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Holoprosencephaly and Ectrodactyly: Report of Three New Cases and Review

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Abstract

Holoprosencephaly (HPE) and ectrodactyly represent congenital malformations of the developing forebrain and developing digits, respectively. The combination of these conditions is rare, with only 15 cases known to date (12 previously reported, and 3 new cases described here). While the findings in these patients overlap with previously described genetic conditions, the similarity in phenotypes among these patients has led to the establishment of at least one distinct syndrome: HPE, ectrodactyly, and bilateral cleft lip-palate syndrome (OMIM 300571). There has been great interest in identifying a genetic cause for the findings in patients with HPE and ectrodactyly; however the cause(s) of this rare association still remain unknown.

Keywords

Holoprosencephaly; HPE; Ectrodactyly

Introduction

Ectrodactyly, or split hand/split foot malformation (SHFM), is a rare congenital malformation of the developing digits in which there is a deep median cleft in the developing hand or foot with aplasia or hypoplasia of phalanges, metacarpals and metatarsals [reviewed in Duij et al., 2003]. This condition may be observed in a wide variety of genetic syndromes, and has been previously described in 12 patients with holoprosencephaly (HPE) [Hartsfield et al., 1984; van Melderger et al., 1992; Young et al., 1992; Imaizumi et al., 1998; Corona-Rivera et al., 2000; Abdel-Meguid et al., 2001; König et al., 2003; Vilain et al., 2009; Zechi-Ceide et al., 2009].

In 1984, Hartsfield described the first known case of a child born with HPE and ectrodactyly. Since that time, this combination has been described as comprising a distinct genetic syndrome: holoprosencephaly, ectrodactyly, and bilateral cleft lip-palate syndrome, also known as Hartsfield syndrome (OMIM 300571). While ectrodactyly is a consistent finding, other limb anomalies, such as radial hypoplasia and polydactyly, have been reported

in patients with this association, though it is possible these are etiologically distinct entities [Hartsfield et al., 1984; Young et al., 1992; Vilain et al., 2009].

Among patients with HPE and ectrodactyly, the presence of a common phenotype has prompted interest in identifying a unifying cause. However, to date such causes have remained elusive. Here we review all previously reported cases, describe three previously unpublished descriptions of patients with HPE-ectrodactyly, and present what is known and suspected about the genetics of this association.

Review of Patients with HPE and Ectrodactyly

Combined Data

Among all known patients with HPE-ectrodactyly, all patients in whom brain imaging was available were diagnosed with either lobar (64%) or semilobar (36%) HPE. The severity and type of hand anomalies varied both between patients and within a single patient. Many patients had ectrodactyly of some extremities and less severe anomalies of other extremities.

While 73% have facial clefting, which is a common feature in HPE, 53% were described as having telecanthus/hypertelorism, as opposed to the hypotelorism typical in patients with HPE, and only 33% were described as being microcephalic (see Table I). Eighty-seven percent have some form of ear anomaly, including posteriorly rotated and low-set ears. Other features include genital abnormalities, such as small penis and hypospadias, likely due to central gonadotropin deficiency, and three patients were diagnosed with hypogonadotropic hypogonadism (endocrine evaluations were not available in all cases) [Van Maldergem et al., 1992; König et al., 2003; Vilain et al., 2009]. Other less consistent findings include craniosynostosis (13%) [Hartsfield et al., 1984; Corona-Rivera et al., 2002] and central diabetes insipidus/elevated serum sodium (40%), the latter of which is common in patients with HPE [Van Maldergem et al., 1992; Imaizumi et al., 1998; Abdel-Meguid et al., 2001; König et al., 2003; Vilain et al., 2009; Muenke lab, this report]. Finally, and importantly, we present the first two reports of female patients (Patients 14 and 15) with this condition.

New Patients

Patient 13 was a 2-year-old male with semilobar HPE and bilateral ectrodactyly of both his hands and feet, with absent central rays. Family history was unremarkable and there was no history of maternal diabetes. Physical examination revealed bilateral ear microtia (R>L), bifid nose with a broad nasal tip, bilateral cleft lip and palate, and micropenis. MRI of the brain and spine revealed partial absence of the anterior genu of the corpus callosum, midline fusion of the caudate, a small third ventricle, and mildly hypoplastic medial temporal lobes and hippocampi (Fig.2). Spinal MRI showed sacral dysgenesis suggesting a degree of caudal deficiency and a low-lying spinal cord extending to approximately T5 with fat signals seen with the filum terminale, suggesting a tethered spinal cord. Abdominal ultrasound showed organoaxial rotation of the stomach. Echocardiogram revealed no anomalies. Karyotype was 46, XY, and no anomalies were detected by oligonucleotide microarray. No mutations were identified in *SHH*, *SIX3*, *ZIC2*, or *TGIF*.

