

Polysyndactyly, gelastic seizures, hypothalamic hamartoma and precocious puberty - a variant of Pallister-Hall syndrome?

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ABSTRACT

A girl with polysyndactyly presented gelastic seizures during the neonatal period. Magnetic resonance examination at two years of age revealed a hypothalamic lesion suggestive of a hamartoma. Pubic hair appeared soon after. These characteristics suggest that this is a variant of the Pallister-Hall syndrome. A conservative therapeutic course was chosen despite the poor response to anticonvulsants.

INTRODUCTION

Hypothalamic hamartomas - congenital tumors composed of a heterotopic mass of neurosecretory neurons, fiber bundles, and glial cells - usually involving the posterior hypothalamus are the tumors most frequently associated with the development of precocious puberty (Pescovitz *et al.*, 1986; Rieth *et al.*, 1987). In addition to directly involving the hypothalamus, the tumoral mass may also act as an autonomous secretory source of gonadotropin releasing hormone, GnRH (Judge *et al.*, 1977).

Although many children with hamartomas are neurologically normal (Cacciari *et al.*, 1983), they may develop convulsive disorders including a special type of seizure called gelastic seizure or ictal laughter (Berkovic *et al.*, 1988). The hamartoma-gelastic seizure-precocious puberty triad has been extensively studied (Brenningstall, 1985).

A new element, however, may be associated with this entity. In 1993, Topf *et al.* described a case of hamartoma and precocious puberty in a patient with some malformations, including polysyndactyly. The case was interpreted to be a variant of the Pallister-Hall syndrome, first described in 1980 and characterized by a hypothalamic hamartoma, polysyndactyly, other somatic anomalies, and endocrine alterations involving the pituitary (Hall *et al.*, 1980). A second case of hamartoma-gelastic seizures-precocious puberty-polysyndactyly syndrome was reported from Japan (Katayama *et al.*, 1993).

The objective of the present report was to describe a new patient with this association of findings.

CASE REPORT

A female infant born at term by normal delivery after an uneventful pregnancy presented the following characteristics at birth: length 48.5 cm (25th percentile), weight 3200 g (25-50th percentile), dolichocephaly, bluish sclerae, median frenum joining the upper lip to the upper arcade, mammary hypertelorism, mongolian

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spots on the dorsum and pelvis, polydactyly, and hypoplastic nails. She had seven fingers bilaterally, some of them with syndactyly, and six bilateral toes with syndactyly. The mother was normal and denied consanguinity or similar cases in the family. Other relatives were not examined.

The karyotype was normal. The patient was submitted to cardiological evaluation, with normal results. Radiological evaluation of the whole body was also normal, except for the presence of seven metacarpals on the right hand and six on the left, as well as six metatarsals on the right and five on the left, one of them with bifurcation. Since the neonatal period, the patient had gelastic seizures characterized by frequent stereotyped and unmotivated laughing and crying episodes occurring in association, followed by absence of reactivity for a few seconds.

Traditional neurological examination revealed no abnormalities at two years of age. Psychomotor development at that time was about 12 months. A videoelectroencephalogram demonstrated abnormal wakefulness and sleep states, with a slow and disorganized basal rhythm, interhemispheric asymmetry with an area of relative electrical suppression in the right frontal-central region, areas of slowness in the posterior quadrants of both hemispheres, frequent electroencephalographic ictal seizures (during sleep) and clinical ictal seizures (during sleep and wakefulness) characterized by trains of generalized polyspikes, in which the clinical preceded the electroencephalographic manifestation. Magnetic resonance (MR) performed on that occasion showed a solid tumescent lesion of defined contours, 2.0 x 2.0 cm in diameter, located in the hypothalamus in a supra- and retrosellar position, hypointense in T1 in relation to the nervous parenchyma, and hyperintense in T2, with no hydrocephalus or other encephalic alterations. The pituitary gland was normal.

At two years and six months of age, the patient was submitted to endocrine evaluation, consisting of basal measurements of T4 (13.9 mg/dl; NV = 4.8-12.5), TSH (1.2 mIU/ml; NV = 0.3-0.5), GH (below 0.5 ng/ml; NV = 0-10.0), cortisol (23.5 mg/dl; NV = 5-25.0), prolactin (13.0 ng/ml; NV = 3-24.0), FSH (1.3 mIU/ml; NV = 3.1-15.7) and LH (0.8 mIU/ml; NV = 0.7-35.2).

