Hamartoma, Pituitary☆

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Glossary

Gelastic seizures Brief, repetitive, stereotyped episodes of pleasant laughter or giggling lasting a few seconds, associated or not to loss of awareness, facial myoclones and/or abnormal eye movements. Onset in infancy, high frequency and gelastic-type attacks are strongly related to the presence of hypothalamic hamartomas.

Hamartoma Congenital, non-neoplastic, pedunculated or sessile lesion consisting of heterotopic nervous tissue with no growth potential, mostly arising from the hypothalamus between the tuber cinereum and the mammillary bodies.

Precocious puberty Generally defined as the onset of secondary sexual characteristics before 8 year of age in girls and 9 years in boys; this definition is arbitrary, however, because of the marked variation in age when puberty begins in normal children, particularly if they belong to different ethnic groups.

Introduction

Hypothalamic hamartomas are rare, congenital, non-neoplastic tumor-like lesions of varying size (diameter ranging from less than 1 m to 6.5 cm) made up of heterotopic grey matter, neurons, glial cells, and fibre bundles. They usually originate in the posterior hypothalamus, the tuber cinereum or the mamillary bodies, have a sessile or pedunculated attachment, extend postero-inferiorly into the interpeduncular space and sometimes bulge into the floor of the third ventricle. Most hamartomas have a spherical shape below the tuber cinereum.

In rare cases, they may be prechiasmatic in location or may lie free in the interpeduncular fossa. They are often associated with single or combined cerebral and extracerebral congenital abnormalities, including polymicrogyria and/or heterotopia, arachnoid cyst, callosal defects, polydactyly, facial anomalies and heart malformations. An inheritance factor has been observed in individual patients.

Hypothalamic hamartomas may be asymptomatic but they generally present with central precocious puberty (CPP), gelastic seizures, generalized seizures, mental retardation, behavioral disturbances and memory difficulties. The hallmark of the epileptic syndrome is the gelastic seizure — a brief, repetitive, stereotyped attack of laughter — which begins in early childhood, often in the neonatal period. Later, in the first decade, a generalized epileptic encephalopathy develops, characterized by tonic, atonic, and other seizure types in association with a slow spike-and-wave discharge and cognitive deterioration. Hamartomas of the central nervous system do not usually grow or grow very slowly; they generally lack malignant characteristics.

Hypothalamic hamartoma is part of the Pallister-Hall syndrome, though it has exceptionally been reported in association with oral, facial, digital syndrome (OFD), Laurence-Moon-Biedl syndrome and other conditions.

Classification

Different classifications of hypothalamic hamartoma have been proposed according to the topographic and clinical data available. Hypothalamic hamartoma can be classified into two types:

- pedunculated, which is more likely to be associated with precocious puberty;
- sessile, often associated with seizures.

Another classification has been suggested based on topography and associated surgical risks:

- Type Ia and Ib are generally small pedunculated hamartomas that are attached to the tuber cinereum (Ia) or to the mamillary bodies (Ib) and are usually associated with precocious puberty.
- Type IIa and IIb are relatively large lesions that displace the hypothalamus slightly (IIa) or markedly (IIb) and are usually associated with gelastic or other types of seizures. Surgery has been recommended for types Ia, Ib, and IIa, especially when epileptic activity and behavioural abnormalities are severe and difficult to control.

A further classification has been proposed based on magnetic resonance (MR) imaging:

- The parahypothalamic type (PHH) is attached to the floor of the third ventricle or suspended from the floor by a peduncle. PHH is generally associated with precocious puberty but without seizures or development delay

☆*Change History*: January 2016. G. Patti, G. Morana, N. Di Iorgi, and M. Maghnie updated the text and reference.

This article is an update of Mohamad Maghnie, Stefano Ghirardello, Giulia Meloni, Hamartoma, Pituitary, In Encyclopedia of Endocrine Diseases, edited by Luciano Martini, Elsevier, New York, 2004, Pages 427-433.