Patient 14 was identified at approximately 24 weeks gestation due to abnormalities on routine ultrasonography. Ultrasound showed a fetus with measurements appropriate for gestational age, but with brain structures consistent with lobar HPE as well as splaying of the cerebellar vermis, a midline facial cleft, an absence of a definitive nose, but the presence of a small proboscis, a normal left upper extremity, right hand ectrodactyly with absent middle rays, and a dysmorphic spine with hemivertebrae and several areas of lordosis and kyphosis extending from the cervical through lumbar regions. The fetus had normal external

female genitalia. Fetal echocardiogram showed the presence of an interrupted aortic arch and a ventricular septal defect. Genetic testing was not performed.

Patient 15 (Fig. 3) was a female with lobar HPE with congenital ectrodactyly involving bilateral upper and lower extremities. There were no known risk factors; the mother had a previous miscarriage of a male fetus at approximately 16 weeks gestation, though no anomalies were reportedly observed. Family history was otherwise unremarkable. In addition to severe neurocognitive dysfunction and diabetes insipidus, she has a history of frequent mild infections (conjunctivitis and otitis media). Physical exam was notable for severe microcephaly with brachycephaly, mild hypotelorism, a single maxillary central incisor, a high palate, and dysplastic, protruding ears with a right overfolded helix. Her ectrodactyly consisted of split hands and feet with absence of rays 2-4 and deep clefts between the present rays. Brain MRI showed holoprosencephaly with fusion of the frontal lobes and aplasia of the frontal corpus callosum as well as globally delayed myelination. Ophthalmologic exam, renal ultrasound, and skeletal X-rays (with the exception of the described limb anomalies) were all normal. Karyotype and FISH for 7q21.3 and for subtelomeric regions were normal, as were parental karyotypes. Sequencing of *TP63* showed was normal except for a polymorphism in exon 12.

Genetic Etiologies

Due to the common phenotypic spectrum, there has been great interest in identifying a genetic basis for this association of HPE and ectodactyly. With the exception of one patient with a balanced translocation, with chromosome analysis reported as 46,XY,t(2;4)(q14.2;q14), no chromosomal abnormalities have been identified in any of these patients [Corona-Rivera 2000]. Since *GLI2*, an HPE-associated gene, is located in the 2q14 region, it has been hypothesized that perhaps mutations in or microdeletions affecting this gene are responsible. Obviously other genes in the region could also be involved, and the application of newer techniques to this patient's sample could potentially be elucidating. Vilain and colleagues [2009] conducted *GLI2* sequencing analysis in 5 affected patients and array-CGH analysis in two patients, none of which revealed abnormalities [Vilain et al., 2009]. Since patients previously described with this association have been male, some have suggested an X-linked genetic basis, but further work is needed to support this possibility, and no strong candidate genes on the X chromosome have been identified to date [König et al.; 2003; Vilain et al., 2009; Zechi-Ceide et al., 2009].

There is notable overlap between this cohort of patients and those diagnosed with ectrodactyly, ectodermal dysplasia, and cleft lip/palate syndrome (OMIM 604292), a disorder associated with heterozygous mutations in the *TP63* gene located on chromosome 3q27. Clinical manifestations in this syndrome, in addition to ectrodactyly and facial clefting, may include sparse hair, thin and/or dry skin, and dystrophic nails [reviewed in Rinne et al., 2006]. Genitourinary findings have also been reported, with ureter and kidney abnormalities more commonly observed than frank genital anomalies. Structural brain anomalies and cognitive impairment are not specifically associated with this syndrome. While Van Maldergem and colleagues (1992) suggested mutations in *TP63* as a possible etiology for HPE-ectrodactyly, genetic testing in five patients with HPE and ectrodactyly demonstrated no mutations in any of the coding regions of *TP63* [Vilain et al., 2009; Zechi-Ceide et al., 2009]. Although thin hair was described in one patient with HPE-ectrodactyly, no findings typical of ectodermal dysplasia have been seen in other patients with HPE and ectrodactyly [van Maldergem et al., 1992]. Taken together, these data suggest that the etiology of HPE-ectrodactyly may be distinct from that of EEC syndrome.