At three years of age, the patient started to present tonic and atonic seizures in addition to the gelastic episodes. Several drugs, including phenobarbital, primidone, vigabatrin, valproic acid and carbamazepine, administered separately or in combination, failed to control these seizures.

At three years and seven months of age, pubic hair was noted. On that occasion, height was 95 cm

(between the 10th and 25th percentile). Estradiol level was 40 pg/ml (prepuberal NV, up to 12.0), basal LH was 1.5 mIU/ml, with a maximum response of 17.7 to GnRH, and basal FSH was 8.0 mIU/ml, with a maximum response of 19.5 to GnRH. These results were compatible with a puberal gonadotropin response. Total and free testosterone, androstenedione, dehydroepiandrosterone and 17-hydroxyprogesterone levels were normal. Hand and wrist X-rays at three years and 11 months showed a bone age of two years and six months (within 2 SD for age range).

Neurological examination of the patient at four years of age revealed a lack of visual attention and bilaterally pale optic papillae. The pupillary light and blink reflexes were normal. Psychomotor development determination revealed 24-month motor behavior and 12-month language. Tonic seizures, atypical absences, and gelastic and simple partial seizures with motor symptoms during wakefulness and/or sleep continued to be present under treatment with 200 mg primidone at 8-h intervals. Control MR showed a pattern similar to the previous one. Treatment with a GnRH analogue was then started.

DISCUSSION

During the postnatal period, the polysyndactyly of the patient was interpreted to be a single phenomenon not belonging to a specific genetic syndrome. Thus, the initial care was directed at the control of gelastic seizures. These convulsions are of unknown physiopathology and usually occur at a frequency of three to 20 episodes per day (Cascino *et al.*, 1993). The seizures usually start during infancy and only exceptionally during the immediate neonatal period (Sher and Brown, 1976). Their response to antiepileptic agents is disappointing (Berkovic *et al.*, 1988) and prognosis is poor, with the possible development of other types of seizures, as observed in the present case. Even the focal cortical resection to which children with intractable gelastic seizures were submitted failed to produce a significant reduction in the tendency to convulsions (Cascino *et al.*, 1993), with consequent limitation of corticectomy to exceptional cases only (Berkovic *et al.*, 1988).

Although a biopsy was necessary for a definitive diagnosis of hamartoma, the hypothalamic lesion observed by MR was suggestive of its presence. According to several investigators, the diagnosis of hypothalamic hamartoma can be made on the basis of the presence of precocious puberty and/or epileptic syndromes without focal neurological signs in the

presence of an isodense mass that does not increase with time (Pescovitz *et al.*, 1986; Berkovic *et al.*, 1988). Since these lesions are small, ranging from 0.5 to 3.5 cm in diameter but generally smaller than 2.0 cm (Comite *et al.*, 1984; Rieth *et al.*, 1987), MR is the most appropriate method for diagnosis (Berkovic *et al.*, 1988; Cacciari *et al.*, 1990).

Hamartomas usually course without neurological symptoms (Cacciari *et al.*, 1983) but may occasionally be associated with gelastic seizures. In turn, hamartomas and gelastic seizures, separate or combined, have been associated with precocious puberty (Matustik *et al.*, 1981; Zúñiga *et al.*, 1983; Breningstall, 1985).

Zúñiga *et al.* (1983) presented 50 cases of hypothalamic hamartomas reported over the last five decades and confirmed by surgical exploration or at autopsy. Of these cases, 74% had precocious puberty with a 2:1 male:female ratio. In the child presented here, despite the isolated manifestation of pubarche, the diagnosis of true precocious puberty was based on the adult estradiol levels and on the predominant LH response, characteristic of puberty. The onset of secondary sex traits in children with precocious puberty associated with hamartomas usually occurs early, during the first or second year of life (Matustick *et al.*, 1981; Zúñiga *et al.*, 1983; Pescovitz *et al.*, 1986; Rieth *et al.*, 1987; Cacciari *et al.*, 1983, 1990). Since the hamartoma rarely progresses, medical therapy is usually recommended to retard the progression of puberty (Comite *et al.*, 1984) as long as no change occurs in mass size in sequential contrasted examinations, and the patient does not present signs of neurological deterioration (Sher and Brown, 1976). The most effective treatment in the management of sexual precocity is that based on GnRH analogues (Comite *et al.*, 1984).

