Epileptic Disord 2011; 13 (2): 209-13

Transcallosal endoscopic resection of hypothalamic hamartoma in a case with Pallister-Hall syndrome

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Received January 13, 2011; Accepted April 1, 2011

ABSTRACT – Pallister-Hall syndrome (PHS) is a very rare syndrome characterized by hypothalamic hamartoma (HH), polydactyly, panhypopituitarism, imperforate anus and other visceral anomalies. Contrary to patients with isolated HH, neurological dysfunction and precocious puberty are uncommon and seizures are usually well controlled with anticonvulsant medication. Therefore, conservative management of HH is advised. To the best of our knowledge, seven cases of PHS with surgical resection of the HH have so far been reported. Five patients were either seizure-free or had >90% seizure reduction postoperatively. Here, we present a case of PHS of a patient who also underwent transcallosal endoscopic resection of the HH with a subsequent 70% reduction in seizure frequency.

Key words: Pallister-Hall syndrome, hypothalamic hamartoma, polydactyly, gelastic seizures, surgery

In 1980, Hall and colleagues delineated a fatal syndrome characterized by hypothalamic hamartoma (HH), polydactyly, panhypopituitarism, imperforate anus and other visceral anomalies including pulmonary segmentation anomalies, congenital heart defects and renal anomalies (Hall *et al*., 1980). All cases were sporadic, without any apparent chromosomal abnormalities. Later, familial cases of Pallister-Hall syndrome (PHS) were discovered with autosomal dominant inheritance and the disorder was mapped to chromosome 7p13, co-localising with the gene for the GLI3 zinc finger transcription factor (Kang *et al*., 1997a; Kremer *et al*., 2003). In the following years, numerous cases were described and milder cases were also assigned to the same diagnosis. When compared to patients with isolated HH, seizures in PHS were less severe and easier to control with medication (Boudreau *et al*., 2005). Conservative management of HH has been advised due to the benign nature of the lesion. So far, only seven surgical cases have been reported (Ng *et al*., 2005, 2006, 2008), five of whom cases were either seizure-free or had >90% seizure reduction.

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doi:10.1684/epd.2011.0440

Here, we report a male patient with HH, polydactyly, severe mental retardation and behavioural problems who underwent transcallosal endoscopic resection of the HH with a subsequent 70% reduction in seizure frequency postoperatively.

Case study

A 24-year-old male patient was admitted to hospital because of severe drug-refractory epileptic seizures. He first started having gelastic seizures in infancy, which were later followed by tonic seizures, secondary generalised tonic-clonic seizures with head and eye deviation to the left (four to five times/day for the last five years) and myoclonic jerks. Previously, treatment with phenytoin, phenobarbital, carbamazepine, primidone (PRM), valproate, oxcarbazepine (OXC), levetiracetam and lamotrigine had failed. Currently, he is on OXC (1200 mg/day), PRM (500 mg/day) and olanzapine (10 mg/day). Physical examination revealed marked obesity and bilateral polydactyly of the hands. He was severely mentally retarded with almost no verbal output. He also had marked behavioural disturbances such as aggression and biting and beating himself. Neurological examination, as far as he could cooperate, was unremarkable except for brisk deep tendon reflexes. His parents were unrelated. He was the last offspring in the family and had four healthy brothers. The pre- and perinatal history was unremarkable, as was family history. There was no precocious puberty.

His cranial MRI disclosed a right hypothalamic hamartoma *(figure 1A)*. Interictal EEG revealed bilateral fronto-central spike-wave and multiple spike-wave discharges besides diffuse background slowing *(figure 2)*. Resective surgery of the HH was planned and the patient was hospitalized. His pituitary hormone levels including FSH, LH, prolactin, TSH and ACTH were within the normal range, whereas GH level was decreased (<0.05 ng/mL). Thoracal and abdominal CT were normal. An antero-posterior conventional radiograph of both hands showed five metacarpals on both sides; there was an accessory sixth digit on the ulnar side of the right hand and on the left side both the fifth and sixth digits were attached to the fifth metacarpal, each with two phalanges *(figure 3)*. The patient underwent transcallosal endoscopic partial resection of the HH *(figure 1B)*. The diagnosis of hamartoma was confirmed histopathologically. Postoperatively, he remained seizure-free for 20 days. Later, the family reported infrequent generalised tonic-clonic seizures, similar to the pre-operative seizures. On the last visit of follow-up (five months after surgery), there was almost 70% reduction in seizure frequency compared to baseline. He also had increased appetite with some weight gain and was given additional topiramate (TPM), after which he started to lose weight. Genetic analysis could not be performed due to financial reasons.

