Open Journal of
Clinical & Medical
Case Reports

Volume 2 (2016)
Issue 8

ISSN 2379-1039

Polysyndactyly in Pallister-Hall Syndrome

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Abstract

Polydactyly and syndactyly are common congenital anomalies that may occur as isolated disorders or as signs of underlying genetic syndromes. This report describes a 7-month-old Caucasian male with known Pallister-Hall syndrome (PHS) who presented to the pediatric hand surgery clinic for management of complicated bilateral polysyndactyly. Description of his anatomy contributes to the ongoing characterization of PHS, a rare syndrome caused by mutations in the GLI3 gene. This patient's previously unreported mutation contradicts the genotype-phenotype correlations previously outlined in the literature.

Keywords

Polydactyly; syndactyly; Pallister-Hall syndrome; GPI3

Abbreviations

PHS: Pallister-Hall syndrome; GCPS: Greig cephalopolysyndactyly syndrome

Introduction

Polydactyly and syndactyly are among the most common congenital anomalies of the upper limb. Both polydactyly and syndactyly may occur unilaterally, bilaterally, as an isolated disorder, or as part of a pleiotropic developmental syndrome [2]. Polydactyly occurs among 1 in 100-300 African Americans and 1 in 3000 Caucasians [1], while syndactyly occurs in up to 1 in 2000 live births. Polydactyly, or the presence of an extranumary digit, is defined by the location (preaxial (radial), postaxial (ulnar), or rarely, mesoaxial (central)) and complexity of the extra digit (type A with a fully formed digit or type B with a rudimentary and nonfunctional digit). Syndactyly, defined as partial or complete fusion of digits, most often affects the third web space and is described as complete (fusion all the way to the fingertips) or incomplete (partial regression of the webspace). The presence or lack of bony involvement dictates whether it is complex or simple syndactyly, respectively. Polydactyly in particular has been associated with 290 different malformation syndromes [3], and practitioners must remain vigilant for the presence of additional anomalies in newborns presenting with hand abnormalities.

Pallister-Hall (PHS, MIM146510) is one such syndrome. First described in 1980 as a uniformly lethal affliction in six newborns [4], it has since been characterized to include a wide range of severities and clinical features. Diagnosis is established either by molecular testing or by the simultaneous presence of mesoaxial polydactyly and hypothalamic hamartoma [5]. Other suggestive traits include postaxial polydactyly type A or B, bifid epiglottis, imperforate anus, and genitourinary and renal

abnormalities. An autosomal dominant disorder, PHS is caused by a mutation in the GLI3 zinc finger transcription factor gene on 7p14.1 [6]. Mutations in this gene are also known to cause Greig Cephalopolysyndactyly Syndrome (GCPS, MIM175700), Acrocallosal Syndrome (MIM200990), and preaxial polydactyly type IV, and postaxial polydactyly type A.

PHS is a rare syndrome, the precise prevalence of which is unknown. Complete characterization of clinical features is ongoing, thus far stemming primarily from three case series describing a total of 90 PHS patients [7, 8, 9]. Here we present a previously unreported patient with complicated polysyndactyly and known Pallister-Hall syndrome in an effort to better describe PHS, to contribute to current efforts at genotype-phenotype correlation, and to highlight one of the syndromes that may present to hand surgeons as polysyndactyly.

Case Presentation

A 7-month-old Caucasian male with previously diagnosed Pallister-Hall syndrome presented to our pediatric hand surgery clinic for management of complicated polysyndactyly.

The patient's Pallister-Hall Syndrome had been suspected shortly after birth and confirmed by genetic testing at 1 month of age. At birth, in addition to the polysyndactyly, he was noted to have micropenis with hypospadias and bilateral inguinal testes, neonatal hypoglycemia, hyperbilirubinemia, and respiratory distress requiring brief intubation. Evaluation for his respiratory distress revealed a bifid epiglottis. Brain MRI on day of life 4 showed a hypothalamic hamartoma, absence of the anterior pituitary and pituitary infundibulum, and premature closure of the metopic suture with trigonocephaly. The combination of a bifid epiglottis, hypothalamic hamartoma, postaxial polydactyly, micropenis, and cryptorchidism led to a presumptive diagnosis of PHS. Sequencing of the GLI3 gene later revealed a C>G transversion at nucleotide 2331, resulting in replacement of histidine with glutamine at amino acid 777. This was a *de novo* mutation not present in either parent.

