Case Report

Craniosynostosis; a Rare Complication of Endoscopic Third Ventriculostomy for Complex Hydrocephalus Associated with MAN2B1 Gene Mutations (Alpha-mannosidosis)

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ABSTRACT

Due to lower risk of postoperative complications and shunt-independence, endoscopic third ventriculostomy (ETV) is a compelling alternative to CSF-shunt implantation in the management of hydrocephalus. While craniosynostosis is an uncommon complication of CSF-shunt-based procedures, to our knowledge, no reports on post-ETV craniosynostosis, exist. The authors describe a case of a 2-year, 4-month-old female presented with pan-craniosynostosis after endoscopic treatment of complex hydrocephalus performed at the age of 2 months. A 3-Dimensional CT-scan of the cranium revealed craniosynostosis involving all skull sutures, which was treated with fronto-orbital advancement and cranial vault reconstruction. Genetic study revealed two pathogenic copies of MAN2B1 gene (alpha-mannosidosis), which had probably contributed to the development of craniosynostosis in this patient. To the best of our knowledge, this is the first case of craniosynostosis occurring after ETV procedure. A close follow-up of this patient group allows early detection and management of rare yet correctable complication.

INTRODUCTION

Management of hydrocephalus is considered one of the major challenges to both neurosurgeons and patients. Due to progressive nature of this condition, and the lack of effective therapeutic alternatives, surgical intervention remains the preferred line of long-term management. Among the several surgical approaches, endoscopic third ventriculostomy (ETV) and CSF-diversionary techniques have been suggested to have equivalent outcomes, although with lower surgery time, postoperative complications, and reoperation rate in cases of ETV1. The overall complication rate of ETV was estimated to be 8.5%, with permanent morbidity occurring in 2.38% of the cases2. Leak of CSF, and central nervous system (CNS) infections are the most common postoperative complications of ETV, affecting 2.3% and 1.8% of patients, respectively2.

Although shunt-induced craniosynostosis has been previously described, no reports of ETV-induced craniosynostosis, to our knowledge, exist3-6. Herein, we describe a rare case of post-ETV-pan-craniosynostosis, after 2 years of endoscopic treatment of congenital hydrocephalus in a child discovered to have MAN2B1 gene mutation. This gene mutation is known to cause Alpha-Mannosidosis, which is a lysosomal storage disorder with variable clinical presentations; typically include CNS abnormalities, mental retardation, and skeletal deformities, but rarely cause craniosynostosis7. The diagnosis of alpha-mannosidosis was established in the patient and her parents by finding MAN2B1 mutations.

CASE REPORT

A 2 years & 4-month-old female patient was noticed by her parents to have slowly progressive dysmorphic head shape and protrusion of both eyes. They reported normal development and milestones since she recovered from endoscopic treatment of congenital hydrocephalus at the age of 2 months when presented with enlarging head, and asymmetrical ventricular dilatation. There were no associated congenital anomalies and endocrine and metabolic work up was normal.

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On examination, the child development was normal to her age, with good eye fixation & communication, and examination of motor and sensory system was within normal. Head circumference was 48 cm at the fiftieth percentile. The head appeared oxy-cephalic with a palpable midline bony ridge in the anterior part of the sagittal suture. This was seen clearly in the 3D cranial computed tomography (CT) scan, which demonstrated pan-craniosynostosis (Fig. 1a-f). Both eyes were moderately protruded, and examination of the face, hands and feet was within normal.

![Fig. 1 a-f: 3D Cranial CT scan showing right frontal hole of the previous endoscopy [white arrow (a)], and pointed top of the skull forming conical deformity or oxycephaly [black arrows (b)]. Note all sutures are totally fused [sagittal (c) Lambdoid (d), right and left coronal (e&f)].](image)

