous imaging.

Figure 1 CT non-contrast brain demonstrating subarachnoid haemorrhage with intraventricular extension.

Figure 2 Cerebral angiogram demonstrating the left vertebral artery fusiform aneurysm.

His GCS also dropped to 7/15 and he was transferred to the intensive care unit (ICU) for further management. He underwent an emergency ventriculostomy at this stage and this was converted to ventriculo-peritoneal shunt 5 days later. He developed aspiration pneumonia in the ICU but made a gradual recovery.

His medical history included multiple fractures during childhood. Incidentally during his admission, he was noted to have blue-tinged sclerae. He had irregular bilateral tibial bones on general examination. The patient reported that he had had several fractures in childhood following minimal trauma.

INVESTIGATIONS

A series of radiographs showed multiple old fractures in long bones (tibia) (figure 5), healed rib fractures on chest x-ray (figure 6). CT skull also revealed abnormally pneumatized calvarium with large airspaces (figure 7). A blood sample was sent for genetic analysis of the collagen-encoding gene. This confirmed a COL1A1 gene mutation – consistent with a previously undiagnosed OI type 1.

TREATMENT

The vertebral artery aneurysm was successfully coiled by endovascular route (figure 3).

OUTCOME AND FOLLOW-UP

Post coiling he developed ischemic stroke due to vasospasm secondary to the SAH. Communicating hydrocephalus from SAH was treated with ventriculostomy initially and converted to ventriculo-peritoneal shunt.

Figure 3 Coil embolisation of the vertebral artery aneurysm with a patent arterial branch from the aneurysm.

The patient is undergoing intense rehabilitation following the stroke. His condition improved and was transferred back to referring hospital for rehabilitation. His Glasgow Outcome Scale at discharge was 3/5.

DISCUSSION

OI is a genetic disorder wherein abnormal collagen disrupts connective tissue matrix assembly. Eight clinicopathogenetic types 1 share the common feature of bone fragility which manifests clinically as bone fractures occurring after little or no trauma. A mutated gene encoding a component or modifier of the Type 1 collagen triple helix is responsible for this. OI type 1, the case we describe, occurs due to chain exclusion, wherein the mutant chain is unable to incorporate itself into the collagen triple helix (probably due to steric hindrance caused by aberrant amino acid interaction).¹ This unincorporated chain is proteolytically degraded thereby placing heavy reliance on the non-mutated allele to produce a structurally weaker triple helix.

Other well-described clinical features of type 1 OI include blue sclerae, progressive conductive hearing loss occurring secondary to gradual damage to the ossicles of the middle ear (a conductive/sensorineural type hearing loss may result from a pathologic process similar to otosclerosis), relative ligamentous laxity and rarely brittle opalescent teeth (referred to as dentinogenesis imperfecta).² Stature is generally within normal range although most children will be of shorter stature than their parents.

OI type 1 is autosomal dominant and the commonest variety of OI accounting for approximately 50% of cases. The diagnosis is usually established on the basis of a strong family history of OI or recurrent fractures, fractures occurring in a setting of no or minimal trauma especially in children, and a prominent scleral bluish hue.³ ‘Codfish

Figure 4 MRI brain T2 weighted imaging demonstrating the area of ischaemic infarction in the left fronto-parietal region.

Figure 6 Chest x-ray demonstrating multiple deformed ribs.

Figure 5 X-ray of tibia and fibula demonstrating deformed bony architecture and old healed fractures.

vertebrae' (the x-ray manifestation of spinal compression fractures) may occur principally in the adult. Wormian bones defined as 'sutural bones that are 6×4 mm or larger, in excess of ten in number with a tendency to arrangement in a mosaic pattern'. These are present in up to 60% of

Figure 7 CT head bone windows demonstrating abnormally pneumatised calvarium in osteogenesis imperfecta.

affected children.⁴ Abnormalities are also present in other membranous bones.

A prominent pathologic feature of cerebral artery aneurysms is a reduced collagen content.^{5 6} Conventionally, this may be attributable to increased metalloproteinase and cathepsin.^{7 8} Expression of procollagen type 1 and 3 has been shown to be down regulated in cerebral artery aneurysm walls at the transcriptional level.⁹ A key feature of vessel wall competence, which is breached in the

aneurysm setting, is collagen cross-linking, which affords the vessel tensile strength. Lysine oxidase (LOX), which catalyses this cross-linking, is down regulated in cerebral artery aneurysms. This has been verified experimentally and is supported by genetic analysis revealing that a single nucleotide polymorphism of LOXL 2, a member of the LOX family of genes, showed a strong association with cerebral artery aneurysm susceptibility.¹⁰ COL3 has previously been epidemiologically linked to cerebral artery aneurysms specifically with reference to expression in the ruptured dome of intracranial aneurysms (where samples were derived from on table tissue sampling at the time of craniotomy).¹¹ We infer that the pathogenetic basis of OI overlaps with the etiologic mechanism of cerebral artery aneurysms. The reason for the reduced predilection for aneurysms in OI versus some other connective tissue diseases such as Ehlers Danlos or Marfan's syndrome is not entirely clear. Cystic medial necrosis – a phenomenon which results from severe elastic fiber degeneration, necrosis of muscle cells and cystic spaces become filled with mucoid material (a picture of accelerated vessel ageing) is not a feature of OI. While cystic medial necrosis is relevant for vessels with a thick tunica media, it is unlikely to be relevant in the very thin-walled cerebral vasculature. Defective cross-linking of collagen, as occurs in OI, is a major contributor to cerebral artery aneurysms.

Learning points

- ▶ Aneurysmal SAH can occur secondary to rupture of vertebral artery aneurysm in OI and endovascular route may be preferred to surgical treatment due to the underlying collagen vascular defect.
- ▶ General physical examination may appear to be the only clue for the diagnosis accompanied by radiological and genetic investigation to aid the diagnosis of OI, as our patient was clinically well and asymptomatic prior to the SAH.
- ▶ MRI/MRA is recommended for follow-up post coiling of the aneurysm in OI.
- ▶ Genetic counselling is essential to the patient and family and must be offered as a part of management.

Competing interests None.

Patient consent Obtained.

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