EGALENCEPHALY is an abnormally high volume of brain parenchyma and can occur in association with no specific etiology or be secondary to abnormal intracellular accumulations within the brain parenchyma. Intracranial hypertension usually does not occur because the immature skull expands to accommodate the increased brain volume. Secondary etiologies are attributable to defects in metabolism such as in the storage diseases, to neurocutaneous syndromes such as tuberous sclerosis or to leukodystrophies without proven enzyme deficiencies such as Alexander’s and Canavan’s diseases. We describe an unusual case, in which multiple prematurely fused cranial sutures and macrocephaly in association with a lysosomal storage disease, $\alpha$-d-mannosidase deficiency. This 3-year-old boy presented with a history of frequent naps, headaches, florid papilledema, enlarged head (> 95th percentile), elevated opening pressure by lumbar puncture, a “beaten copper” appearance on skull radiographs, and no hydrocephalus. Multiple synostectomies were performed. Postoperatively, the child’s headaches and papilledema resolved and his level of physical activity increased dramatically. The authors discuss the paradoxical presentation of prematurely fused sutures and macrocrania in light of this lysosomal storage disease and its subsequent management.

**Case Report**

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🔍 The authors present an unusual case in which increased intracranial pressure developed because of multiple-suture craniosynostosis and megalencephaly in a child with a previously undiagnosed lysosomal storage disease, $\alpha$-d-mannosidase deficiency. This 3-year-old boy presented with a history of frequent naps, headaches, florid papilledema, enlarged head (> 95th percentile), elevated opening pressure by lumbar puncture, a “beaten copper” appearance on skull radiographs, and no hydrocephalus. Multiple synostectomies were performed. Postoperatively, the child’s headaches and papilledema resolved and his level of physical activity increased dramatically. The authors discuss the paradoxical presentation of prematurely fused sutures and macrocrania in light of this lysosomal storage disease and its subsequent management.

**Key Words** • $\alpha$-d-mannosidase • craniosynostosis • intracranial pressure • lysosomal storage disease • macrocephaly • mannosidosis

MEGALENCEPHALY is an abnormally high volume of brain parenchyma and can occur in association with no specific etiology or be secondary to abnormal intracellular accumulations within the brain parenchyma. Intracranial hypertension usually does not occur because the immature skull expands to accommodate the increased brain volume. Secondary etiologies are attributable to defects in metabolism such as in the storage diseases, to neurocutaneous syndromes such as tuberous sclerosis or to leukodystrophies without proven enzyme deficiencies such as Alexander’s and Canavan’s diseases. We describe an unusual case, in which despite macrocrania, intracranial hypertension developed because of multiple prematurely fused cranial sutures and megalencephaly in association with a lysosomal storage disease, $\alpha$-d-mannosidase deficiency (mannosidosis). By directly affecting both skull and brain, mannosidosis is unique in its ability to cause the paradoxical situation of macrocrania, prematurely fused sutures, and intracranial hypertension without hydrocephalus.

**Case Report**

A routine tonsillectomy performed on a 3-year-old boy revealed foamy histiocytosis of the tonsils. With the odd presentation of tonsillar “foamy histiocytes,” which suggested a possible storage disease, further evaluation led to the diagnosis of mannosidosis, as suggested by extraordinarily high urinary levels of oligosaccharide and abnormally low levels of $\alpha$-d-mannosidase activity in leukocytes and cultured skin fibroblasts. Similar tests of the parents revealed them both to be heterozygous for mannosidosis. The child had a life-long history of macrocrania (> 95th percentile), which had plateaued in recent months.

**Examination.** Developmentally he had achieved motor milestones appropriate for his age and had no evidence of hearing or communication difficulties. In the month of presentation his mother described episodes of unexplained head holding and irritability. The history of macrocrania prompted a skull radiograph. The skull radiograph revealed a “beaten copper” appearance of the inner table, bulging of the squamous temporal bones, and no coronal, lambdoid, or sagittal sutures (Fig. 1 upper). Cranial computerized tomography showed no hydrocephalus or parenchymal abnormality and confirmed the gyral erosions into the inner table. The child was then referred for neurosurgical evaluation. Physical examination showed an occipitofrontal circumference of 53 cm (95th percentile), a palpable sagittal ridge, no palpable coronal sutures, and mildly coarse facies. Funduscopic examination showed
florid papilledema. The remainder of the physical and neurological examination was normal.

A lumbar puncture, with the child sedated, had an opening pressure of 25 cm H₂O with normal cerebrospinal fluid parameters. Because of the elevated intracranial pressure (ICP), papilledema, and fused sutures, we decided to release the fused sutures to allow for cranial expansion and normalization of his ICP and to prevent any visual deterioration.

