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Case report

Goldenhar syndrome and medulloblastoma: A coincidental association? The first case report

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ABSTRACT

Background: Features of Goldenhar syndrome include several craniofacial anomalies of structures derived from the first and second pharyngeal arches, as well as vertebral, cardiac and renal systems abnormalities. In addition, Goldenhar patients were reported to manifest a variety of central nervous system anomalies and several types of neoplasias.
Case history and discussion: The first case of medulloblastoma in a patient with Goldenhar syndrome is presented here. There is no clear association between these two pathologies. We speculate that aberrant events during the migration of neural crest cells in early stages of development could be the basis of an association between medulloblastoma and Goldenhar syndrome. The case history suggests other possible etiological contributing factors to the development of medulloblastoma, such as patient's history of trauma and/or early childhood exposure to ionizing radiation.

1. Introduction

Oculo auriculo vertebral spectrum (OAVS) encompasses both hemifacial microsomia (HFM) and Goldenhar syndrome (GS). It is thought that GS may be a more severe version of OAVS while HFM may be a milder version. GS is observed in around 1 per 5600 live births (Gorlin, 1990). The aetiology of GS can be explained by genetic and nongenetic factors. Both autosomal recessive and dominant patterns of inheritance were reported; cases compatible with an autosomal dominant pattern of inheritance were reported in about 2–10% of the cases (Gabbett et al., 2008; Vendramini-Pittoli and Kokitsu-Nakata, 2009). However, most cases are sporadic. Possible etiological factors mentioned in the literature include diabetic mothers (Ewart-Toland et al., 2000; Wang et al., 2002), teratogens such as thalidomide (Smithells and Newman, 1992; Jacobsson and Granström, 1997), and retinoic acid (Johnston and Bronsky, 1995). The clinical features of GS are generally characterized by anomalies involving structures derived from the first and second pharyngeal arches. Thus the mandible is severely affected leading to HFM. Several classifications were proposed to grade the severity of HFM (Kaban et al., 1988; Vento et al., 1991; Pruzansky, 1969). In addition to mandibular hypoplasia, facial cleft, ear malformations, ocular anomalies, epibulbar dermoids, upper eyelid colobomas and macrostomia were reported. Patients with HFM often present with facial nerve weakness and hearing loss. The prevalence of facial nerve palsy with HFM varies between different authors: 22% (Bassila and Goldberg, 1989); 25% (Murray et al., 1984); 45% (Vento et al., 1991). Seventh nerve palsies correlate well with both the severity of mandibular hypoplasia and the presence of sensorineural hearing loss. The trigeminal nuclei/nerve and other cranial nerves may also be deficient.

Clinical abnormalities are not limited to the craniofacial region. Vertebral, cardiac and renal abnormalities are also reported in the literature (Rollnick et al., 1987; Gawrych et al., 2011). A variety of congenital CNS abnormalities associated with Goldenhar syndromes have been reported including lipomas, cerebellar hypoplasia, agenesis/hypoplasia/dysgenesis of the corpus callosum,

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microcephaly, hydrocephalus secondary to stenosis of the aqueduct of Sylvius, dilated lateral cerebral ventricles, Arnold–Chiari malformation and encephaloceles. In addition, Dandy Walker variant, choroid plexus cysts, cerebellar vermis hypoplasia, intracerebral calcifications, dermoid cysts, polymicrogyria, cortical dysplasia, cranium bifidum, holoprosencephaly, unilateral arhinencephaly ipsilateral to the side of the Goldenhar microtia and HFM, asymmetric lateral cerebral ventricles, absence of septum pellucidum, porencephalic cyst and teratomas have been reported (Aleksic et al., 1984; Schrander-Stumpel et al., 1992; Naidich et al., 1996; Tasse et al., 2005; Touliatou et al., 2006; Engiz et al., 2007; Rosa et al., 2010).

Neoplasias are also a frequent finding in patients with Goldenhar syndrome. Cases with intracranial lipoma (Beltinger and Saule, 1988), acute myeloid leukaemia (Pavithran and Kapoor, 2002), neuroblastoma (Michel-Adde et al., 2003), mesenchymal chondrosarcoma (Ostlere et al., 1999), congenital ameloblastic fibroma of the mandible (Naidoo and Stephen, 1998), metatarsal and cuneiform chondromyxoid fibroma (Goldenhar et al., 1994), haemangioma of the sculp (Krause, 1970), portal vein cavernoma (Stringer et al., 2005) and hepatoblastoma (Barton and Keller, 1989; Corona-Rivera et al., 2006) have been reported previously.