- The intrahypothalamic type (IHH), enveloped by the hypothalamus to displace the third ventricle, is more likely to be associated with medically intractable seizures. Two thirds of IHH patients suffers from severe developmental delay, cognitive impairment and have a poor quality of life

Histology and Pathophysiology

Hypothalamic hamartoma is thought to be a developmental aberration, but its origin is unclear. Remnants of brain tissue left along the floor of the third ventricle when chorda withdraws may account for its origin in the central nervous system (CNS). Histologically, it consists mainly of normal brain elements: neurons, glial cells, and fiber bundles that are frequently myelinated and connected to surrounding hypothalamic structures. Frequently, however, hamartomas do not reproduce the normal architecture of neighbouring tissue.

The hypothalamic hamartoma functions as an ectopic luteinizing hormone-releasing hormone (LHRH) pulse generator that escapes the intrinsic CNS inhibitory mechanism. In the mouse, monkey and human, LHRH neurons originate in the medial olfactory placode of the developing nose, migrate across the nasal septum, and enter the forebrain with the nervus terminalis, arching into the septal-preoptic area and hypothalamus. In hypothalamic hamartoma a significant number of LHRH neurons migrate beyond the medial basal hypothalamus to the region of the mammillary bodies and tuber cinereum and form one of the constituents of the heterotopic mass of CNS tissue. The defect in migration could be related to an imbalance of diffusible chemotrophic factors that are secreted by restricted cell populations within the brain or to neural cell adhesion molecules, which play an important role in axonal pathfinding.

Since the number of LHRH neurons is limited, it is possible that a majority of the LHRH neurosecretory neurons may migrate into the hamartomas during CNS development. On the other hand, hypothalamic hamartoma may be related to aberrant differentiation among other cell types of neural primordia, including progenitor cells with the capacity to form LHRH neurosecretory neurons.

Histological specimens observed after surgery reveal hamartomas of low cell density containing irregularly structured groups of ganglionoid cells with variably sized unipolar and bipolar neurons interspersed among glial cells with myelinated and unmyelinated fibres connected to sorrounding hypothalamic structures. The tissue is highly vascular and many of the vessels have fenestrated endothelium and double basement membranes. Each vessel is almost totally sorrounded by axons. There is no or very little tendency to proliferation.

Immunohistochemical studies confirm the neuronal origin of hypothalamic hamartoma showing positive staining for neuron-specific enolase, synaptophysin and neurofilament protein.

Different immunohystochemical studies demonstrate the presence of membrane-bound, electron-dense granules (100 nm in diameter) which contain LHRH within the perikarya, the axons and the axons terminals and which are the elements of an independent neuroendocrine unit.

The examination of two hypothalamic hamartomas associated with sexual precocity revealed that they contained astroglial cells expressing TGFα, but not LHRH neurons. These findings imply that some hypothalamic hamartomas induce sexual precocious puberty by activating endogenous LHRH secretion via astroglial-derived factors such as TGFα and/or TGFβ. This activation appears to require a close proximity of hypothalamic hamartoma to either LHRH neurons or their axonal processes in the median eminence. In some cases, the hamartoma itself does not initiate precocious sexual maturation due to its location, but rather a lesion of the adjacent hypothalamic tissue resulting from surgery may cause activation of astroglial cells which may then lead to increased LHRH secretion from hypothalamic LHRH neurons.

A number of findings suggest that hamartomas are themselves epileptogenic. Electroencephalography (EEG) recordings revealed focal spikes arising from the depth contacts within hypothalamic hamartomas, while electrical stimulation studies reliably reproduce gelastic episodes, suggesting a close relationship between hamartomas and the generation of laughing attacks. The most fascinating studies based on ictal single-photon emission-computed-tomography demonstrated marked blood flow in the hypothalamus and thalamic structures during gelastic events. Improvement in intractable epilepsy has been reported in some cases after the resection of hamartoma.