On exam, he was noted to have bilateral post-axial polydactyly, broad thumbs (Figure 1), and syndactyly of the left first and fourth webspaces. A number of specific findings were noted. On the right hand, there was an accessory digit containing bone attached by soft tissue to the ulnar side of the small finger. The ring finger was hypoplastic and free floating (Figure 2). The index and long finger PIP joints had limited range of motion, with 30 and 45 degrees of motion respectively. On the left, there was likewise postaxial polydactyly, here attached by a soft tissue bridge to the radial side of the small finger. Range of motion was similarly limited, with no motion at the index PIP and 60 degrees of motion at the long finger PIP. Additionally, there was simple syndactyly of the fourth webspace extending to the distal phalanx and the first webspace was narrow (Figure 3). There were no abnormalities of the feet.

Radiographs of bilateral hands were reviewed. These confirmed postaxial polydactyly on the right (Figure 4) with an extra digit lateral to the fifth digit containing a single tiny ossification center, and postaxial polydactyly on the left (Figure 5) with an extra digit fused to the radial aspect of the fifth digit containing a distal phalanx and hypoplastic middle phalanx. The right fourth and fifth digits appeared small with short phalanxes. All metacarpals of both hands were shortened and broad, and the right fourth metacarpal was absent, possibly represented by a small ossific structure between the distal third and fifth metacarpals. Also noted was a small, slightly irregular osseous structure between the distal aspects of the left second and third metacarpals.

Surgical repair of the hands was completed at 16 months of age and included a left fourth webspace syndactyly repair with a dorsal V-Y flap [10], left first webspace syndactyly reconstruction using a jumping man flap, left small finger polydactyly reconstruction including bone, left small finger digital neuroma excision, and right small finger polydactyly reconstruction including bone.

Discussion

In this report, we describe a case of unusual polysyndactyly in a two-pronged effort: to expand the growing database of clinical features of a rare genetic disorder, and to bring to the attention of neonatologists and hand surgeons a syndrome that may initially present as postaxial polydactyly. Because the primary features of PHS—hypothalamic hamartoma and bifid epiglottis—can be asymptomatic, the clinician caring for a patient with polydactyly must be prepared to consider the diagnosis. Particularly when postaxial polydactyly occurs in Caucasians rather than African Americans in whom it is more common [11], there is a strong syndromic association.

With regard to the phenotypic variability of PHS, our patient's polysyndactyly is consistent with previous reports. For example, a recently published series of 21 cases demonstrated that like our patient, 48% had postaxial polydactyly, 38% had syndactyly, and 52% had brachydactyly or brachytelephalangism. What is perhaps a bit unusual about our patient is the broad thumbs, which are reported in 22% of patients with GCPS (also caused by GLI3 mutations), but are less commonly mentioned as a feature of PHS, and his lack of Y-shaped metacarpals which occur in the vast majority of PHS patients. Furthermore, the craniosynostosis is also far more common in GCPS than in PHS [9].

While our patient shares the clinical features of known PHS cases, he brings into question previously delineatedgenotype-phenotype correlations [7, 8, 9]. To the best of our knowledge, the C2331G point mutation in GLI3 has not been reported before now. Prior investigations report that PHS is reliably caused by frameshift of nonsense mutations in the second third of the gene (nucleotides 1998-3481). The only known exception before now is a single family with PHS that has a splice mutation instead of a frameshift or nonsense mutation, although it's thought that the mutation likely still produces a truncated gene product [7]. Our patient's mutation is in the “PHS” domain of the gene, but it neither a frameshift nor a nonsense mutation. In fact, the His777 amino acid is only moderately conserved in other species, implying that it could be expected to be a fairly neutral mutation, although clearly in our patient it was not. This case thus introduces some uncertainty into the formerly quite precise predictive value of the specific GLI3 mutation and corresponding clinical characteristics.

