Child's Nervous System (2019) 35:1621–1624
https://doi.org/10.1007/s00381-019-04250-9

CASE REPORT

GAPO syndrome with craniosynostosis and intracranial hypertension

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Received: 3 May 2019 / Accepted: 4 June 2019 / Published online: 23 June 2019

Abstract

Background GAPO (growth retardation, alopecia, pseudoanodontia, and optic atrophy) as a rare genetic disorder includes growth retardation, alopecia, pseudoanodontia, and optic atrophy. It was reported to be associated with craniosynostosis and intracranial hypertension.
Case Report A patient with such a rare disorder associated with multisuture craniosynostosis and headache is presented. Surgery has been done due to intracranial hypertension.
Conclusions Abnormal intraoperative findings including sever pericranium and dural adhesions and extraordinary bleeding related to this syndrome are described.

Keywords GAPO syndrome · Craniosynostosis · Pericranium · Dura

Introduction

GAPO syndrome—an acronym for growth retardation, alopecia, pseudoanodontia, and optic atrophy—is a rare genetic disorder first described in 1947 [1]. It is a disorder caused by a mutation in ANTXR1 gene [7]. However, it is very rarely reported in association with craniosynostosis and intracranial hypertension. Here, a patient with such an association is presented. To the best of our knowledge, this is the third case with craniosynostosis and the second case that underwent surgery due to intracranial hypertension.

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Case presentation

The patient was a 4-year-old girl admitted for severe headache and blindness since several months ago. She was born subsequent to an uneventful pregnancy with normal delivery as the fourth child from nonconsanguineous illiterate parents. Family history was negative for a similar problem. The patient have had hair on the head and face during the first months of life but lost all of them before the age of 8 months.

She had marked growth retardation, in terms of height, weight, and neurodevelopmental status, according to the chronological age. There were no apparent teeth and no hairs on the head. She had optic atrophy without any light perception. Glaucoma was diagnosed during her admission and was operated before cranial surgery.

The head circumference was small (46 cm), with left plagiocephaly. She had prominent dilated scalp veins, as well as right side frontal bossing and a highly oriented fontanel similar to acrocephaly. The fontanel was bulging and open about 2 × 2 cm. Her face seemed to be unusually old without eyebrows, accompanied with telecanthus, buphthalmos, depressed nasal bridge, large tongue, and retrognathia (Fig. 1).

Brain computed tomography (CT) showed multisuture craniosynostosis (partial sagittal, left coronal, and metopic), open fontanel, with sulci effacement and some bone defects like thumb impressions (Fig. 2).

Thyroid function tests confirmed hypothyroidism which was subsequently treated. The diagnosis of GAPO was considered for the patient and she was scheduled to undergo craniotomy due to neglected craniosynostosis associated with severe intracranial

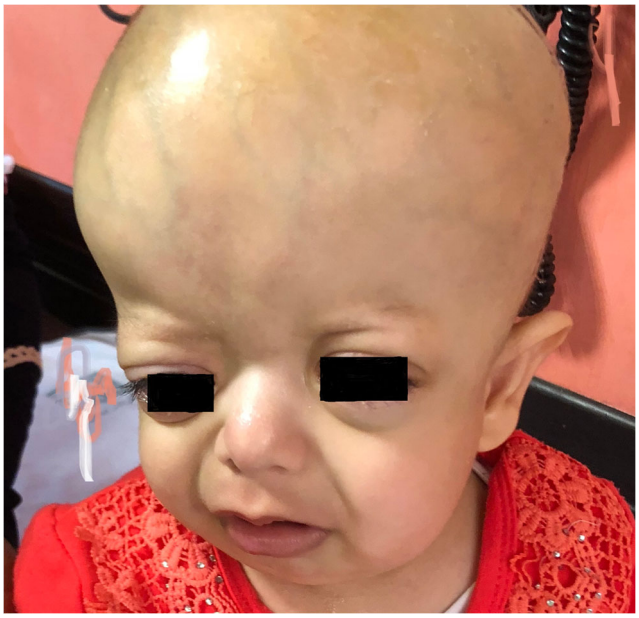

Fig. 1 Child showing no eyebrows and hair on the head and she has telecanthus, buphthalmos, depressed nasal bridge, and retrognathia

hypertension. After preparing the patient for craniotomy, a bicoronal incision was made for cranial remodeling surgery. The skin had severe attachment to pericranium with abnormal hemorrhage and large dilated veins. Pericranium was robustly attached to the bone so that subperiosteal dissection was performed hardly. The dura matter was firmly attached to the bone which made separation impossible without dural tearing. Due to severe attachment of all anatomical layers associated with severe bleeding, the standard approach of craniosynostosis was changed from craniotomy and flaps reconstruction to suturectomy of closed sutures (Fig. 3). She needed 20 mg/kg pack cell transfusion to compensate the intraoperative hemorrhage. The postoperative course was uneventful and the