**Past History and Imaging**

The patient was diagnosed to have dilated cerebral ventricles detected antenatally on routine third-trimester ultrasound morphology scan, with which no other anomalies were found. The patient had an uneventful birth and showed normal growth at her one-month follow-up visit. At 2 months of age, her head grew bigger with sun set appearance of the eyes and had several episodes of vomiting. Head circumference was 42.5 cm above the 97th percentile, and anterior fontanelle was full and slightly tense. A non-contrast CT of the brain showed significant dilatation of the right lateral ventricle involving mainly its body, occipital and temporal horns and shift of midline structures. Septum pellucidum was to the left side. The left ventricle was moderately dilated and bilateral frontal periventricular lucency was seen. Third ventricle and fourth ventricles appeared within normal (Fig. 2). She underwent neuroendoscopy; the telescope was introduced into the right lateral ventricle, choroid plexus was visualized and followed to the anatomical site of foramen of Monro where a thick, avascular, thin tough membrane was found occluding the foramen of Monro (Fig. 3). A hole was made in the membrane using a ventriculostomy forceps and the hole widened by a Fogarty catheter-balloon. The telescope was navigated into the third ventricle and at the middle of its floor ETV was performed by making a hole and widening it using the same technique. The scope was retrieved to the lateral ventricle and a hole was made in the septum pellucidum creating a communication between both lateral ventricles. A temporary EVD was left in the right lateral ventricle.
Fig 2 a-d: MRI of the brain T1WI; axial view. (a), Coronal view (c&d) showing dilated right lateral ventricle, origin of septum pellucidum at the left of midline seen curving to the left (a&c; solid white arrow). Right Foramen of Monro covered with a membrane (black arrow). T2WI, sagittal view (b) showing hypoplastic cerebellum (two white arrows), a membrane at the foramen of Monro (black arrow).

Fig. 3 a&b: Endoscopic picture of the right lateral ventricle showing a: avascular thin membrane totally occluding the foramen of Monro, note choroid plexus at the medial lower margin of Monro foramen, and picture. b: showing after creation of a wide opening of the foramen of Monro membrane.

Post-operative Course
The patient experienced a tonic-clonic seizure in the recovery room soon after surgery, necessitating intubation and shifting her to the pediatric intensive care unit. She was pale and her hemoglobin was 7.8 g/dl for which she was transfused packed RBCs. She was extubated in the second postoperative day, EVD was removed and she steadily gradually recovered till discharged home in the second week. Serial post-operative CT scans showed improvement of ventricular dilatation, a relaxed brain, and persistent extra-axial fluid collection (Fig. 4). She was lost in the follow up after one month till she presented with craniosynostosis.
At 2 years and 4 months of age, her parents sought for neurosurgical advice when they noticed abnormal head shape with moderate protrusion of the eyes, and some behavioral changes. Cranial CT scan showed ventricular dilatation with patent surface CSF spaces and basal cisterns, and 3D cranial CT scan showed evidence of pan-craniosynostosis with turricephaly. All sutures were non visualizes with central frontal bony hump seen (Fig. 1).

Surgical Correction and Postoperative Course

She underwent multiple osteotomies and calvarial remodeling with supra orbital bar advancement, aiming to improve the shape of the head and providing space for the growing brain. She tolerated the procedure very well and intra-operative, two units of packed RBCs were transfused. Her postoperative hospital stay, which lasted for 7 days, was uneventful. She was discharged with regular follow-ups. A genetic work up was performed and through research-based testing revealed 2 homozygous mutations of the MAN2B1 gene affecting NM_000528;c.2397_2398insG:p.Q799fs. She was last seen after 12 months, her head shape was satisfactory and head circumference followed the head growth chart at the 50th percentile. She was developing normally to her age and neurological examination was essentially normal.

DISCUSSION

Hydrocephalus has been managed, for decades, with placement of CSF-shunt. However, with recent advances in neuroendoscopy, treating hydrocephalus with ETV has become possible. With shunt-independence and low-risk profile of postoperative complications, many authorities consider ETV is the first line treatment of obstructive hydrocephalus. Despite being a low-risk procedure, complications of ETV have been well documented. Such complications include; CSF leak, neurological damage, and infections. As a delayed complication, craniosynostosis has been reported to occur after shunt placement. To our knowledge, no previous reports on post-endoscopic treatment of craniosynostosis exist in the English literature. Our report documents the first case of pan-craniosynostosis developing in endoscopy-treated obstructive hydrocephalus.

The child’s development was normal after ETV for about 2 years, and when presented with dysmorphic features suggestive of craniosynostosis, she was investigated for metabolic and genetic abnormalities. She was found to have alpha-mannosidosis, which is a lysosomal storage disorder caused by mutations in the MAN2B1 gene. No other clinical or neurological abnormalities were detected at that time.