Conclusion

Polydactyly and syndactyly are common congenital malformations of the upper limb and as such are conditions with which any pediatric clinician must be familiar. Here we have emphasized the need for practitioners to consider rare congenital syndromes when faced with polysyndactyly. The case presented here contributes to the growing collection of PHS features described in the literature, and notably contradicts previously reported genotype-phenotype correlations for the GLI3 gene. Further investigation as more cases are identified will be required to resolve this incongruity.

Figures

Figure 1: The patient has bilateral broad thumbs, shown here on the right hand.
Figure 2: Hypoplastic right ring finger, found on x-ray to be lacking a metacarpal base.
Figure 3: Left postaxial polydactyly with fourth webspace syndactyly.

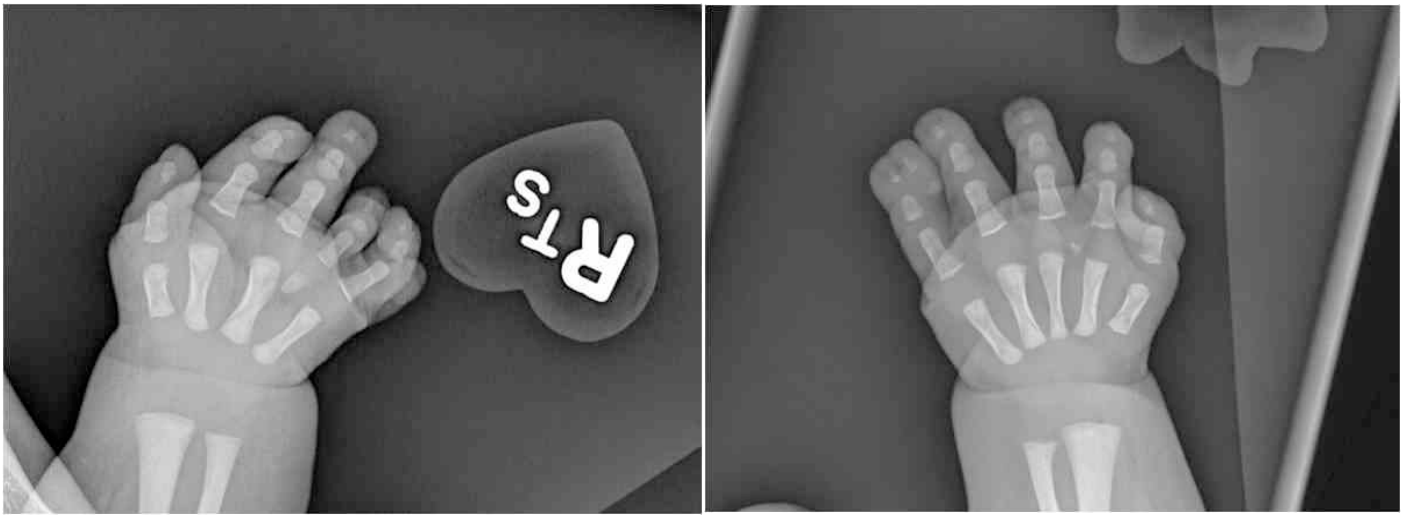

Figure 4: X-ray of right hand showing postaxial polydactyly with single ossification center, short metacarpals, and absent 4th metacarpal.
Figure 5: X-ray of left hand showing postaxial polydactyly; the supernumerary digit contains a distal phalanx and hypoplastic middle phalanx.

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Manuscript Information: Received: December 17, 2015; Accepted: April 17, 2016; Published: April 18, 2016

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Citation: Olsen J, Nelson J, Chang B. Polysyndactyly in Pallister-Hall syndrome. Open J Clin Med Case Rep. 2016; 1104

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