In this report we present the case of a 7-year-old girl suffering from Goldenhar syndrome, who developed a medulloblastoma. Medulloblastomas are the most common primary malignant brain tumours in children (McNeil et al., 2002; Gajjar et al., 2004). Previously, medulloblastomas were thought to be a subgroup of primitive neuroectodermal tumours (PNETs) of the posterior fossa (Rorke, 1983; Bigner et al., 1998). However, recent genetic studies have shown that medulloblastomas are molecularly distinct from other PNET tumours (Pomeroy et al., 2002). They typically arise in the fourth ventricle and can spread easily through CSF (Thurnher, 2009). In rare cases, the tumours can spread beyond the central nervous system. Medulloblastomas often result in hydrocephalus, expressed in a variety of symptoms, including nausea and vomiting, headaches, weakness, seizures, change in behaviour, weight loss or weight gain. At a later stage, symptoms include loss of coordination, double vision, dizziness and problems with walking and balance. Current treatment protocol includes surgery, radiation therapy, chemotherapy and sometimes implanting a ventriculoperitoneal shunt. The prognosis is relatively good, with a 5-year survival rate over 75%, but they carry significant morbidity. Cognitive, neurological and endocrine deficits are associated with treatment (Zeltzer et al., 1999). The development of a medulloblastoma in association with a Goldenhar syndrome has not been previously reported, therefore the aim of this report is to describe this unique occurrence and to discuss its possible aetiology.

2. Case report

This study was approved by the Rambam Health Care Campus local institutional review board.

The patient was born to non-consanguineous parents, weighing 4.570 g at 42 weeks of gestation following caesarian delivery. Goldenhar syndrome was genetically confirmed prior to her release from the hospital. Her family history includes a mother, grandmother and a cousin with Goldenhar syndrome, which suggests an autosomal dominant pattern of inheritance (Fig. 1). Clinical examination revealed a hypoplastic auricle with atresia of the external auditory canal, a preauricular tag and a cheek cleft on the right side. Facial asymmetry was noted due to a right mandibular hypoplasia. CT of the facial and temporal bones was performed. At the age of 2 months she was seen by an ENT specialist who established deaf right ear and normal hearing on the left one (Fig. 2).

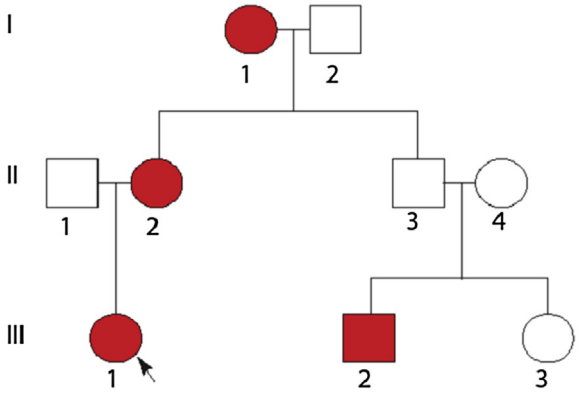

Fig. 1. Patient's family tree (marked with an arrow) with syndromatic individuals shown in red.

At the age of three the patient underwent combined surgical orthodontic manipulation using the distraction osteogenesis technique to elongate the right mandibular ramus commonly done for this type of craniofacial anomaly (Nada et al., 2010). CT examination was performed as part of the diagnostic protocol done prior to distraction osteogenesis (Mahrous et al., 2011). Due to lack of patient's cooperation, most of the procedures were done under sedation.

2.1. Trauma

At the age of four, the patient was injured in a car accident and diagnosed with liver rupture. She was hospitalized in an ICU for 1 week, followed by the admission to the paediatric surgery department. Since then the patient continued to complain about recurrent stomach aches and vomiting. On one occasion she was hospitalized for severe dehydration after an intense bout of vomiting and was treated with fluids. Later on, at the age of seven, she suffered episodes of intense vomiting roughly three times a day for 2 months prior to the last hospitalization. Upon her admission, gastroscopy and ultrasound of the stomach were performed revealing nodular gastritis due to *Helicobacter pylori* infection for which she received "triple therapy" treatment. Drusen were found by paediatric neurologist while performing a fundus examination. This fact coupled with a history of persistent vomiting unrelated to food led to a medical decision to perform a brain MRI.

2.2. Medulloblastoma diagnosis and treatment

The MRI revealed a tumour mass filling the fourth ventricle and expanding it, causing secondary hydrocephalus. All the features were consistent with preliminary diagnosis of medulloblastoma (Fig. 3). Subsequently, the patient was put on steroids and admitted to a department of paediatric neurosurgery. The patient was fully conscious and cooperative. She complained of headache and a leg ache. A neurological examination revealed unsteady gait and diplopia. Eye movements were normal, pupils were equal, no "cross-eyed" vision. Her tongue deviated slightly to the right. There was no ataxia, nor clonus. Babinsky flexor signs on both sides revealed slightly low tonus. She had difficulty performing tandem, but without falling; jumping on each leg was difficult; alternative movements were normal. Physical exam also revealed several hyperpigmentation café-au-lait spots on her back, stomach and legs. These findings were consistent with central cerebellum disturbance. The patient was admitted to a paediatric neurosurgery