According to Breningstall (1985), 18 cases of gelastic seizures associated with precocious puberty, including two reported by the author himself, had been reported by 1985. At least 10 of them were associated with hypothalamic hamartomas. Mental retardation and variable cognitive deficiencies have been described in the hamartoma-gelastic seizure-precocious puberty association (Matustik *et al.*, 1981; Berkovic *et al.*, 1988). Psychomotor retardation was observed in the child presented here.

Up to 1992, 28 patients with hamarto(blast)oma and associated defects had been reported (Verloes *et al.*, 1992). Cases of association of any one of the elements discussed above, i.e., gelastic seizures, hamartoma and precocious puberty, with polysyndactyly are rare in the literature. The first series with a similar association was

reported by Hall *et al.* (1980). They described six children with lethal malformations during the neonatal period, including hypothalamic hamartoblastoma and postaxial polydactyly, as well as other organic malformations and hypopituitarism due to pituitary dysgenesis. These association was later called the Pallister-Hall syndrome (Huff and Fernandes, 1982).

In 1991, Finigann *et al.* summarized the anomalies detected in 17 cases of the syndrome described up to that time, and added two more. Hypothalamic hamartoma was present in 94% of the patients, dysplastic nails (also observed here) in 65%, polydactyly in 59%, syndactyly in 35%, as well as several other CNS lesions or endocrine alterations such as hypopituitarism, hypothyroidism, hypoadrenalism, micropenis, and cryptorchidism.

The occurrence of the syndrome in a male patient was first reported in 1993, consisting of hamartoma, polysyndactyly and precocious puberty (Topf *et al.*). In the same year, a case of hamartoma, polysyndactyly, precocious puberty and gelastic seizures was also described (Katayama *et al.*, 1993).

In conclusion, the present child is probably affected by the Pallister-Hall syndrome, a syndrome of broad phenotype and still undefined etiology, probably involving an autosomal dominant inheritance (McKusick number 146510; 1994).

RESUMO

Os autores relatam o caso de uma menina portadora de polissindactilia, que apresenta crises gelásticas desde o período neonatal. Aos dois anos de idade, foi detectada, através da ressonância magnética, lesão hipotalâmica sugestiva de hamartoma. Logo após, a partir do surgimento de pelos pubianos, foi diagnosticada puberdade precoce. As características mencionadas sugerem tratar-se de uma variante da síndrome de Pallister-Hall. A conduta terapêutica tem sido conservadora, apesar da resposta pobre aos anticonvulsivantes.

REFERENCES

- Berkovic, S.F., Andermann, F., Melanson, D., Ethier, R.E., Feindel, W. and Gloor, P. (1988). Hypothalamic hamartomas and ictal laughter: evolution of a characteristic epileptic syndrome and diagnostic value of magnetic resonance imaging. *Ann. Neurol.* 23: 429-439.
- Breningstall, G.N. (1985). Gelastic seizures, precocious puberty, and hypothalamic hamartoma. *Neurology* 35: 1180-1183.
- Cacciari, E., Fréjaville, E., Cicognani, A., Pirazzoli, P., Frank, G., Balsamo, A., Tassinari, D., Zappulla, F.,