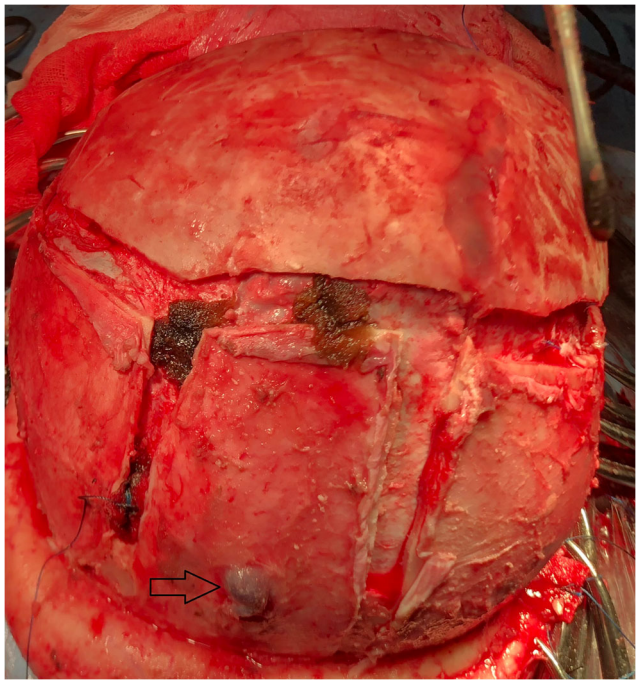

Fig. 3 Intraoperative photography shows suture craniectomy over the closed sutures due to severe adhesion of pericranium and dura matter to the bone. The arrow shows the engorged vein of scalp reaching to the midline sinus

headache substantially improved. She did not experience headache or any new symptoms during 1 year follow-up.

Discussion

GAPO syndrome, a rare genetic disorder was first described in 1947 [1] and later named GAPO by Tipton and Gorlin in 1984. The syndrome has been proposed to have an autosomal

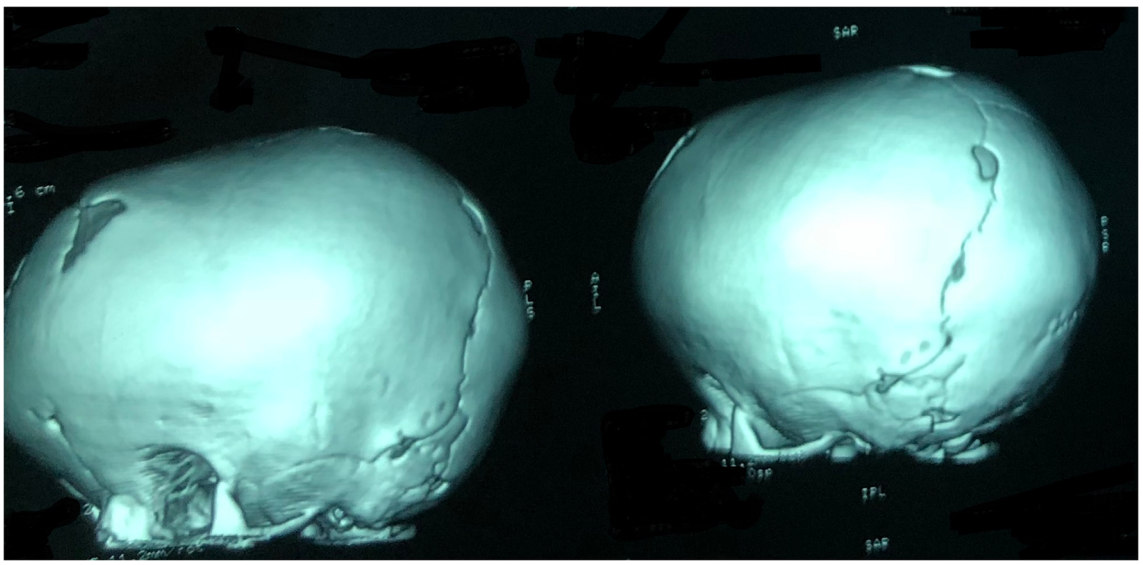

Fig. 2 Bone window 3D CT scan confirms closed left coronal and sagittal sutures associated with open fontanel

recessive pattern due to often consanguinity of the parents and numerous reports of affected siblings [8].

