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Case Report

Chiari 1 malformation in patient with Noonan syndrome: A case report and review of literature

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ABSTRACT

Background: Different theories exist about the pathogenesis of Chiari 1 malformations (CM-I), but none of them is thought to be exhaustive. Likewise, the role of genetic factors contributing to these conditions has not yet been elucidated, but there is a co-occurrence of CM-I with genetic syndromes such as Noonan syndrome (NS) and other RASopathies.

Case Description: We describe the case of a 16-year-old female known with NS, currently presenting with Valsalva-induced headaches. Imaging of the brain and spine showed a CM-I with extensive syringohydromyelia. The patient was treated with a foramen magnum decompression and C1 laminectomy with duraplasty. The postoperative course was uneventful and the symptoms improved postoperatively.

Conclusion: In the literature, sixteen cases of CM-I in patients with NS are reported. Our reported case illustrates the co-occurrence between CM-I and RASopathies. We review current literature about the understanding of the possible association or pathogenetic link between the two conditions. This case report highlights the clinical importance of recognizing the co-occurrence of CM-I and NS, potentially guiding early diagnosis and management strategies.

Keywords: Chiari decompression, Chiari I malformation, Noonan syndrome, RASopathy

INTRODUCTION

Chiari 1 malformations (CM-I) are a group of disorders characterized by herniation of the cerebellar tonsils through the foramen magnum. Different theories about the pathogenesis of CM-I exist, but none of them is thought to be exhaustive.[3] CM-I occurs isolated in otherwise healthy individuals or association with other abnormalities. The contribution of genetic factors to CM-I is not yet elucidated, but there is a co-occurrence of CM-I with genetic syndromes.[6] Several case reports exist describing CM-I in patients with Noonan syndrome (NS).

NS is a part of the family of RASopathies, a group of genetic conditions caused by mutation in genes encoding for proteins in the Ras/MAPK-signaling pathway. It is characterized by facial deformities, cardiovascular abnormalities, and thoracic deformities, but other organ systems can also be involved.[14]

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The exact link between CM-I and NS is not completely elucidated. It is, however important to be aware of a possible association between CM-I and NS. In the management of patients with NS, clinicians have to be vigilant for neurological complaints caused by CM-I. When treating patients with CM-I, clinicians should start the appropriate diagnostic workup when features of NS are encountered.

In this article, we report the case of a 16-year-old female known with NS and diagnosed with CM-I. Furthermore, we discuss the current evidence on the association between the two disorders.

CASE DESCRIPTION

We report the case of a 16-year-old female diagnosed with NS at infantile age as a result of aberrant facial characteristics. The diagnosis was supported by genetic testing, showing a PTPN11 mutation compatible with NS.

She presented to the neurosurgical department with complaints of Valsalva-induced headaches. Upon clinical examination, we noticed that the patient was small for her age and displayed classical morphological features, as seen in NS. Neurological examination showed a symmetrical hyperreflexia in the four limbs without the presence of pathological reflexes. Further neurological testing was normal.

A magnetic resonance imaging scan of the brain showed a CM-I with the descent of the cerebellar tonsils of thirteen millimeters below the foramen magnum [Figure 1]. The posterior fossa volume was calculated using the abc/2 method, yielding a value of 155cm^3. A syringohydromyelia was present, craniocaudally extending from C2 up to T5 and axially with a diameter of up to 10 mm. Furthermore, a discrete S-shaped spinal scoliosis was seen.

Taking into account the patient's complaints, with a typical Valsalva-induced headache and the iconographic findings, with a CM-I with extensive syrinx, a surgical treatment was proposed.

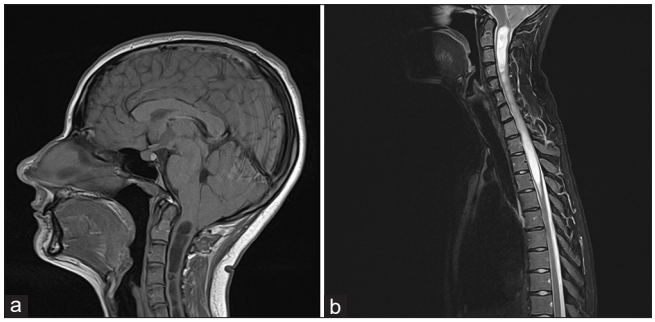

Figure 1: (a) Sagittal T1-weighted magnetic resonance imaging (MRI) of the brain showing the presence of a Chiari 1 malformation with an extensive syrinx. (b) Sagittal T2-weighted MRI of the cervicothoracic spine illustrating the presence of a syrinx from C2 down to T5.

The patient underwent a foramen magnum decompression with C1 laminectomy and duraplasty. Preoperative coagulation tests were normal, and no specific measurements were taken perioperatively. The procedure was uneventful, and the postoperative recovery proceeded without complications. During follow-up, the patient reported an improvement in headaches and decreased need for analgesics. One year after the surgery, the patient continues to be free of any complaints.