Discussion

The clinical presentation of PHS ranges from polydactyly associated with asymptomatic HH to neonatally lethal malformations (Hall *et al*., 1980; Low *et al*., 1995). Pallister-Hall syndrome is either sporadic or inherited with autosomal dominance in familial cases. It is associated with frameshift mutations of the gene for GLI3 which plays a role in the sonic hedgehog pathway (Kang *et al*., 1997b) and is a key developmental morphogen of the CNS and many other organ systems. GLI3 mutations are present in 95% of all patients with clinically diagnosed PHS (Johnston *et al*., 2005). Mutations in the first third of the GLI3 gene cause PHS, whereas mutations in the other two thirds are responsible for Greig cephalopolysyndactyly syndrome. Cases reported in the literature so far suggest that there is no genotype-phenotype correlation in PHS.

Isolated cases of HH, on the other hand, are also quite rare (approximately 1/1,000,000 births) and are often accompanied by various seizure types (most commonly gelastic seizures), mental retardation, precocious puberty and severe behavioural problems. Recently, Boudreau *et al* (2005) compared the clinical and MRI characteristics of patients with isolated HH and PHS. It was concluded that patients with isolated HH had more severe seizures and neurological dysfunction and were more likely to have precocious puberty, whereas PHS patients usually had well controlled seizures and endocrine disturbances other than precocious puberty.

The co-existence of polydactyly and HH, GH deficiency and absence of precocious puberty suggests a diagnosis of PHS in our case. However contrary to the findings of Boudreau *et al*., our patient had severe mental retardation, behavioural problems and frequent drug-resistant seizures, similar to patients with isolated HH. This suggests that there may be significant overlap of various symptoms between the two disorders. Given the lack of similar cases in the family, our patient is a sporadic case probably due to a *de novo* mutation in the GLI3 gene.

Based on cranial MRI findings, two categories of HH have been described: the "parahypothalamic type" which is attached to the floor of the third ventricle and is associated with precocious puberty; and the "intrahypothalamic type" where the hamartoma involves the hypothalamus and is associated with seizures (Arita *et al*., 1999). Depth electrode recordings from the HH have revealed the ictal origin of gelastic seizures within the lesion (Munari *et al*., 1995).

