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CASE REPORT - PEDIATRICS

Mucopolysaccharidosis type I and craniosynostosis

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Abstract Mucopolysaccharidosis type-I is caused by a deficiency of the lysosomal enzyme α-L-iduronidase, resulting in gradual deposition of glycosaminoglycans in multiple body organs, affecting physical appearance and system functioning. We present the first reported case associating MPS-I (Hurler-Scheie subtype) with craniosynostosis. A 2.5-year-old girl presented initially with macrocrania. On clinical and radiological examinations we noted a scaphocephaly with dysmorphic facial features of MPS confirmed later on. Intracranial hypertension was documented at fundoscopy (papilloedema) and ICP monitoring, and then surgically treated. This association of scaphocephaly and MPS-I highlights the importance of a meticulous physical examination performed by craniofacial, metabolic and ophthalmologic teams.

Keywords Mucopolysaccharidosis · Craniosynostosis · Scaphocephaly · Intracranial hypertension · Papilloedema · Cranial vault decompression

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Introduction

Mucopolysaccharidoses are a heterogeneous family of rare inherited metabolic diseases, caused by an impaired or a deficient lysosomal enzyme involved in the degradation of glycosaminoglycans, formerly called mucopolysaccharides. Mucopolysaccharidosis type-I (MPS-I), also called Hurler syndrome, is a rare autosomal recessive disease with an estimated incidence of 1 case per 100,000 live births [9]. It is caused by mutations of the gene encoding for the α-L-iduronidase, a lysosomal enzyme, resulting in a defective degradation of glycosaminoglycans. The subsequent accumulation of the upstream metabolites (heparan and dermatan sulfates) will affect various tissues and organs including bone, cartilage, tendon, cornea, skin, connective tissue, brain and liver. This multi-systemic involvement leads to remarkable morphologic changes that vary across a large phenotypic spectrum from the severe form of the disease called Hurler syndrome associated with neurological involvement to the more attenuated forms of the disease called also Hurler–Scheie (with significant skeletal and visceral involvement) and Scheie syndrome (with minimal visceral but non-negligible skeletal and joint disease) [11]. Skeletal deformities can present as short stature, facial dysmorphism with macrocrania, dysostosis multiplex and spinal deformities [14]. Ophthalmological features comprise corneal clouding, glaucoma, retinal degeneration, optic disc swelling with subsequent atrophy, pseudo-exophthalmos, amblyopia, strabismus and large refractive errors requiring important correction [3, 6, 12]. Other systemic features include mental retardation (in Hurler patients), hepatosplenomegaly, cardiac complications and hernias. However, affected children appear normal at birth, and develop those morphologic changes in the first months or years of life [14]. The complex multisystem involvement of MPS-I patients requires a multidisciplinary management and follow-up by geneticists, pediatric metabolic specialists,

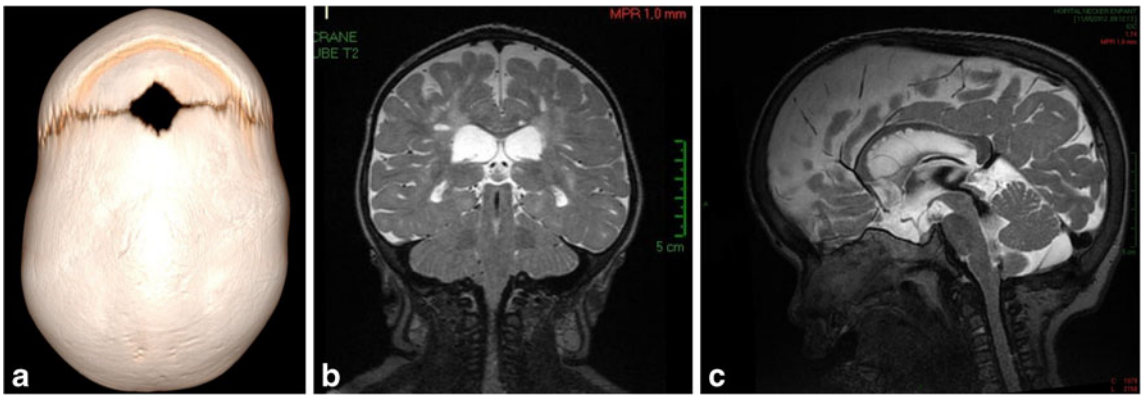

Fig. 1 Scaphocephalic head with sagittal suture fusion on preoperative 3D skull CT scan (**a**). Scaphocephalic head showing low-set cerebellar tonsils and ventricular dilatation on a preoperative brain MRI (**b&c**)

ophthalmologists, otorhinolaryngologists, general, orthopedic and craniofacial surgeons, as well as physiotherapists.

The diagnosis of MPS-I can be made by the documentation of increased amounts of glycosaminoglycans in the urine, but confirmed and classified after an enzyme assay demonstrating a deficient enzymatic activity in leukocytes or fibroblasts, or by a molecular genetic testing (*IDUA* gene).