Clinical and experimental evidence suggest that the hypothalamus and adjacent structures, in particular the mamillary bodies and its immediate connections, may comprise an important sub-cortical pathway for seizure propagation. Sessile hypothalamic hamartomas with displacement of the hypothalamus are associated with seizures.

Recent evidence shows that, unlike laughing and focal seizures, slow spike-and-wave discharges and associated tonic and atonic seizures do not arise directly from hamartoma. Indeed, postoperatively, these seizures may progressively "run down" after removal of the hamartoma, suggesting that they are the result of secondary epileptogenesis. Most HH cases are sporadic. Approximately 5% of HH cases are associated with Pallister-Hall syndrome, which is caused by haploinsufficiency of GLI3. Craig et al have identified somatic GLI3 mutations in sporadic HH cases, suggesting a role in the etiology of HH lesions.

Clinical Presentation

Endocrine Aspects

Hypothalamic hamartoma is considered the most common *organic cause* associated with CPP. The incidence of hypothalamic hamartoma in determining CPP varies widely ranging from 2% to 28%.

The age of onset of the first signs of CPP has been reported between 0 and 4 years (frequently before 2 years) while CNS lesions (gliomas, germinomas, arachnoid cysts) tend to occur in association with CPP later in life.

CPP associated with hypothalamic hamartoma has all of the hormonal hallmarks of puberty, including plasma estradiol levels, a pubertal pattern of pulsatile LH and a pubertal LH response after gonadotopin-releasing factor administration. Higher levels of peak LH response and peak LH/FSH ratio after LHRH have been reported in girls with CPP associated with hypothalamic hamartoma compared to idiopathic precocious puberty.

Neurological and Behavioral Aspects

Epilepsy is the main neurologic manifestation of hypothalamic hamartoma (HH). Gelastic seizures beginning in infancy, often in the neonatal period, are the classic epileptic presentation of HH. In a proportion of patients, there is a progression through other partial seizure types to a generalized epileptic encephalopathy.

Gelastic seizures associated with HH are refractory to medical treatment. Generalized seizures are reported in approximately 70% of patients. Generalized seizures most often appear after a period of gelastic and complex partial seizures manifestations. The development of generalized seizures is usually paralleled by the development of behavioral disturbances.

Several studies reported a characteristic, recognizable epileptic syndrome that shows a typical evolution over time. The syndrome begins with laughing attacks; the resemblance to normal laughter is so close in some patients that delayed diagnosis is possible. The pattern is quite stereotyped, with some variations over time. After a few years, the laughing attacks are associated with momentary loss of awareness, facial myoclonus and/or abnormal eye movements. Autonomic phenomena are common. In the later childhood, typically between the ages of 4 and 10 years, features of secondary generalized epilepsy appear with multiple seizure patterns including tonic, atonic, and tonic-clonic seizures and progressive cognitive impairment.

Behavioral disturbances, including attention deficit hyperactivity disorder like symptoms in patients with HH is generally associated with intractable seizures.The recurrence of these seizures promotes cognitive deterioration and behavioral disturbance. In a review of all reported patients with HH, 49% manifested cognitive disturbance and 31% had behavioral problems, while all patients had seizures. Children with gelastic seizures and HH are often emotionally unstable, easily irritated restless and agitated, aggressive and antisocial. HH patients with CPP but without evidence of seizure activity rarely have cognitive defects.

In a study with a large cohort of patients, it has been demonstrated that patients with hamartomas display a statistically significant increase in co-morbid psychiatric conditions, including oppositional defiant disorders, attention-deficit/hyperactivity disorder, high rates of conduct disorders, speech retardation/learning impairment and anxiety and mood disorders. At the present time, there are no definitive data to indicate exactly how the epileptic pathology interferes with a patient's development and behaviour and why a majority of patients have a cognitive-behavioural deficit which often worsens with age.