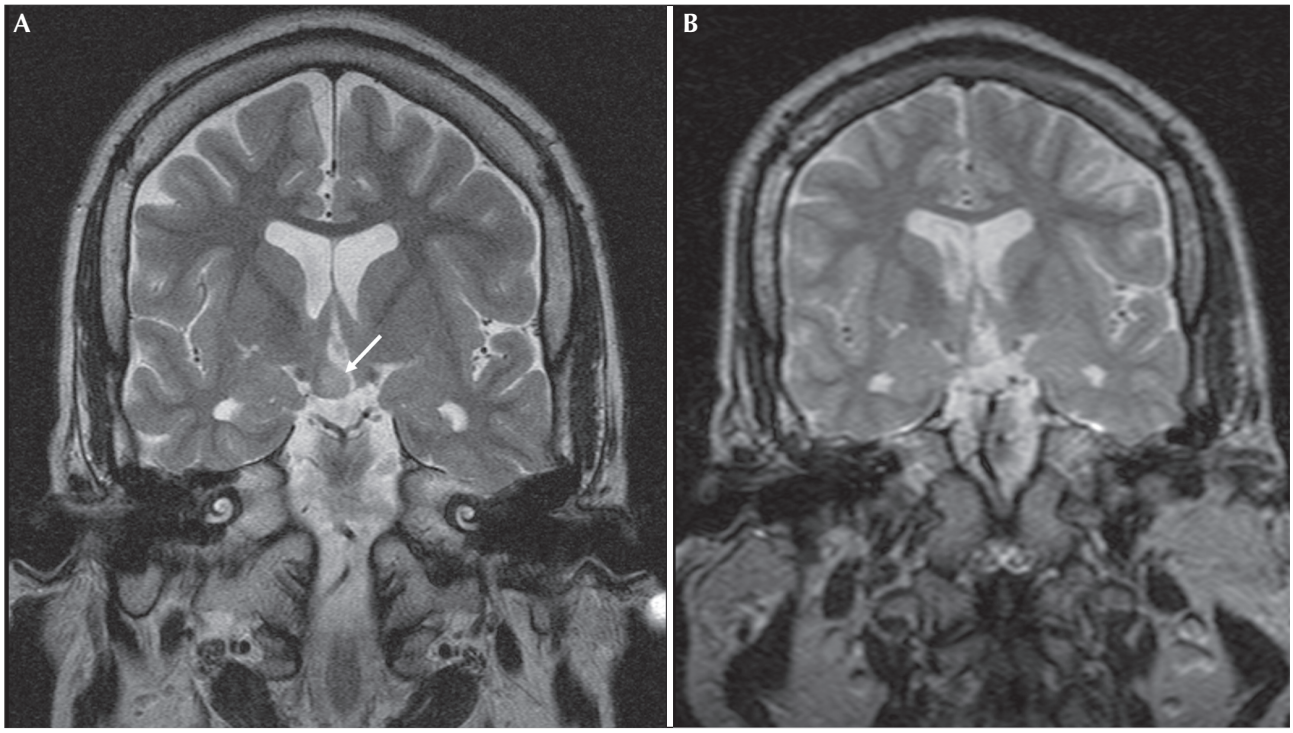

Figure 1. **A**) Coronal T2-weighted MR image demonstrating a hyperintense hamartoma on the right side of the hypothalamus and **B**) partial resection of the hamartoma.

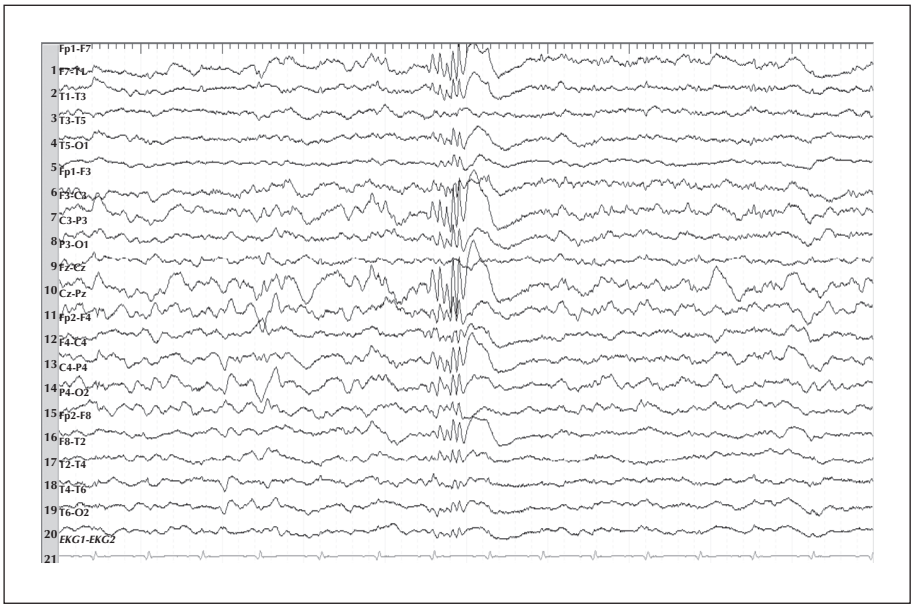

Figure 2. Interictal EEG indicates bilateral fronto-central spike-wave discharges (more prominent on the left) with diffuse background slowing.

