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# Humoral Immune Deficiency and Hemifacial Microsomia Seen in One Family

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**We present a patient with hemifacial microsomia and immune deficiency. The patient is a 5-year-old with grade III microtia and Pruzansky type I right mandibular hypoplasia. She developed 25 pulmonary infections in 3 years, required hospitalization every 6 weeks to receive antibiotics, and experienced recurrent herpes stomatitis and esophagitis, staphylococcal bacteremia, urinary tract, sinus, and ear infections. She had low total IgG, IgG1, IgG2, IgA, and anti-pneumococcal antibody levels. She was unable to maintain protective pneumococcal titers following vaccination. The patient's 7-year-old sister also suffered from recurrent infections, had a left facial skin tag, and a left arachnoid cyst. We conclude that immune deficiency can occur in association with hemifacial microsomia.**

KEY WORDS: *hemifacial microsomia, hypogammaglobulinemia, immune deficiency, oculoauriculovertebral spectrum*

Hemifacial microsomia (HFM) denotes asymmetrical hypoplasia of several structures that arise from the first and second pharyngeal arches (Gorlin et al., 1963). It is estimated to occur in 1 in 5600 live births (Castori et al., 2006). Although HFM primarily affects the craniofacial region, extracraniofacial abnormalities occur in more than 50% of patients (Horgan et al., 1995). The expanded range of HFM is often referred to as oculoauriculovertebral spectrum (OAVS) (Fan et al., 2005), and manifestations include cardiac, skeletal, renal, pulmonary, and central nervous system involvement (Gorlin et al., 1963; Rollnick et al., 1987; Horgan et al., 1995). These associated defects have suggested that HFM is a disorder of blastogenesis and the developing midline (Opitz et al., 2002). The etiology of HFM is unclear; teratogenic agents, socioeconomic risk factors, and chromosomal abnormalities have been described (Cohen et al., 1989; Kaye et al., 1992; Stoll et al., 1998; Werler et al., 2004; Tasse et al., 2007). Genetic transmission is suspected because several families have been described with an autosomal-dominant pattern of inheritance (Cohen et al., 1989; Kaye et al., 1992; Stoll et al., 1998; Llano-Rivas et al., 1999; Tasse et al., 2007). Furthermore, up to 45% of HFM patients have extended family members with minor clinical manifestations consistent with HFM (Rollnick and Kaye, 1983; Llano-Rivas et al., 1999).

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## Case Report

The patient is a 5-year-old white girl born to a 25-year-old Gravida 4, Para 1-2 mother following a pregnancy complicated by hyperprolactinemia. She was born at 42 weeks gestation via vaginal delivery and weighed 3300 g. She had right grade III microtia, narrow auricular canal, preauricular tag, and mandibular hypoplasia (Fig. 1A and 1B). Computed tomography showed atresia of the right external auditory canal with a membranous plate and no tympanic membrane. The mastoid segment of the right facial nerve was positioned more anteriorly than normal. Magnetic resonance imaging (MRI) of the facial bones documented Pruzansky type I right mandibular hypoplasia (Fig. 2). Her audiogram showed normal hearing on the left. Sonography of the kidney and the heart as well as MRI of the brain and the cervical spine were normal. Her diagnosis was right predominant HFM.

She suffered from recurrent infections. Her first episode of pneumonia occurred at 3 months of age. She had 24 more pulmonary infections in the first 3 years of life, requiring hospitalization every 6 weeks for intravenous antibiotics and hydration. She also suffered from recurrent herpes stomatitis and esophagitis, staphylococcal bacteremia, and recurrent urinary tract, maxillary sinus, and ear