Operation. With the child in the “sphinx” position, the scalp was incised across the vertex with a biparietal incision, and strip craniectomies of 5 to 12 mm were performed along the coronal, sagittal, and lambdoid sutures. The posterior parietal bone was markedly thick. Initially the dura was nonpulsatile and bulged abnormally into the cranial defects. The parietal bones then spontaneously spread apart a few millimeters allowing for normal dural pulsations. By applying lateral traction, we made the parietal bones hinge outward further on the squamosal sutures to enhance the cranial expansion.

Postoperative Course. Skull radiographs were obtained on the 1st postoperative day to document the degree of cranial expansion (Fig. 1 lower). The boy was discharged home 3 days after the operation in good condition. Skull radiographs 6 weeks postoperatively showed persistent separation of the bone plates. The child’s level of activity increased dramatically following the operation with a notable decline in his frequent daytime naps. No more behavior suggestive of headache has occurred. The occipitofrontal circumference since the operation has remained at 53.75 cm. Funduscopic examination has shown resolution of the papilledema with normal venous pulsations 10 weeks postoperatively.

Histopathological Examination. Examination of the removed calvarial strips revealed two notable findings: 1) complete ossification without any evidence of cranial sutures in the coronal, lambdoid, and sagittal regions, and 2) absence of a normal inner table (Fig. 2).

Discussion

Mannosidosis was first described in 1967 as a generalized storage disorder resembling Hurler’s syndrome. The disease is transmitted as an autosomal recessive gene. Variable expression of coarse facies, slowed psychomotor development, hearing loss, hepatomegaly, and abdominal wall hernias usually become clinically apparent by 1 to 3 years of age. The term “dysostosis multiplex” has been used to describe the varied and widespread bone changes seen in association with mannosidosis of which thick calvaria and prematurely fused sutures are manifestations in the skull. Plain skull radiographic features of mannosidosis in 10 children revealed macrocrania (three), thick calvaria (five), brachycephaly (six), and dolicocephaly (two) secondary to prematurely fused sutures. One of six examples of skull radiographs shown in the article by Spranger, et al. had a “beaten copper” appearance, and two had abnormal widening of the coronal sutures suggesting intracranial hypertension. One report described a child with mannosidosis who had papilledema and bouts of headache and vomiting thought to be secondary to increased ICP. This child underwent no further investigation or treatment and eventually died during one of these bouts of presumed elevated ICP.

Magnetic resonance imaging in three patients with mannosidosis revealed thick calvaria (three), incomplete pneumatization of the sphenoid (three), brachycephaly (two), partially empty sella (two), and macrocrania (one). No comment was made about the sutures, although the two cases of brachycephaly suggest premature fusion of the coronal or lambdoid sutures. The partially empty sella seen in two patients may serve as an indication of occult increased ICP. No comment was made concerning the presence of optic sheath distention.

Our case is the first in which increased ICP could be documented and in which treatment was administered to reverse the manifestations of increased ICP (for example, papilledema and behavioral changes) in mannosidosis. Megalencephaly from neuronal, astrocytic, and endothelial accumulation of mannosose-rich oligosaccharides led to macrocephaly, while the dysostosis multiplex of mannosidosis caused prematurely fused sutures prohibiting further cranial expansion (except for some temporal bulging). This combination of fused sutures and abnormally high brain volume (megalencephaly) led to increased ICP, manifested as papilledema, headaches, abnormal skull
Synostosis, macrocephaly, and intracranial hypertension

radiographs, and high opening pressure on lumbar puncture. Further evidence of increased ICP and restricted cranial expansion occurred intraoperatorively when the non-pulsatile dura bulged into the sites of synostectomy, followed by spontaneous separation of the parietal bones and normal dural pulsations.

A likely explanation for the absence of an inner table on histopathological examination of the removed calvarial strips is that the chronically elevated ICP leading to gyral indentation (“beaten copper” appearance by skull radiograph) either attenuated or prevented the formation of a normal inner table. The influence of the metabolic disturbance on bone formation in mannosidosis (dysostosis multiplex) cannot be discounted as a contributing factor to the absence of an inner table. The histopathological absence of sutures supported the clinicoradiographic diagnosis of multiple suture craniosynostosis. The squamosal suture, which virtually never fuses, was the only suture unaffected by synostosis.

This case illustrates that absolute macrocrania can be relative microcrania in mannosidosis because of the associated megalencephaly and lack of open sutures. Physicians evaluating patients with macrocrania and fused sutures should consider mannosidosis as an etiology and rule out intracranial hypertension, because release of the prematurity fused sutures allows for cranial expansion and resolution of papilledema and symptoms secondary to elevated ICP.

References


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