DISCUSSION

CM-I is a group of disorders characterized by a descent of the cerebellar tonsils through the foramen magnum of more than 5 mm in adults and 3 mm in children, possibly associated with syringomyelia. The diagnosis can be incidental in asymptomatic cases or can be prompted by symptoms. Classical symptoms are a Valsalva-induced occipital headache or symptoms due to brain stem compression, like central sleep apnea.[10]

Different theories about the pathogenesis of Chiari malformations have been described.[3] Generally accepted is that the cause is multifactorial, with the presence of either a downward pressure due to a disbalance between the cranial box and the cranial contents or a downward traction due to a tethered cord. It can be an isolated disorder, or it can be associated with other anomalies. The contribution of genetic factors to this condition remains unclear, but a co-occurrence with genetic syndromes and familial clustering is seen. Genetic factors that have been associated with CM-I are the reticular activating system (RAS) genes.[6]

RAS genes are involved in the Ras/mitogen-activated protein kinase (MAPK)-pathway.[13,14] This is an important signal transduction pathway involved in the regulation of cell proliferation, differentiation, survival, and metabolism. Germline mutations in genes encoding for components or regulators of the Ras/MAPK-pathway can lead to dysregulation of the pathway and disturb development in embryonic and later stages. This leads to a group of malformation syndromes, altogether referred to as RASopathies. These include, among others, neurofibromatosis type 1, cardiofaciocutaneous syndrome, Costello syndrome, and NS.[13]

NS is a heterogeneous and multisystemic genetic disorder first described by Jacqueline Noonan in 1962. It is a relatively common condition with an estimated prevalence of 1 in 1000 to 1 in 2500 live births.[12] Like all RASopathies, NS is inherited in an autosomal dominant fashion. Multiple genes have been implicated in NS, all encoding for proteins in the Ras/MAPK pathway. About 50% of cases of NS are caused by

a missense gain-of-function mutation in PTPN11, which is a gene encoding for SHP2 and is mapped to chromosomal band 12q24.1. Other genes linked to NS are Son of sevenless homolog 1 (SOS1), neuroblastoma RAS viral oncogene homolog (NRAS), kirsten rat sarcoma viral oncogene homolog (KRAS), RAF proto-oncogene serine/threonine kinase 1 (RAF1), B-Raf proto-oncogene serine/threonine kinase (BRAF), SHC (Src homology 2) domain-containing transforming protein 2 (SHOC2), and Casitas B-lineage lymphoma (CBL).[14]

NS is characterized by distinct facial and musculoskeletal features, which most often lead to the diagnosis of NS. The typical facial features include a tall forehead, hypertelorism, epicanthal folds, ptosis, and low-set posteriorly rotated ears. Musculoskeletal features are short stature, a short neck with low posterior hairline, a chest deformity with superior pectus carinatum and inferior pectus excavatum, and scoliosis. In over 80% of patients with NS, cardiovascular disorders can be found. The most commonly found disorder is pulmonary valve stenosis, but an atrium septum defect and hypertrophic cardiomyopathy are also frequent. Other manifestations of NS include a developmental delay, lymphatic issues, bleeding diathesis, and cryptorchidism.[14,15] Less frequent but important are the association of NS with myeloproliferative disorder as well as solid tumors such as giant cell tumors.[2]

Few neurological disorders have been described in NS. Cognitive and developmental issues are reported more frequently in NS but are very variable. Structural disorders of the nervous system are rare. In literature, the presence of a CM-I in patients with NS is described in sixteen patients.[6,7,9,17,19]

In several studies, a co-occurrence of CM-I and RASopathies has been described. For example, in a paper reviewing 500 children who underwent surgery for CM-I, 5% had a diagnosis of neurofibromatosis type 1.[18] A retrospective cohort study by Saletti *et al.*[16] showed that 62% of children with CM-I were classified as syndromic, with a molecular diagnosis in 28%. Mutations in the RAS/MAPK pathway were found in 26% of these cases. As stated earlier, several case reports describe the presence of CM-I in patients with NS. In these reports, most of the patients did not have typical CM-I symptoms.

It is often thought that NS is associated with CM-I because of the associated skull deformities. NS primarily influences facial features.[16] A morphometric analysis of the posterior fossa of 21 children with NS did reveal a smaller than normal posterior fossa.[1] In mice, SHP2 deletion predominantly results in frontal and facial abnormalities while relatively sparing the posterior fossa.[11] In our patient, the posterior fossa volume was comparable to previously reported values in literature, based on the same calculation method.[8] Thus, the skull deformities observed in NS may not fully account for the association with CM-I. This could mean that there are other genetic mutations involved in NS with co-existing CM-I or that there is another cause. An alternative theory is that patients with NS display posterior fossa overcrowding due to an abnormal gliogenesis leading to megalencephaly.[5,16] The exact causal relationship or the link between the two has not been elucidated yet due to the overall rarity of the co-occurrence, with only sixteen reported cases in the literature. It is, therefore, difficult to determine whether the association is true or coincidental and to unveil the true pathology behind it.

To manage CM-I in patients with NS, an understanding of the natural history of CM-I is essential.[10] Asymptomatic patients can be followed clinically with serial imaging since over 90% of these patients remain clinically stable. In case of clear symptoms related to CM-I or a syrinx, surgical treatment is proposed. Symptoms responding best to treatment are the Valsalva-induced headache and symptoms related to the presence of the syrinx. Surgery can comprise a foramen magnum decompression with or without duraplasty.[10] Patients must be followed clinically in the long term due to reported long-term failure rates of about one in three patients.[4]

The knowledge of the co-occurrence between RASopathies and CM-I is clinically relevant. First, it stimulates clinicians who regularly follow patients with RASopathies to remain vigilant for neurological symptoms or abnormalities during neurological examination and to perform appropriate imaging in a timely manner. Vice versa, it is a reminder to perform genetic work-up in patients with CM-I with possible features of RASopathies.

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