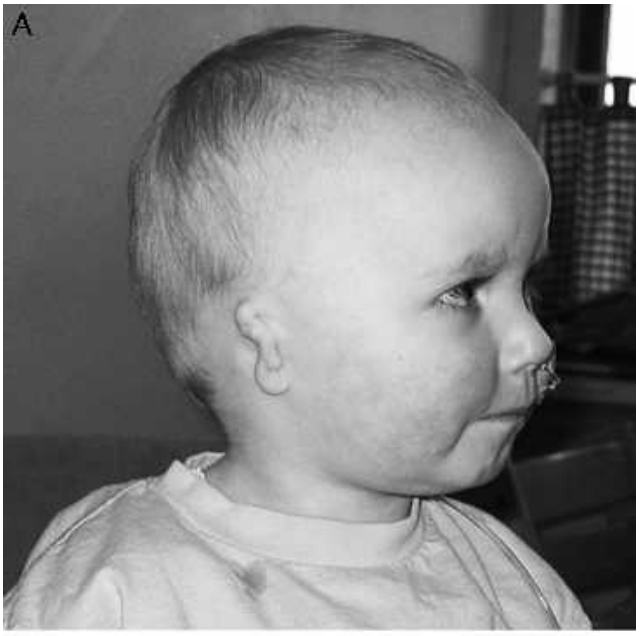



**FIGURE 1A Photograph of the patient shows grade III microtia.**
**FIGURE 1B Photograph of the patient shows right facial hypoplasia.**

infections. She was given prophylactic daily sulfamethoxazole.

The patient's 7-year-old sister was born at 32 weeks gestation via normal vaginal delivery with a birth weight of 3200 g. She had a skin tag on her left cheek and an abnormal brain MRI, which showed a large arachnoid cyst in the left middle cranial fossa, extending into the left frontal area (Fig. 3A and 3B). The sister had a normal audiogram, echocardiogram, and renal ultrasonography. The sister's infectious history also was extensive but not as severe as the patient's. The sister had 10 to 15 episodes of pneumonia, monthly outbreaks of herpes stomatitis, and approximately 20 ear infections as well as recurrent sinus and urinary tract infections. She required hospitalization for intravenous antibiotics four times a year and was maintained on prophylactic daily sulfamethoxazole. Neither the patient nor her sister was up to date with immunizations because vaccines resulted in frequent adverse reactions including emesis, dehydration, and rashes.

The father was Danish/Icelandic, and the mother was German, Danish, English, and Icelandic. The father described that his mandible looked similar to that of his daughter until he underwent two operations at 8 and 12 years of age. His medical records were not available. One of the father's eyes was smaller than the other. The father's ear tags, which were removed, and his small eye were ipsilateral to his mandibular abnormality. The father did not have recurrent infections. There was no history of cystic fibrosis or consanguinity. The mother and her family did not have a history of HFM or immune deficiency.

## Materials and Methods

Blood samples were drawn after informed consent. Cytogenetic, molecular cytogenetic, metabolic, and immune studies were performed by standard clinical methods. The case of patients was conducted in accordance to the Patients' Bill of Rights at Children's Hospital, Boston, and followed the Principles of the Declaration of Helsinki.

## Results

The patient, her sister, and the father had normal karyotypes including 22q11 and 10p13-p14 fluorescence *in situ* hybridization (FISH) and microarray studies. DNA testing was negative for cystic fibrosis for the three most common mutations in Iceland: del F508, N1303K, and 1078 delT. Multiple attempts in both the patient and her sister for sweat chloride determination were unsuccessful due to insufficient perspiration. Metabolic studies including plasma amino acids, organic acids, and acylcarnitine profile were normal. EYA1 gene sequencing for branchiootorenal syndrome revealed two known normal variants: Exon 16: c.1656T>C (p.His552His) and Exon 12: c.1179C>T (p.Gly393Gly).