Brief infantile attacks are not associated with any significant change in EEG. However in later childhood, with the progression of the epileptic syndrome, EEG abnormalities develop with generalized suppression of background rhythm, generalized low-voltage fast activity or both. Interictally, there are generalized slow spike-and-wave discharges and background activity that is abnormally slow for the child's age as hallmarks of secondary generalized epilepsy.

Magnetic Resonance Imaging

MR imaging is the diagnostic method of choice for the evaluation of hypothalamic hamartomas. They appear as well defined round to oval masses, generally isointense to grey matter on both T1- and T2-weighted images. Following gadolinium injection they never enhance (**Fig. 1**). However, hypothalamic hamartomas may sometimes be slightly hyperintense on T2-weighted (**Fig. 2**) and FLAIR images. The variance in myelinated axons and the presence of gliosis can affect the variability of the T2 signal. Proton MR spectroscopy (**Fig. 2**) can show decreased N-acetylaspartate and increased myoinositol. These findings correlate with the proportion of glial cells within the hamartoma.

Another characteristic feature of hypothalamic hamartomas is their relative stability in size, shape and signal in long-term MR follow-up during and after medical treatment. Signal or cystic changes have occasionally been observed: in these cases, the differential diagnosis should include low grade gliomas.

Overall the MR findings which commonly indicate hypothalamic hamartomas are: an isointense mass with a pedunculated or sessile attachment to the hypothalamus without contrast enhancement, stable in size and shape during follow-up, associated with endocrinological and clinical features of CPP, mostly before 2 years of life and associated with gelastic seizures.

Treatment

Precocious Puberty

The aims of treatment are to arrest physical maturation, to prevent early menarche or sexual adult psycho-physical maturation and to improve adult height to within the range of target height combined with normal body proportions. GnRH agonists are the therapy of choice to halt premature sexual development in patients with a HH if precocious puberty is its only manifestation.

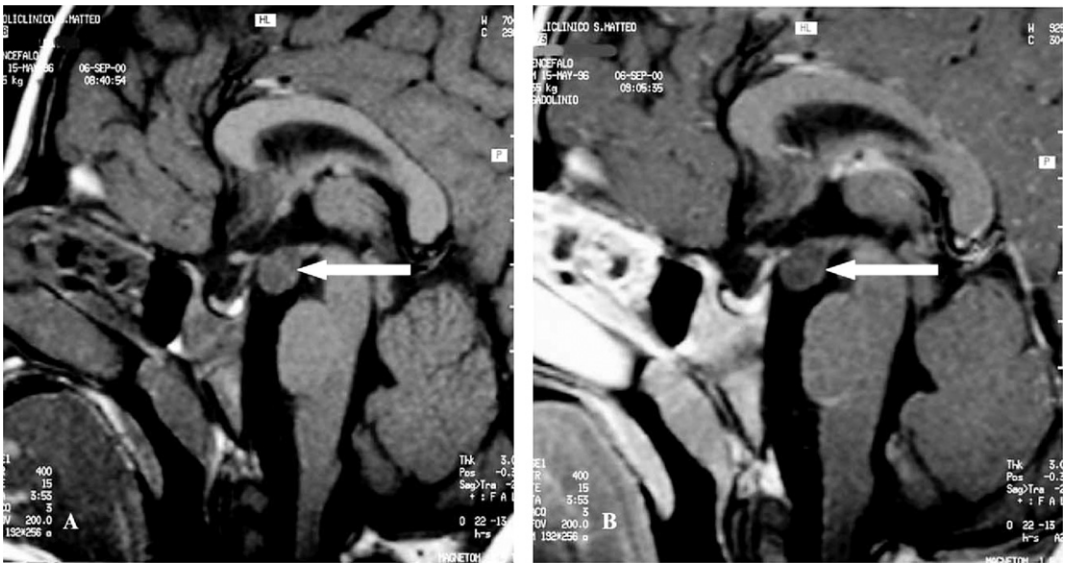

Fig. 1 (A) Sagittal T1-weighted image; (B) Gd-enhanced sagittal T1-weighted image. Sessile hamartoma in typical third ventricular location, isointense to gray matter before (A) and after (B) gadolinium administration (*white arrow*).