Nonsyndromic HPE itself has been associated with mutations or deletions in at least 12 genes (the most commonly affected genes are *SHH*, *SIX3*, *ZIC2*, and *TGIF*) [reviewed in Dubourg et al., 2007; Pineda-Alvarez et al., this issue]. As several of the patients summarized here do have findings similar to those seen in non-syndromic, non-chromosomal HPE, (including cleft lip/palate, microcephaly, and hypothalamic and pituitary dysfunction) it has been hypothesized that patients with ectrodactyly represent a rare variant of classic HPE [Zechi-Ceide, 2009; Vilain 2009]. To date, no mutations have been found in the most common HPE-associated genes, though not all patients (including those newly described here) with HPE-ectrodactyly have been tested for mutations in these genes [Zechi-Ceide et al., 2009; Valain et al., 2009; Muenke lab, this report]. However, the facial gestalt in most patients with HPE-ectrodactyly is distinct from that of classic HPE, suggesting a different set of candidate genes in at least some patients described here.

Discussion

In summary, much remains to be elucidated regarding patients with the combination of HPE and ectrodactyly. The craniofacial findings in this cohort of patients are similar in some respects to patients with non-chromosomal, non-syndromic HPE, and more uniform testing of HPE-associated genes may show previously undiscovered mutations. However, it is important to remember that limb anomalies such as ectrodactyly are not commonly associated with non-syndromic, non-chromosomal HPE, and other features in HPE-ectrodactyly patients do not mirror those of patients with HPE but no ectrodactyly. Candidate genes beyond those traditionally associated with classic HPE may need to be considered. New advances in molecular genetics, such as expanded testing with DNA microarray platforms, may aid in identifying previously undiscovered genetic alterations in these patients, and should contribute to our understanding of the complex etiology of HPE and other malformations.

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References

- Abdel-Meguid N, Ashour AM. Holoprosencephaly and split hand/foot: an additional case with this rare association. *Clin Dysmorphol*. 2001; 10:277–279. [PubMed: 11666003]
- Corona-Rivera A, Corona-Rivera JR, Bobadilla-Morales L, Garcia-Cobian T, Corona-Rivera E. Holoprosencephaly, hypertelorism, and ectrodactyly in a boy with an apparently balanced de novo t(2;4)(q14.2; q35). *Am J Med Genet Part A*. 2000; 149:1277–1279.
- Duijff PHG, van Bokhoven H, Brunner HG. Pathogenesis of split-hand/split-foot malformation. *Hum Mol Genet*. 2003; 12:R51–R60. [PubMed: 12668597]
- Gropman, AL.; Muenke, M. Holoprosencephaly. In: Cassidy, SB.; Allanson, JE., editors. *Management of Genetic Syndromes*. New York: Wiley-Liss; 2005. p. 279-96.
- Hartsfield JK, Bixler D, DeMeyer WE. Syndrome identification case report 119. Hypertelorism associated with holoprosencephaly and ectrodactyly. *Clin Dysmorphol*. 1984; 2:27–31.
- Imaizumi K, Issii T, Masuno M, Kuroki Y. Association of holoprosencephaly, ectrodactyly, cleft lip/palate and hypertelorism: a possible third case. *Clin Dysmorphol*. 1998; 7:213–216. [PubMed: 9689997]
- König R, Beeg T, Tariverdian G, Scheffer H, Bitter K. Holoprosencephaly, bilateral cleft lip and palate and ectrodactyly: another case and follow up. *Clin Dysmorphol*. 2003; 12:221–225. [PubMed: 14564207]

- Rinne T, Hamel B, van Bokhoven H, Brunner HG. Pattern of *p63* mutations and their phenotypes: update. *Am J Med Genet Part A*. 2006; 140:1396–1406. [PubMed: 16691622]
- Van Maldergem L, Gillerot Y, Vamos E, Toppet M, Watillon P, Van Vliet G. Vasopressin and gonadotropin deficiency in a boy with the ectrodactyly-ectodermal dysplasia-clefting syndrome. *Acta Paediatr*. 1992; 81:365–367.
- Vilain C, Mortier G, Van Vliet G, Dubourg C, Heinrichs C, de Silva D, Verloes A, Baumann C. Hartsfield holoprosencephaly-ectrodactyly syndrome in 5 male patients: further delineation and review. *Am J Med Genet Part A*. 2009; 149:1476–1481. [PubMed: 19504604]
- Young ID, Zuccollo JM, Barrow M, Fowlie A. Holoprosencephaly, telecanthus and ectrodactyly: a second case. *Clin Dysmorphol*. 1992; 1:47–51. [PubMed: 1342859]
- Zechi-Ceide RM, Ribeiro LA, Raskin S, Bertolacini CDP, Guion-Almeida ML, Richieri-Costa A. Holoprosencephaly, ectrodactyly, and bilateral cleft lip and palate: exclusion of *SHH*, *TGIF*, *SIX3*, *GLI2*, *TP73L*, and *DHCR7* as candidate genes. *Am J Med Genet Part A*. 2009; 143:1277–1279. [PubMed: 19449411]

Biographies

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Fig. 1.