Based on current literature, the manifestations of this syndrome include growth retardation, alopecia, pseudoanodontia, bossed forehead, depressed nasal bridge, micrognathia, midface hypoplasia, buphthalmos, glaucoma, optic nerve atrophy, and hypertelorism among others [4].

Our patient with complaint of severe headache had been blind for several months owing to either optic atrophy or glaucoma and had lost all her hair since she was 8 months. Her brain CT scan revealed multiple suture craniosynostosis and open fontanel.

Craniosynostosis has been reported with GAPO syndrome only twice before. In 2013, Goyal et al. reported a 19-year-old female, known case of GAPO syndrome that presented with headache. On CT scan, it was revealed that she had pansutural craniosynostosis and intracranial hypertension [4]. The other case was reported by Abdel-Hamid et al., a boy that was 3 years and 8 months old with bilateral partial coronal craniosynostosis and dilated scalp veins and papilledema. As in other syndromic causes of craniosynostosis, GAPO syndrome seems to cause multisuture craniosynostosis.

Headache in patients with GAPO syndrome may be due to high intracranial pressure or glaucoma or even intracranial vasculature anomalies. Goucha et al. performed MRI, MRA, and cerebral angiography on a 12-year-old boy with GAPO syndrome and found multiple anomalies including prominent cortical veins, hypoplasia of the left transverse sinus, and agenesis of the left jugular vein [3]. Moriya et al. had a 3.5-year-old boy in whom cranial angiography suggested a disturbed intracranial venous return in sigmoid sinus and/or jugular veins. They hypothesized that chronic elevated venous pressure could lead to elevated intraocular venous pressure and thus chronic papilledema [6]. Cerebral angiography in another patient with GAPO syndrome showed abnormal venous circulation with occluded transverse and/or sigmoid sinus or internal jugular vein. Venous drainage seemed to be through the external jugular veins [5]. Zeydan et al. took an MR venography and MR angiography of a 31-year-old man with GAPO syndrome who presented with severe headache, progressive dysphagia, and recurrent and transient episodes of weakness and numbness in his left arm. The MR angiography revealed total occlusion of the right internal carotid and moderate stenosis of the left internal carotid artery. Cerebral MR venography revealed chronic thrombotic changes in the distal left sigmoid sinus, proximal right sigmoid sinus, and bilateral jugular veins. It later turned out to be a skull base osteomyelitis and was treated with antibiotics and anticoagulants [10].

Many cases in the literature including our case have dilated scalp veins. This could be due to intracranial hypertension secondary to multisuture craniosynostosis or impaired venous drainage that seems to be present in many patients with GAPO syndrome.

Another issue requiring attention in such patients with craniosynostosis is the difficulties encountered during the cranial surgery. As in our case, Goyal et al. also faced difficulties during operation. They had to raise a bifrontal bone flap in three different locations due to severe adhesion of dura to the bone, even then a dural tearing occurred intraoperatively [4]. We faced similar problems, the pericranium and dura were severely attached to the bone and skin in such a way that we decided to change our operation plan from standard craniotomy and reconstruction to suturectomy.

Strancky et al. showed that GAPO syndrome is caused by a mutation in ANTXR1 gene which is involved in extracellular matrix homeostasis [7]. Cullen et al. performed histopathological analysis on ANTXR1 knockout mice. Interestingly, they observed excess of extracellular matrix in many tissues including the ovaries, uterus, skin, and periodontal ligament of the incisors [2].

Wajmtal et al. performed an autopsy on a patient with GAPO syndrome and observed excess extracellular matrixes on skin necropsy. This accumulation of extracellular components leads to the gradual but progressive appearance of the symptoms [9]. This theory supports our intraoperative observations of severe adhesion between all anatomical layers. So we propose that the sooner we perform the surgery means we will face a less progressed disorder and we will encounter less problems intraoperatively.

Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

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