Hemifacial Myohyperplasia Sequence

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This is a report of an additional patient affected by hemifacial myohyperplasia (HMH). We postulate that this condition originates around the fourth gestational week at any step of cranial muscle development from somitomeres to branchial arches, most probably due to prolonged period of proliferation during cranial muscle development, subsequent abnormal contact between cranial neural crest (CNC) cells and cranial myoblasts, and an impaired interaction among CNC cells and cranial myoblasts derivatives. HMH may represent another example of somatic mosaicism and its features can be explained by a combination of morphostatic and morphodynamic mechanisms of pattern formation during development. Here we suggest that HMH is a sequence in which the primary defect is hyperplasia of the facial muscles and the other findings are secondary to this.

Key words: facial asymmetry; congenital or acquired asymmetry of the face; hemifacial myohyperplasia; cranial neural crest; branchial arch; pharyngeal arch; somitomeres; myocyte; muscle cells; development; morphostatic mechanisms; morphodynamic mechanisms; positional information

INTRODUCTION

Hemifacial myohyperplasia (HMH) is a condition characterized by enlargement of the muscle mass of the facial muscles due to increased number of myocytes with ipsilateral hypoplasia of the facial skeleton. Two major groups have been described: (1) isolated involvement of the muscles of facial expression (derived from the second pharyngeal arch); (2) combined involvement of the muscles of facial expression and the muscles of mastication (derived from the first pharyngeal arch). Facial asymmetry progresses after birth and treatment is necessary in order to improve skeletal growth on the affected side. Treatment strategies are up to date limited to just two options: (1) surgery; (2) Botulinum toxin. Its cause, risk of recurrence and pathogenesis remain unknown. Here we discuss some of the findings reported by Lee et al. and use an experiment developed by Ericsson et al. to model the pathogenesis. Our final aim is to contribute to better understand this disorder.

How to Cite this Article:

CLINICAL REPORT

This patient was first seen by us at the age of 22 months. She was the first-born and only child of healthy nonconsanguineous parents of Colombian origin. She was previously diagnosed as having the Goldenhar anomaly. Pregnancy history and family history were unremarkable. She had marked left facial asymmetry, enophthalmos, orbital dystopia, periocular asymmetry, and narrowing of the left palpebral fissure. The left ala of the nose was deviated upwards. Dimpling of the skin on the left side of the chin and left corner of the mouth was evident when she smiled. Ipsilateral downward auricular displacement and contralateral chin displacement were present. Facial paresis of the affected side was evident. Initially she had a normal bite and right deviation of maxillary and mandible, but in time, she developed a right posterior cross-bite. Intelligence was normal (Figs. 1 and 2).

MRI and CT scan of the face showed increased thickness of the depressor anguli oris, depressor labii inferioris, orbicularis oris, zygomaticus major, buccinator, zygomaticus minor, levator labii superioris, levator lippii superioris alaque nasi and nasalis muscle on the left side of her face. Additionally, there was increased thickness of the superficial fascia without impairment of the subcutaneous tissue. Skeletal findings included mild ipsilateral maxillary and sphenoid hypoplasia; as a result, the bony orbit, middle skull base, and maxillary sinus were slightly reduced in size. Salivary glands, floor-of-mouth muscles, tongue, and jaw-closing muscles, were normal. Facial nerve conduction studies (FNCS)

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showed a normal and symmetrical response in amplitude, latency, and velocity. Results of facial electromyography (EMG) were normal.

**DISCUSSION**

Facial asymmetry is a common feature in over 100 distinctive congenital and acquired conditions. Some findings that help in establishing the diagnosis are: (1) hypoplasia/hyperplasia of the facial musculature; (2) skeletal overgrowth/hypoplasia; (3) type of tissue(s) involved (i.e., vascular, lymphatic, fat, nervous, muscle, and bone); and (4) part(s) of the body affected. The correct diagnosis is finally established on the basis of clinical, imaging, and laboratory findings. In our patient, the face was the only part of the body affected. MRI and CT scan showed enlargement of the facial muscles and mild skeletal hypoplasia on the left side. Therefore, HMH was a relatively straightforward diagnosis.