Treatment options include hematopoietic stem cell transplantation for Hurler patients (the only therapeutic modality allowing to preserve cognitive function if performed before 2.5 years) [5], and enzyme replacement therapy for the more attenuated forms of the disease, in which, if started early, it can be more effective in halting disease progression and improving prognosis [4, 9]. Another possible and developing treatment is gene therapy [10].

The macrocrania observed in MPS can sometimes be associated with a secondary craniosynostosis. Management of such synostosis is complex. In fact, the multisystemic involvement can hinder the diagnosis of a craniosynostosis-related increased intracranial pressure. Here we present the first case of MPS-I and craniosynostosis with a documented raised intracranial pressure and papilledema resolving after cranial vault decompression.

Case description

A 2.5-year-old girl with past medical history of operated inguinal hernia, non-operated umbilical hernia, recurrent otitis media operated recently by tympanic ventilation tubes, was addressed to the neurosurgical outpatient clinic for progressive macrocrania. On clinical examination, we noted a dolichocephalic form of the head with a circumference of 56 cm, lying in the normal range for age, facial dysmorphism with small spaced teeth. The child had a normal psychomotor development. Ophthalmological examination revealed bilateral corneal depositions and bilateral optic disc swelling, with features of both papilledema and infiltration, attributable to a mixed mechanism: venous stasis due to increased intracranial pressure (ICP) and glycosaminoglycan infiltration of the optic nerve head. A skull X-ray and a 3D skull CT scan (Fig. 1a) confirmed the scaphocephaly, and the open coronal and lambdoid sutures. A brain MRI (Fig. 1b&c) revealed descended cerebellar tonsils, and abnormally dilated ventricles with periventricular T2/FLAIR hyperintensities related probably to a storage disease. Following these findings, further metabolic and genetic investigations were carried out confirming the diagnosis of MPS-I of Hurler–Scheie subtype, with an enzymatic activity approaching zero. Enzyme replacement therapy was initiated. An intracranial pressure monitoring was decided on the basis of her persistent papilledema, and formally confirmed the increase in intracranial pressure,

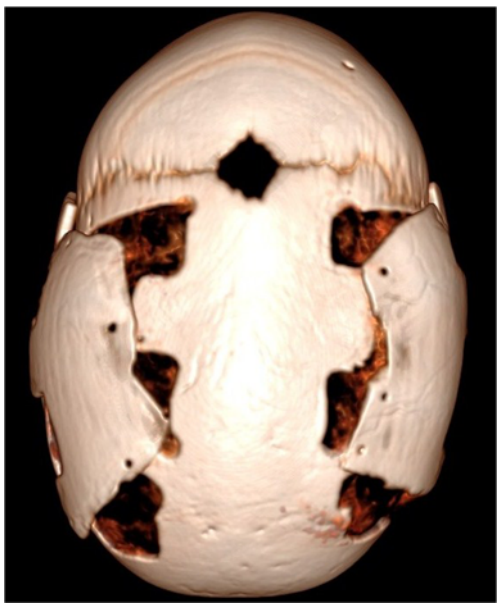

Fig. 2 Postoperative 3D skull CT scan showing the bilateral parietal decompressive craniectomies

justifying decompressive craniectomy. In a supine position, a bicoronal zigzag incision was made, followed by a subgaleal dissection. The synostosis of the sagittal suture and the permeability of both coronal sutures were confirmed. Two parietal craniectomies were performed, and bone flaps were then modified, and repositioned again, in order to reshape the skull vault as shown in the postoperative 3D skull CT scan (Fig. 2). Fundoscopy performed 2 and 6 months later showed continuous regression of papilledema features but still mild infiltration of the optic discs (Fig. 3). On postoperative brain MRI at 1 year, no remarkable improvement of the descent of cerebellar tonsils was found.

Discussion

A high variety of skull abnormalities can occur in patients with MPS, including large head with bulging frontal bones, J-shaped sella turcica, hyperostosis of cranial base and vault, craniovertebral junction and spinal anomalies [7, 8, 11]. Pathogenesis of some of these bony deformities was demonstrated to be related to glycosaminoglycans regulation of the collagenolytic activity of the major osteoclastic protease cathepsin K. Wilson et al. during their study on murine MPS-I have showed that excess heparan and dermatan sulfates inhibit type II collagen degradation by cathepsin K, resulting in a bone maturation defect characterized by impaired osteoclast activity and decreased cartilage resorption, which may explain various skull deformities [13].