The patient's immune workup revealed a low total IgG (443 mg/dL), low IgG1 (307 mg/dL) and IgG2 (24 mg/dL) subclasses, a low IgA (21 mg/dL), and low titers to all pneumococcal antigens tested. Her pneumococcal titers increased after two doses of pneumococcal vaccine, but she was not able to maintain protective titers two years after immunization. Treatment with intravenous immunoglobulin for hypogammaglobulinemia resulted in a dramatic improvement with complete resolution of her infections, including her recurrent herpes stomatitis and esophagitis infections. Temporary discontinuation of this therapy led to resumption of her infections; therefore, the patient was maintained on intravenous immunoglobulin. The sister's immune deficiency was milder. The sister had a low IgG2 level (108 mg/dL) with low pneumococcal titers but responded well to one dose of pneumococcal vaccine. Both

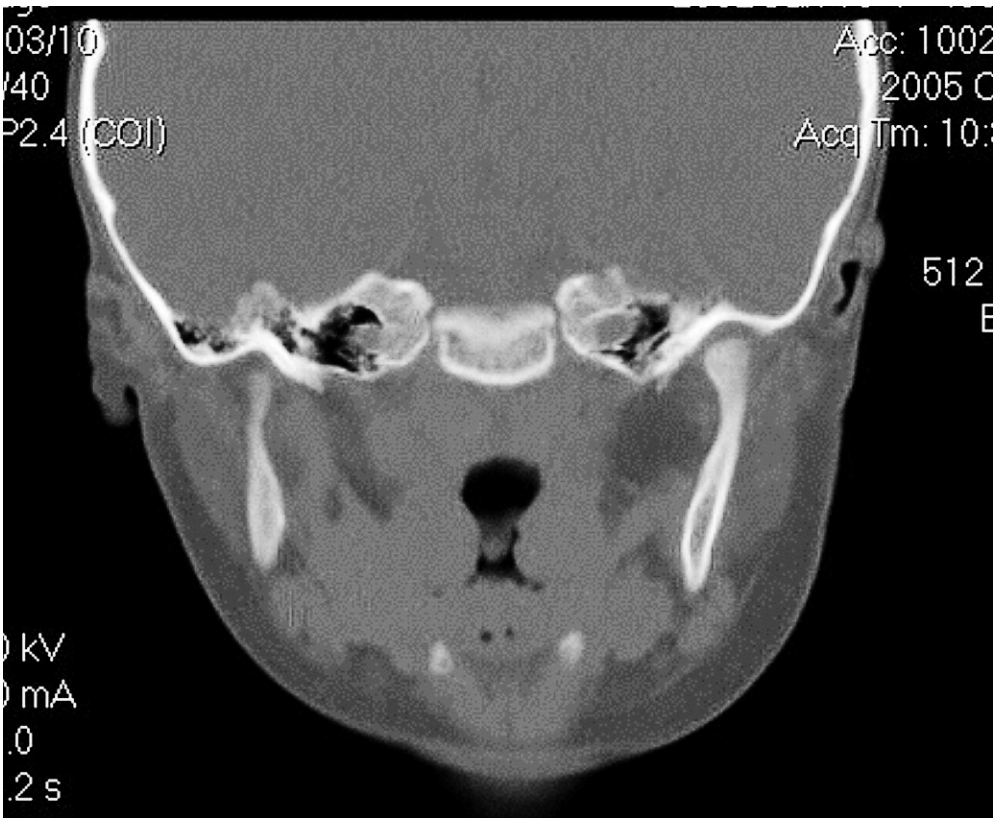


**FIGURE 2 The patient's MRI of the facial bones reveals Pruzansky type I right mandibular hypoplasia.**

the patient and her sister had normal T-cell numbers, T-cell subsets, T-cell function, and NK cell function as well as protective titers to protein antigens, tetanus, and polysaccharide ribose phosphate. In addition, the percentages of memory and naïve T cells were normal.

## Discussion

Recurrent middle ear infections can occur in patients with middle ear anatomic abnormalities. Nevertheless, when the severity and/or frequency of these infections are excessive, patients should be evaluated for other contributing factors, such as immune deficiency. The immunologic evaluation should include measures of both humoral and cellular immunity. Total serum immunoglobulin levels and specific antibody titers are necessary to evaluate the patient's ability to develop antibody responses to invading microbes. T-cell numbers, T-cell subsets, and T-cell responses to mitogens and antigens are used to study the patient's ability to establish cell-mediated immunity to pathogens. In its most severe form, humoral immune deficiency presents as agammaglobulinemia with complete absence of B cells and immunoglobulin. In most patients, humoral immune deficiency is characterized by a deficiency of one or more classes of immunoglobulin (IgA, IgM, IgG, and IgG subclasses) with or without the ability to make specific antibody responses (Finocchi et al., 2002). Alternatively, immunoglobulin levels may be normal; although, specific antibody responses may be insufficient (Gross et al., 1992).