Actually some authors consider HMH as a type of partial (or limited) hemifacial hemihypoplasia (PHFH) [Islam et al., 2007] whereas others think HMH as a completely different entity [Lce et al., 2001]. We believe classifications like those proposed by Ward and Lerner [1947] (see Table I) and Rowe's [1962] (see Table II) are clinically useful and should be applied in clinical settings even though they might be grouping etiologically different entities. In fact, HMH is a PHFH in the strict sense of the term. Also, it seems reasonable to think that, at least in some cases, partial and total hemifacial hypertrophy may represent two ends of a clinical spectrum. However, we believe is worthy for the geneticist to consider HMH as a different entity since this condition seems to be a primary disorder of the somitomeric myoblasts as we show below.

<table>
<thead>
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<th>TABLE I: Ward and Lerner Classification of Congenital Hypertrophy</th>
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<tr>
<td>1. Total hypertrophy (involves all systems)</td>
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<tr>
<td>2. Limited hypertrophy (in which one or more, but not all systems are involved)</td>
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- Segmental
- Crossed
- Hemi hypertrophy (entire side)
- Muscular
- Skeletal
- Vascular
- Neurologic
Facial paresis was described in 8 of the 11 previously reported cases [Lee et al., 2001; Castillo Taucher et al., 2003]. The normal FNCS finding in our patient is important since it demonstrates the lack of involvement of the VII cranial nerve, excluding the relationship between the VII cranial nerve in the pathogenesis of HMH and VII cranial nerve paresis as one of the manifestations in the condition. Normal EMG results and normal biopsy findings suggest the muscles fibers are structurally and functionally normally differentiated. Therefore, it is evident that facial muscle paresis in HMH is associated with a normal FNCS and EMG. Myocytes are normally differentiated but there is global disturbance in the three-dimensional morphological pattern. This implies that myocytes themselves are intrinsically normal and that the change in the developmental pattern of the muscles is related either to the relationship among myocytes or the relationship between the myocytes and their microenvironment.

Muscle growth during the embryonic period of development is characterized by an increase in myoblast cell numbers through hyperplasia. These cells or their precursors are the only dividing cells of the muscle lineage. Muscle growth in further steps of muscle development takes place through hypertrophy. Therefore, prenatal events that govern the extent of muscle precursor cell proliferation and the timing of differentiation determine the number of fibers a muscle will contain in postnatal life [Smith, 1963]. Coutinho et al. [1993] found that a delay in myoblast differentiation allow additional rounds of cell division for a longer time, resulting in an increase in the pool of myogenic cells. Further molecular studies had shown that growth factors (i.e., FGF2) and extracellular matrix components (i.e., heparan sulfate containing proteoglycans) stimulate the proliferation, prolong the period of proliferation, and inhibit the differentiation of myoblasts resulting in muscle growth through hyperplasia [Velleman, 2007]. Also, the inhibition of myostatin, a strong inhibitor of myoblast differentiation, results in a significant muscle overgrowth due to both hyperplasia and hypertrophy [McPherron et al., 1997]. Therefore, an imbalance between differentiation and proliferation of somitomeric myoblasts seems to be the mechanism by which muscle hyperplasia is produced in HMH patients. Mutations in major pathways involved in muscle development (i.e., HGF, FGF2, IGF, TGFβ, and myostatin) can explain the aforementioned imbalance. The asymmetrical muscle growth and the phenotype confined to a single region can be considered as a sign of somatic mosaicism. In many disorders that share similar phenotypic expression somatic gene mutations have been proved or thought [Erickson, 2003]. Hence, HMH might be another example of a disorder caused by somatic mosaicism. In fact, a somatic mutation that occurs in the cranial somitomes can explain the differential muscle group involvement in this disorder. Previous reports showed that ~60% of the HMH patients have enlargement of the muscles derived from the first and second pharyngeal arches, while ~40% have hyperplasia only in the muscles derived from the second pharyngeal arch [Staffenberg et al., 1998; Lee et al., 2001]. Up to date there is no evidence of physical intersomatomeric discontinuities or boundaries [Noden and Trainor, 2005], thus it is possible that noxious agents or paracrine signals can affect one or more somitomes at once. From this point of view, somitomeric myoblasts may become affected in situ (at the somitomes) and then travel to their respective pharyngeal arch establishing an abnormal relationship with the CNC cells. Since environmental exposures were reported as negative during the pregnancy by the mother of our patient and previous reports of HMH patients does not have mention in this regard, teratogenic etiology seems to be unlikely. Finally, epigenetic abnormalities (i.e., gene silencing) should also be considered.