Successful suppression treatment with GnRH analog preparations has been reported by several groups for a duration of up to 8 years with homogeneous endocrinological response characterized, after an initial phase of increased serum LH and FSH levels (flare-up), by a reduction to prepubertal ranges of basal LH, FSH, testosterone and E2, a prepubertal peak LH and FSH-response to GnRH stimulation test and prepubertal LH/FSH ratio with improvement of adult height towards predicted final height and close to target height; no adverse events have been reported. A variety of GnRH formulations are available and efficacious. The depot preparations are preferred because of improved compliance. In most children, monthly injections adequately suppress the gonadotropic axis, but some children require more frequent injections.

A controversial outcome of precocious puberty has been reported after surgical resection of hamartomas. It has been suggested that surgery is safe and it can be considered an option when compared to the cost of medical treatment, monthly treatment administration up until puberty (sometimes poorly tolerated), painful injections in some cases, the psychological implications, and in some rare cases an intolerance to treatment. Total resection, however, cannot be achieved in all hamartomas.

Females with hypothalamic hamartoma have a higher incidence of irregular menses, obesity, neurological and behavioural problems with a normal reproductive axis within 4–5 years after discontinuation of GnRH analog therapy; pregnancies resulted in normal, live infants.

Seizures

Treatment options for intractable gelastic seizures in HH patients include direct open surgery with craniotomy, endoscopic surgery, radiosurgery with gamma knife (GKS) and stereotactic radiofrequency thermocoagulation.

In the last few years, it has become clear that epileptic encephalopathy associated with hypothalamic hamartoma is a treatable condition. Strong evidence now exists that removal, destruction or disconnection of the hamartoma leads to remarkable control of the seizures, as well as to an improvement in behaviour and probable cessation of cognitive decline.

Gelastic seizures are resistant to all currently available medications. Rarely, treatment of the focal seizures and of tonic and atonic attacks can be moderately successful with conventional anti-epileptic drugs. However, recent and sufficient experience suggests that long-lasting control of these seizures can be effected by complete removal, destruction, or disconnection of the hamartoma, thanks to important improvements in imaging and surgical techniques. There now exist various possible surgical approaches to the lesion and the debate is currently focused on the best technique to use (i.e., it must be tailored to the specific surgical anatomy of the hamartoma) in order to guarantee, in each single case, the possibility of total removal or disconnection of the lesion. The transcallosal approach (suited for intraventricular lesions) presently appears the technique with the highest rate of success, with 90% of cases free or virtually free of all seizures at one year post-surgery follow-up. Prolonged follow-up is necessary to evaluate the real effects on cognitive impairment, whereas behavioural abnormalities tend to show marked improvement in many patients.The pterional approach is useful for targeting peduncolated HHs, which are relatively easy to be completely resected.

Open and endoscopic disconnection surgery is a safe and effective option for small, sessile HHs.

Described secondary effects of surgery are small strokes with good recovery, encephalomalacia, third-nerve palsy, memory impairment, and transient diabetes insipidus. Postoperative mortality has also been reported.

Stereotactic radiosurgery (SRS) is increasingly being utilised. The major attractions of stereotactic radiotherapy involve the avoidance of mortality and morbidity risks associated with invasive neurosurgery. Stereotactic localisation allows attainment of a high degree of accuracy

