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CASE REPORT

Familial Pallister-Hall in adulthood

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Abstract

Pallister Hall syndrome is autosomal dominant disorder usually diagnosed in infants and children. Current diagnostic criteria include presence of hypothalamic hamartoma, post axial polydactyly and positive family history, but the disease has variable manifestations. Herein we report Pallister Hall syndrome diagnosed in a family where both patients were adults. A 59 year old man developed seizures 4 years prior to our evaluation of him, at which time imaging showed a hypothalamic hamartoma. The seizures were controlled medically. He did well until he had visual changes after a traumatic head injury. Repeat MRI showed slight expansion of the mass with formal visual field testing demonstrating bitemporal hemianopsia. There was no evidence of pituitary dysfunction except for large urine volume. He underwent surgery to debulk the hamartoma and the visual field defects improved. There was no hypopituitarism post-operatively, and the polydyspia resolved. His 29 year old daughter also had seizures and hypothalamic hamartoma. Both patients had had polydactyly with prior surgical correction in childhood. The daughter underwent genetic testing, which revealed a previously undescribed heterozygous single base pair deletion in exon 13 of the GLI3 gene causing a frameshift mutation. Further investigation into family history revealed multiple members in previous generations with polydactyly and/or seizures. Pallister-Hall syndrome is caused by an inherited autosomal dominant or de novo mutation in GLI3 gene. This rare syndrome has not had prevalence defined, however. Generally, diagnoses are made in the pediatric population. Our report adds to the few cases detected in adulthood.

INTRODUCTION

Pallister-Hall syndrome (MIM #146510) was first described in 1980. Hall, *et al.* reported 6 infants with hypothalamic hamartoblastoma, postaxial polydactyly and imperforate anus (Hall *et al.* 1980). Subsequently the syndrome was shown to be caused by heterozygous mutations in the GLI3 gene on chromosome 7p14 (Jamsheer *et al.* 2012; Kang *et al.* 1997b; Craig *et al.* 2008; Johnston *et al.* 2010; Hall 2014). Pallister-Hall forms a spectrum from very mildly affected individuals with subtle polydactyly to severely affected individuals with life-threatening malformations and hypothalamic tumors (Demurger *et al.* 2015). The diagnosis is during childhood except for few adults that were

found with a mild phenotype (Penman Splitt *et al.* 1994; Sama *et al.* 1994; Low *et al.* 1995; Kang *et al.* 1997b). While most patients have novel mutations, familial Pallister-Hall with autosomal dominant inheritance is reported (Grebe & Clericuzio 1996; Penman Splitt *et al.* 1994; Topf *et al.* 1993; Biesecker *et al.* 1994; Sills *et al.* 1994a; Sills *et al.* 1993; Sills *et al.* 1994b). Here we describe an adult diagnosis of Pallister-Hall syndrome with seizures, hypothalamic hamartoma, as well as history of surgically corrected polydactyly and a novel GLI3 mutation in a man, and his similarly affected daughter.

CASE REPORTS

A 59 year old man presented to endocrine clinic for evaluation of the hypothalamic pituitary axis. The patient had history of seizures for 4 years and had an MRI done as work up for seizures, which revealed a hypothalamic hamartoma. Seizures were medically controlled and he was asymptomatic until noting vision changes after a traumatic head injury. Repeat MRI showed slight expansion of the mass and formal visual field testing confirmed bitemporal hemianopsia. He was not having signs of pituitary dysfunction other than drinking 7–8 liters of fluid daily. An 8 am cortisol was 17.4 µg/dL. Gonadal axis was intact with FSH, LH, and testosterone in the normal range. Thyroid axis was intact with free T4 of 0.8 µg/dL. Prolactin and IGF-1 were in the normal range. Serum sodium was 138 mEq/L with a urine osmolarity in the upper half of the normal range. He underwent transphenodial surgery with debulking of the hamartoma and visual field defects improved. Hypopituitarism was not found post-operatively. His polydyspia, attributed to dipsogenic DI caused by the mass, resolved. His 29 year old daughter was also diagnosed with seizures during this time period and underwent evaluation with the finding of a hypothalamic hamartoma. Both patients had had polydactyly with prior surgical correction. The daughter underwent genetic testing, which revealed a novel heterozygous single base pair deletion in exon 13 on the GLI3 gene causing a frameshift mutation. Further investigation into family history revealed multiple members in previous generations with polydactyly and/or seizures (Figure 1).