Most of the features of HMH are explained by the disturbance in the three-dimensional morphological pattern during muscle development. Facial myocytes originate from myoblasts formed at cranial somitomes I-VII. Myoblasts from somitomes IV and VI migrate and colonize the core mesenchyme of the mandibular (first pharyngeal arch) and hyoid (second pharyngeal arch) arches, respectively [Noden, 1991; Le Douarin et al., 1993; Trainor et al., 1994; Trainor and Tam, 1995]. Pharyngeal arches are populated by connective tissue progenitors derived from the cranial neural crest (CNC), to form the muscles of the face in conjunction with somitomeric myoblasts [Noden, 1983; Coulby et al., 1992]. CNC-derived connective tissues provide directional guidance important for the proper extension of the cranial muscles and the subsequent attachment to the insertion on the correct cartilage [Olsson et al., 2001; Ericsson et al., 2004]. As Noden and Trainor commented, specific ablations of CNC cells showed that cranial muscles form but are severely distorted. Contacts with CNC cells therefore appear to be unnecessary for pharyngeal arch muscle differentiation, but are critical for correct pharyngeal muscle morphogenesis [Noden and Trainor, 2005]. These experiments support the idea that HMH is related to disturbances in the relationship between the CNC and somitomeric myoblasts. However, since muscle hyperplasia seems to be produced by an imbalance between differentiation and proliferation of somitomeric myoblasts, and the CNC cells appear to be unnecessary for pharyngeal arch muscle formation, the primary defect is unlikely to be located in the CNC cells. In fact, one can expect that other tissues derived from CNC (i.e., sensory ganglia of cranial nerves; facial bones) were affected if the HMH were a primary disorder of the CNC. Regarding the latter, even though about 90% of the previously reported patients showed hypoplasia/dysgenesis of the facial skeleton [Staffenberg et al., 1998; Lee et al., 2001; Castillo Taucher et al., 2003], these changes, as Lee et al. clearly stated, are most probably secondary to the abnormal
musculature rather than primary defects. Facial paresis implies abnormal muscle tone; and abnormal muscle tone affects skeletal growth, according to the functional matrix hypothesis proposed by Moss [1962]. From this point of view, the lesser the muscle tone, the lesser the stress on the bone with reduced skeletal growth. Therefore, skeletal hypoplasia in patients affected by HMH can be explained as secondary to the abnormal muscle function. Furthermore, musculoskeletal disturbances can explain ocular, dermatological, intraoral, and auricular findings. Moreover, the abnormally growing muscle can impair the normal induction by the CNC cells affecting the spatiotemporal co-ordination of cell behaviors of the craniofacial growing tissues, resulting in abnormal cell mass, attachment and insertion. Hence, clinically HMH is a sequence in which the primary defect is hyperplasia of the muscles derived from the second and/or first pharyngeal arches. Since skeletal findings are attributable to a sequence of events, they are most probably not due to CNC disturbances. We think HMH is initially produced by alterations in morphostatic mechanisms [i.e., positional information, Wolpert, 1969, 1989] since hyperplasia is probably a morphological consequence of an abnormal inductive signaling, followed by disturbances in morphodynamic mechanisms [Salazar-Ciudad et al., 2003] in which the abnormal muscle pattern and the pattern of the surrounding tissues are affected in a causally interdependent way.

In any case, the primary insult should occur during cranial myocytes development around the fourth gestational week when they are located either at the cranial somites/embry (IV and/or V1), branchial arches (first and/or second), or in the path between them. Whether the cause of HMH is genetic, epigenetic, or teratogenic remains elusive and needs further investigation.

REFERENCES