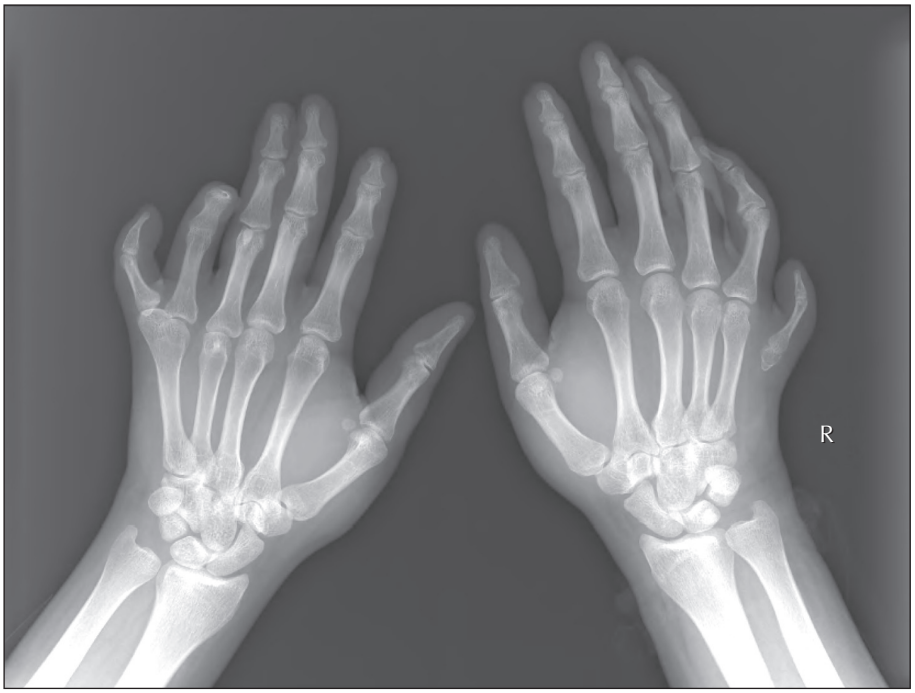

Figure 3. Antero-posterior conventional radiograph of both hands shows five metacarpals on both sides; there is an accessory sixth digit on the ulnar side of the right hand, and on the left side both the fifth and sixth digits are attached to the fifth metacarpal, each with two phalanges.

Numerous surgical techniques have been applied for the resection of HH, including subfrontal, transsylvian, subtemporal, frontotemporal, pterional craniotomy, interhemispheric and translamina terminalis procedures. Surgical interventions (Harvey *et al*., 2003; Fohlen *et al*., 2003; Kuzniecky and Guthrie, 2003; Polkey, 2003) are associated with high complication rates (*e.g*. memory deficits, changes in appetite, diabetes insipidus) and often do not result in adequate resection of the lesion, leading to persistent seizure activity. Interestingly, in their comprehensive study, Boudreau *et al*. (2005) concluded that "...the mechanisms through which HH produce seizures differ between patients with PHS and isolated HH". Since PHS patients usually have well controlled seizures, surgical interventions are seldom applied. To the best of our knowledge, there are seven cases of reported PHS with surgical resection of the HH (Ng *et al*., 2005, 2006, 2008). Postoperative follow-up indicated that five of these patients (Ng *et al*., 2005, 2006) were either seizure-free or had >90% seizure reduction. Although our patient was not rendered seizure-free postoperatively, he had a 70% reduction in seizure frequency. He also reportedly had an increase in appetite with some weight gain. However his appetite decreased dramatically and he started to lose weight after initiation of TPM. In agreement with the literature, our experience with this case also suggests that PHS patients may benefit from resection of the HH without serious side effects, if they have medically uncontrolled seizures. □

Disclosure.
None of the authors has any conflict of interest or financial support to disclose.

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