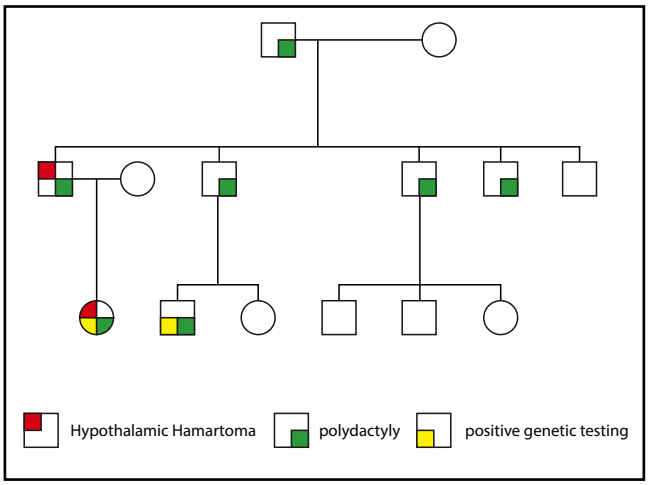

Fig. 1. Family tree of the proband and his daughter with Pallister.

DISCUSSION

Pallister-Hall syndrome is a rare autosomal dominant illness characterized by hypothalamic hamartoma, hypopituitarism, and polydactyly. Many of those diagnosed with the syndrome have other malformations, including renal agenesis, congenital heart defects, imperforate anus, and short stature, among others (Biesecker *et al.* 1996a). Consequently, most patients are diagnosed as children, many at birth when multiple abnormalities are recognized to be syndromic.

Here we report a father and daughter diagnosed in adulthood. Both had postaxial polydactyly but no other findings to suggest Pallister-Hall syndrome in childhood. The father had a hypothalamic hamartoma found incidentally on imaging of his brain. There are only a few other individuals with Pallister-Hall diagnosed as adults, and many of these were diagnosed as part of multigenerational family. Some of these families were part of early genetic linkage studies (Biesecker *et al.* 1996b). For example, Grebe *et al.* (Grebe & Clericuzio 1996) reported a family in which the proband was a 16 year old girl with polydactyly, short stature, kidney malformations, and a hypothalamic harmartoma with intact pituitary function. She had many affected relatives over four generations, some with only isolated polydactyly. Her father was 43 years old and had polydactyly and a hamartoma without other abnormalities. Pathology of the hamartomas examined were thought to have more benign pathology than those reported in infants and children with Pallister-Hall syndrome (Grebe & Clericuzio 1996). Mature hamartomas were found in a 53 year old woman and her 20 year old son who were initially examined because of polydactyly (Low *et al.* 1995). There are other reports of the diagnosis of a child leading to the diagnosis of milder disease in a parent (Topf *et al.* 1993; Penman Splitt *et al.* 1994; Thomas *et al.* 1994). However, in the family we report, the diagnosis of the father in fact led to consideration and eventual confirmation of the diagnosis in his adult daughter. This scenario is rare in Pallister Hall syndrome.

The genetics of Pallister-Hall syndrome have been investigated extensively, including the relationship to Greig cephalopolysyndactyly syndrome (GCPS, MIM# 175700). Several reports of cytogenetically visible chromosomal abnormalities localized the gene (Thomas *et al.* 1994; Kuller *et al.* 1992), as did genetic linkage studies (Grebe & Clericuzio 1996; Biesecker *et al.* 1996b). In 1997, a high LOD score was found near the GLI3 gene locus (Kang *et al.* 1997a) and frameshift mutations in GLI3 were found among those affected by Pallister-Hall

syndrome (Kang *et al.* 1997b). The GLI3 gene product contains a zinc finger motif and is a DNA-binding transcription factor, functioning in the sonic hedgehog signaling pathway (Dai *et al.* 1999).

The gene for GCPS was also localized to the region of GLI3 by genetic linkage and candidate gene studies (Vortkamp *et al.* 1991). Genotype/phenotype correlations were worked out by Johnston and colleagues (Johnston *et al.* 2005), who studied 46 patients with Pallister-Hall syndrome and 89 with GCPS. These investigators determined that GCPS is associated with any type of mutation and these mutations are found in the first third of the gene. Meanwhile, Pallister Hall syndrome is caused by only frameshift or splicing mutations occurring in the second third of the gene, leaving the DNA-binding zinc-finger domain intact (Johnston *et al.* 2005). These observations were confirmed in 46 Pallister Hall syndrome and 21 GCPS probands in 55 families (Demurger *et al.* 2015). Our family had a novel single base pair deletion in exon 13 causing a frameshift, consistent with the previous findings (Demurger *et al.* 2015; Johnston *et al.* 2010; Johnston *et al.* 2005).

Polydactyly is a not an uncommon abnormality, which is frequently not associated with other abnormalities; that is, polydactyly is usually non-syndromic (Malik 2014). Pallister Hall syndrome has variable penetrance and a wide clinical variability, which includes isolated polydactyly. We report a family in which both affected individuals were diagnosed in adulthood when a pituitary hamartoma was found. This family extends the disease spectrum for this syndrome, demonstrating a mild adult phenotype with a novel mutation. Adults with pituitary hamartoma should be questioned concerning a history of polydactyly in order to uncover Pallister Hall syndrome.

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