Patients with the combination of holoprosencephaly and ectrodactyly, demonstrating a wide range of severity, in terms of both craniofacial and limb manifestations. Additionally, some patients (such as the patient pictured top left) show features of classic HPE, while others have craniofacial findings not typical of HPE-spectrum anomalies [Corona-Rivera et al., 2000; Vilain et al., 2009; Zechi-Ceide et al., 2009]. All images reprinted with permission of Wiley-Liss, Inc. a subsidiary of John Wiley & Sons, Inc.

Fig. 2.
Brain MRI of patient 13. Left: axial view showing fusion of the frontal hemispheres. Right: coronal view showing caudate fusion.

Fig.3. Facial views and upper and lower extremity of patient 15, a female with lobar HPE and ectrodactyly of upper and lower extremities. Facial features include hypotelorism, a sharp nasal bridge, a single maxillary central incisor, and an overfolded left helix.

Table 1

Findings. Specific findings are described when available. In instances where details are not available, the presence or absence is indicated by “+”, “-”, or “NS”, respectively, or written as “NS” (Not specified) if unknown. Findings typically given using the original authors' terms. Many findings of all extremities, but did not have true ectrodactyly of all limbs.

HPE Type	Ectro-Dactyly*	Cleft Lip/Palate	Hyper-telorism	Cranio-synostosis	Eye Anomalies	Ear Anomalies	Genital Anomalies	Genetic Testing	Reference
Lower limb	+	Right	+	Bilat coronal, metopic	Microph-thalmia	Low set, post. rotated	NS	NS	Hartsfield, 1984
Lower limb	+	Bilat	+	-	-	Poorly formed, low set	NS	46,XY	Young, 1992
Upper limb	+	Bilat	+	-	-	Left: poorly lobulated	Micro-penis, cryptorchidism	46,XY. No <i>SHH</i> , <i>ZIC2</i> , <i>SIX3</i> , <i>TGIF</i> or <i>GLI2</i> mutations	Van Maldergem, 1992, Vilain 2009
Lower limb	+	Bilat	+	-	-	Left: low set, malformed	-	46,XY	Imaizumi, 1998
Upper limb	+	-	+	Metopic	Microph-thalmia, colobomata	Low-set, dysplastic, post. rotated	NS	46,XY,t(2;4)(q14.2;q14)	Corona-Rivera, 2000
Lower limb	+	-	Hypotelorism	-	-	+	-	46,XY	Abdel-Meguid, 2001
Lower limb	+	Bilat	-	-	-	Large, low-set	Micro-penis, hypo-spadias, no palpable testes	46,XY	König, 2003
Upper limb	+	Bilat	-	-	-	Prominent	Micro-penis, ectopic testes	46,XY. No <i>SHH</i> , <i>TGIF</i> , <i>SIX3</i> , <i>GLI2</i> , <i>TP63</i> , or <i>DHCR7</i> mutations	Zechi-Ceide, 2009
NS	+	Left	+	-	-	Right: malformed, flat, angulated	-	46,XY, no <i>TP63</i> or <i>GLI2</i> mutations	Vilain, 2009
Lower limb	+	Mid-line	Hypotelorism	-	-	Small, simple, round, low-set	NS	46,XY. Normal microarray. No <i>GLI2</i> mutations	Vilain, 2009
Lower limb	+	-	-	-	-	-	Micro-penis, crypt-orchidism	46,XY. No <i>GLI2</i> mutations	Vilain, 2009
Upper limb	+	Bilat	+	-	-	Left pre-auricular tag	Small external genitalia	46, XY. Normal microarray. No <i>TP63</i> or <i>GLI2</i> mutations	Vilain, 2009
Upper limb	+	Bilat	+	NS	-	Bilat microtia	Micro-penis	46, XY. Normal microarray. No mutations in <i>SHH</i> , <i>SIX3</i> , <i>ZIC2</i> , or <i>TGIF</i> .	This report
Lower limb	+	Mid-line	NS	NS	NS	NS	-	None	This report
Lower limb	+	-	Hypotelorism	-	-	Right: overfolded	-	46,XX. Normal subtelomeric FISH and	This report

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HPE Type	Ectro-Dactyly*	Cleft Lip/Palate	Hyper-telorism	Cranio-synostosis	Eye Anomalies	Ear Anomalies	Genital Anomalies	Genetic Testing	Reference
								FISH for 7q21.3. No mutations in <i>TP63</i>	

*: Not present in bilateral hands and feet in all patients, almost all patients had additional anomalies affecting the extremities in which true ectrodactyly was not present. Bilat: Bilateral;