The patient's IgA, which provides mucosal immunity, was low. Her total IgG was also well below the lower limit of normal despite her recurrent bacterial infections. Furthermore, her IgG2, the subclass most protective against encapsulated bacteria (Sanders et al., 1995) such as *Streptococcus pneumoniae*, was only 5% of her total IgG. Finally, her titers to pneumococcal antigens were low in spite of her frequent ear, sinus, and pulmonary infections. Although she initially responded to pneumococcal vaccination, she was unable to maintain protective pneumococcal titers over time. The sister's antibody deficiency was milder, with a low IgG2 level but normal responses to pneumococcal vaccination.

HFM could not be diagnosed definitively in the father due to lack of medical records or in the sister due to lack of facial asymmetry. However, the patient, her sister, and her father all present manifestations along the spectrum of HFM. The father's surgical history and the sister's asymmetric arachnoid cyst and facial tag are consistent with reports that up to 45% of patients with HFM have family members with clinical manifestations suggestive of HFM (Rollnick and Kaye, 1983; Llano-Rivas et al., 1999). Compatible with our patient who had both HFM and immune deficiency, Hattori et al. (2005) reported the prenatal diagnosis of HFM in a 21-week-old aborted fetus with thymic hypoplasia, right auricular and right orbital


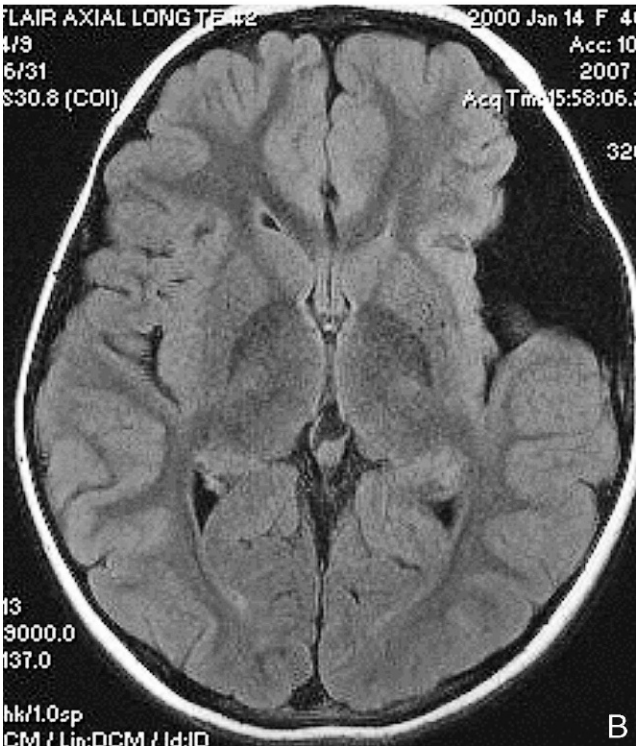


**FIGURE 3A Photograph of the sister shows her left facial skin tag.**
**FIGURE 3B The sister's brain MRI exhibits a large arachnoid cyst in the left middle cranial fossa.**

hypoplasia, ventriculoseptal defect, and right renal agenesis. The hypoplasia of the thymus, which is a midline structure, in this fetus supports the classification of HFM as a disorder of blastogenesis and the developing midline (Opitz et al., 2002). Our patient and her sister had normal T-cell numbers and normal *in vitro* functional T-cell studies. Nevertheless, their exquisite susceptibility to herpes simplex infections suggests *in vivo* T-cell abnormalities. Furthermore, the history of frequent adverse reactions to vaccines may be an indication of T-cell dysregulation.

In conclusion, we describe immune deficiency in association with HFM. We hope that this report will prompt clinicians to evaluate patients with HFM and recurrent infections for immune deficiency.

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