- Bergamaschi, R. and Cristi, G.F. (1983). How many cases of true precocious puberty in girls are idiopathic? *J. Pediatr.* 102: 357-360.
- Cacciari, E., Zucchini, S., Carla, G., Pirazzo, P., Cicognani, A., Mandini, M., Busacca, M. and Trevisan, C. (1990). Endocrine function and morphological findings in patients with disorders of the hypothalamo-pituitary area: a study with magnetic resonance. *Arch. Dis. Child.* 65: 1199-1202.
- Cascino, G.D., Andermann, F., Berkovic, S.F., Kusniecky, R.I., Sharbrough, F.W., Kleene, D.L., Bladin, P.F., Kelly, P.J., Olivier, A. and Feindel, W. (1993). Gelastic seizures and hypothalamic hamartomas: evaluation of patients undergoing chronic intracranial EEG monitoring and outcome of surgical treatment. *Neurology* 43: 747-750.
- Comite, F., Pescovitz, O.H., Rieth, K.G., Dwyer, A.J., Hench, K., McNemar, A., Loriaux, D.L. and Cutler, G.B. (1984). Luteinizing hormone-releasing hormone analog treatment of boys with hypothalamic hamartoma and true precocious puberty. *J. Clin. Endocrinol. Metab.* 59: 888-892.
- Finnigan, D.P., Clarren, S.K. and Haas, J.E. (1991). Extending the Pallister-Hall syndrome to include other central nervous system malformations. *Am. J. Med. Genet.* 40: 395-400.
- Hall, J.G., Pallister, P.D., Clarren, S.K., Beckwith, J.B., Wiglesworth, F.W., Fraser, F.C., Cho, S., Benke, P.J. and Reed, S.D. (1980). Congenital hypothalamic hamartoblastoma, hypopituitarism, imperforate anus, and postaxial polydactyly - a new syndrome? Part I: clinical, causal and pathogenetic considerations. *Am. J. Med. Genet.* 7: 47-74.
- Huff, D.S. and Fernandes, M. (1982). Two cases of congenital hypothalamic hamartoblastoma, polydactyly and other congenital anomalies (Pallister-Hall Syndrome). *N. Engl. J. Med.* 306: 430-431.
- Judge, D.M., Kulin, H.E., Page, R., Santen, R. and Trapukdi, S. (1977). Hypothalamic hamartoma - a source of luteinizing-hormone-releasing factor in precocious puberty. *N. Engl. J. Med.* 296: 7-10.
- Katayama, H., Miyao, M., Kobayashi, S., Yanagisawa, M., Yokota, H., Mashiko, T. and Asuzawa, T. (1993). A case of hypothalamic hamartoma with gelastic seizures, precocious puberty, poly- and syndactyly. *No To Hattatsu* 5: 341-346.
- Matustik, M.C., Eisenberg, H.M. and Meyer, W.J. (1981). Gelastic (laughing) seizures and precocious puberty. *Am. J. Dis. Child.* 135: 837-838.
- McKusick, V.A. (1994). *Mendelian Inheritance in Man*. 11th edn. The Johns Hopkins University Press, Baltimore, pp. 774-775.
- Pescovitz, O.H., Comite, F., Hench, K.H., Barnes, K., McNemar, A., Foster, C., Kenigsberg, D., Loriaux, L. and Cutler, G.B. (1986). The NIH experience with precocious puberty: diagnostic subgroups and response to short-term luteinizing hormone releasing hormone analogue therapy. *J. Pediatr.* 108: 47-54.
- Rieth, K.G., Comite, F., Dwyer, A.J., Nelson, M.J., Pescovitz, O., Schawker, T.H., Cutler, G.B. and Loriaux, D.L. (1987). CT of cerebral abnormalities in precocious puberty. *AJR* 148: 1231-1238.
- Sher, P.K. and Brown, S.B. (1976). Gelastic epilepsy - onset in neonatal period. *Am. J. Dis. Child.* 130: 1126-1131.
- Topf, K.F., Kletter, G.B., Kelch, R.P., Brunberg, J.A. and Blesecker, L.G. (1993). Autosomal dominant transmission of Pallister-Hall syndrome. *J. Pediatr.* 123: 943-946.
- Verloes, A., Gillerot, Y., Langhendries, J.-P., Fryns, J.-P. and Koulischer, L. (1992). Variability versus heterogeneity in syndromal hypothalamic hamartoblastoma and related disorders: review and delineation of the cerebro-acro-visceral early lethality (CAVE) multiplex syndrome. *Am. J. Med. Genet.* 43: 669-677.
- Zúñiga, O.F., Tanner, S.M., Wild, W.O. and Mosier, D. (1983). Hamartoma of CNS associated with precocious puberty. *Am. J. Dis. Child.* 137: 127-133.

(Received January 31, 1995)