The clinical manifestations of mannosidosis have been described as variable, including mental retardation, skeletal abnormalities, immune deficiency, and rarely include craniosynostosis. Grabb et al in 1995 reported a case of multiple sutures craniosynostosis causing macrocephaly and increased intracranial pressure in a child with a previously undiagnosed variant of alpha-D-mannosidase deficiency. In contrary our case has no clinical signs of intracranial hypertension when craniostenosis was discovered.
In general, craniosynostosis has been classically categorized into primary (ossification-related; intrinsic suture-mesenchymal pathology) and secondary (brain-growth-failure-related) types. Yet, other less common secondary causes exist and include endocrine (e.g., thyroid dysfunction), metabolic, hematologic, and iatrogenic ‘triggers’ (e.g., shunt implantation)\(^9\). Interestingly, none of these causes were present in our patient, and when MAN2B1 gene mutation was found, this added to our confusion of what could be the cause of craniosynostosis. However, the absence of active hydrocephalus indicating functioning ETV has probably made the observed craniosynostosis likely to be attributable to the ETV procedure.

Shunt-induced craniosynostosis has been estimated to occur in approximately 1% of the children treated with VP shunts\(^5\). Exact mechanism underlying the development of this complication is not fully understood. It has been postulated that chronic reduction of the intracranial pressure (ICP) may be implicated in its development\(^6\). Alternatively, the attenuation of normal ICP waves—caused by the arterial pulse pressure—that occurs after shunt implantation has been suggested to account for such a phenomenon\(^3\).

With CSF shunts and possible change of the intracranial pressure to be less-than-optimal, the approximation of suture edges and the collapse of cranial vault deprive bone mesenchyme from the necessary signals that would maintain the patency of sutures, resulting in secondary craniosynostosis\(^5\). In support of this hypothesis, the premature suture fusion is observed in primary brain growth failure, which is also associated with decreased outward mechanical forces that would prevent suture-edge approximation\(^6\). Thus, based on this principle, several cranial vault expansion approaches, have been attempted to counteract the underlying force balance and improve clinical outcomes of secondary craniosynostosis\(^4,6\).

While overdrainage and the associated relative intracranial hypotension have been postulated to underlie the development of craniosynostosis in shunt-treated hydrocephalus, the applicability of this mechanism to our patient is uncertain; ETV creates an alternative intracranial physiological CSF circulation, and thus, would not be anticipated to result in decreased ICP. Thus, the ICP-exerted ‘physiologic tension’ on suture lines would be expected to remain applicable after ETV. Despite that, our patient developed pan-craniosynostosis after ETV procedure\(^4,5\). The associated Alpha-mannosidosis would probably played a role in the development of craniosynostosis in this case, although craniostenosis has not been reported yet to occur with Alpha-mannosidosis\(^8\).

To date, despite the improved understanding of the pertinent factors, medical therapy provides little benefit, if any, to patients with secondary craniosynostosis. Surgical correction remains the standard of care\(^6\). Our patient underwent cranial vault reconstruction with supra orbital bar advancement (Fig. 5). The patient was doing well after the procedure with no neurological or cognitive deficits on her 12 months follow-up.

Fig. 5 a-d: Axial CT scan after fronto-orbital osteotomy showing evidence of osteotomies, persistence of ventriculoemgaly, and patent CSF spaces around the brain.
The presence of ventricular asymmetry with dilatation of right lateral ventricle more than the left warranted unilateral obstruction of foramen of Monro. Therefore, the endoscope was introduced to the right lateral ventricle where a membrane was found occluding foramen of Monro (Fig. 3), and successful fenestration of this membrane was first carried out before performing ETV, this was followed by endoscopic septostomy. Congenital occlusion of the foramen of Monro is uncommon and usually occurs in infants. We believe that ETV was important in this patient, even in the absence of aqueductal stenosis, as most of similar cases needed treatment of hydrocephalus either by ETV or later on with shunt insertion.

Clinical management of hydrocephalus is challenging, given the delicate balance of involved factors and the presence of underlying morbidities. A close long-term follow-up for the development of complications is necessary, even after the instillation of a seemingly successful treatment. Despite its extreme rarity, awareness of craniosynostosis occurring as a complication of ETV allows timely diagnosis and treatment.

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Disclosure

The author(s) declare no conflict of interest or any financial support and confirm the approval of the submitted article by the concerned ethical committee.

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