Secondary craniosynostosis, most often scaphocephaly, is one of the features of MPS as well as many other metabolic and genetic diseases [2]. However, while reviewing the literature, it appeared that craniosynostosis was primarily reported in MPS-II. In their study in 2011, Manara et al. found seven out of 36 Italian patients with MPS-II having either scaphocephaly or trigonocephaly [8]. Another case of

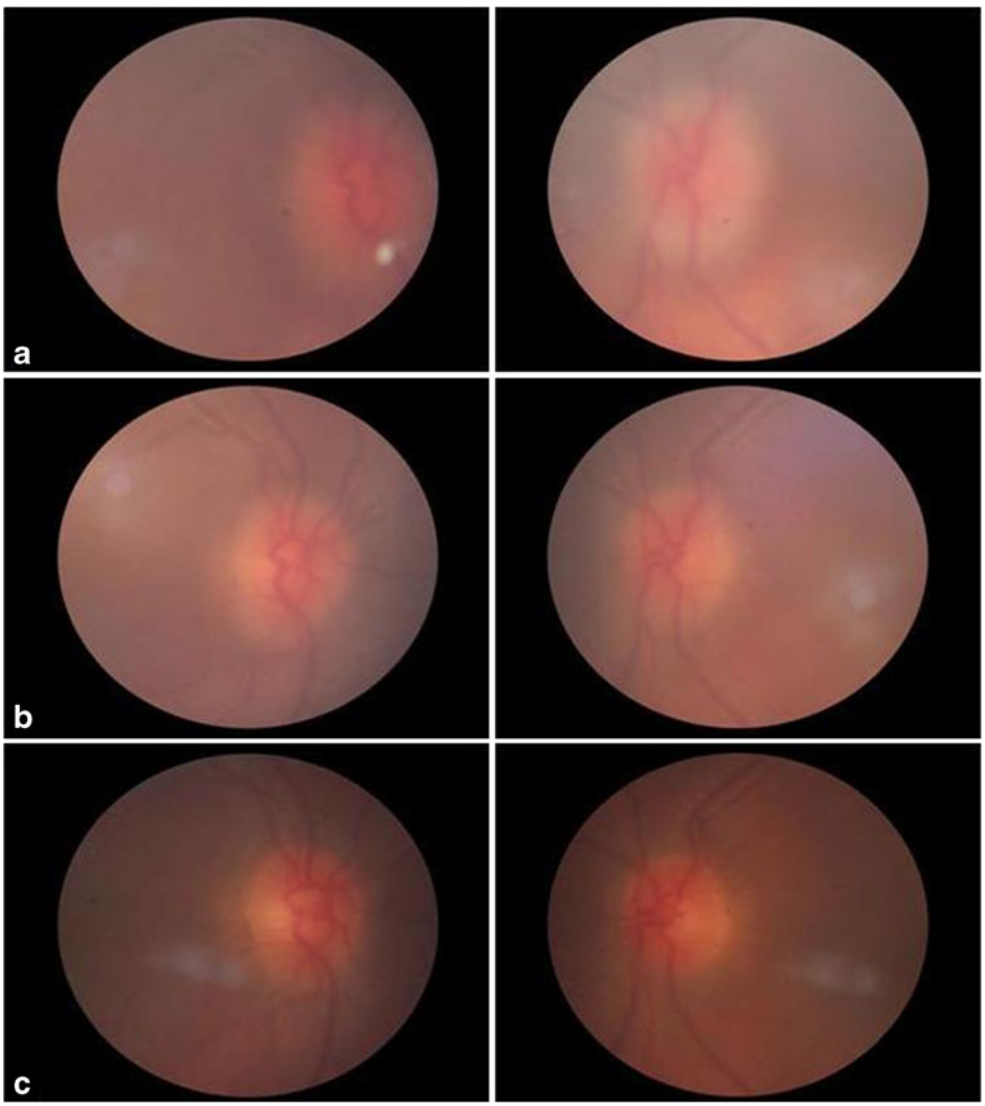

Fig. 3 Preoperative right and left eyes on fundoscopic examination (**a**). Postoperative control at 2 months (**b**) and 7 months (**c**). The blurred appearance of the pictures results from the opacification of the cornea

trigonocephaly occurring in a context of MPS-II has been reported by Brisman et al. in 2004 [1]. To the best of our knowledge, the present case is the first reported one of MPS-I presenting primarily with craniosynostosis.

In this case we may notice, on one hand, how crucial it is for the craniofacial surgeon to be cautious in his physical examination of a child presenting with craniosynostosis, looking for a possible genetic underlying cause, which if discovered and treated early, can preclude disease progression, and improve prognosis. On the other hand, a meticulous ophthalmologic examination is essential, in order to help documenting some ocular changes, such as corneal depositions, supporting the hypothesis of an underlying metabolic disorder, but also to discriminate between the two possible mechanisms of optic disc swelling in such a case: papilledema due to increased intracranial pressure (either resulting from skull deformity or associated with MPS), or optic disc infiltration by glycosaminoglycans. Accuracy in eye examination accelerates craniofacial surgical management, in order to save optic nerves from the deleterious effects of increased intracranial pressure.

In conclusion, it is crucial to identify MPS-I patients promptly before they develop progressive and irreversible complications, potentially leading to death. In order to ensure a timely management and a better prognosis, it is crucial to recognize and evaluate not only the typical facial and body gross morphological changes, but also the presence of premature fusion of a cranial suture, as well as ocular features which may present fairly early in the course of the disease, raising the suspicion of an increased intracranial pressure that requires prompt surgical treatment.

Conflicts of interest None.

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