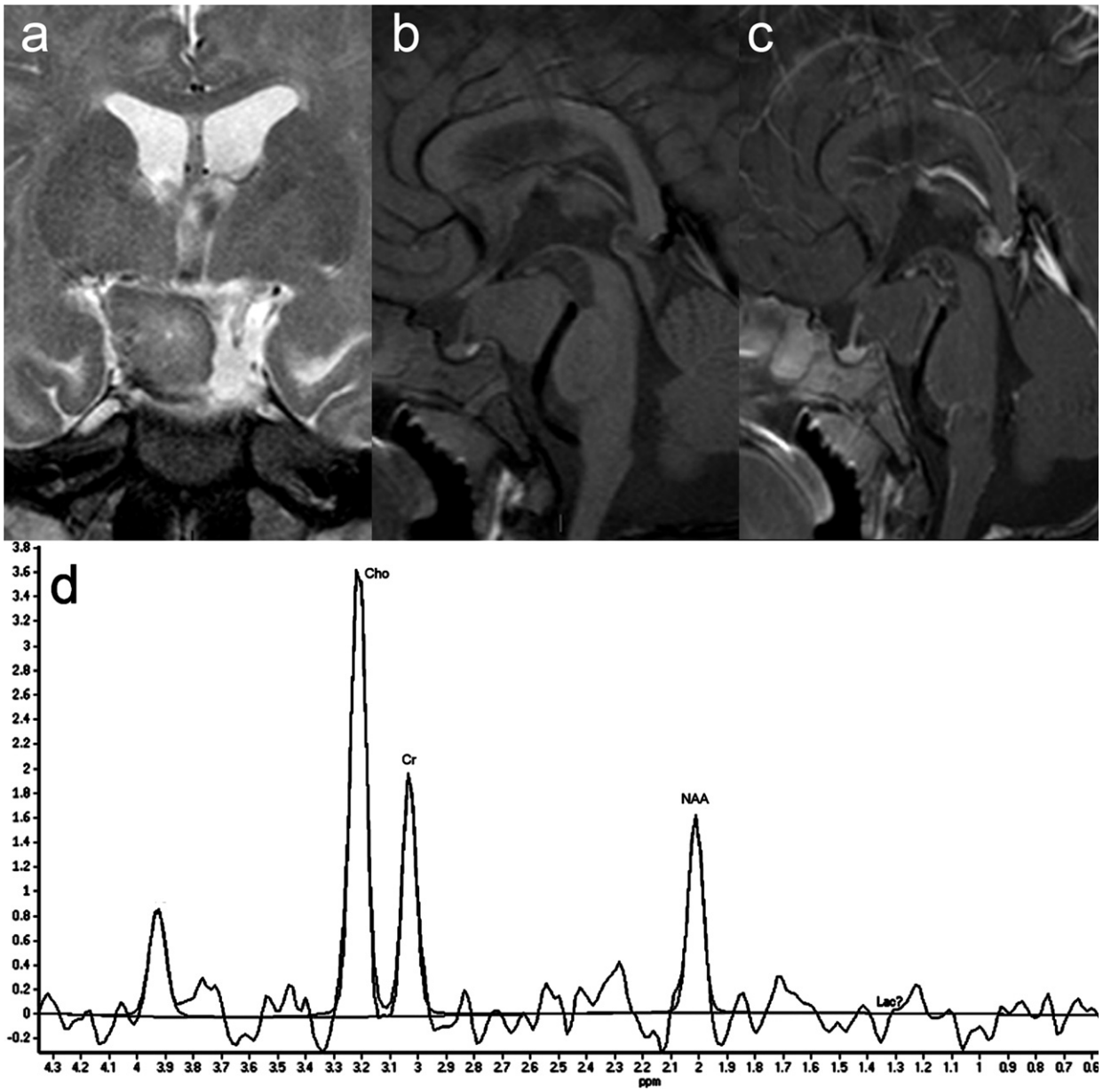

Fig. 2 (A) Coronal T2-weighted image; (B) Sagittal T1-weighted image; (C) Gd-enhanced sagittal T1-weighted image; (D) Single voxel MR spectroscopy (144 ms echo time). Retrosellar median-right paramedian solid mass lesion attached to the floor of the third ventricle and projecting into the interpeduncolar fossa. The lesion is slightly hyperintense on T2 (A), isointense on T1 (B), without contrast enhancement (C). Proton MRS shows mild increase of Cho/NAA and Cho/Cr ratios (D).

and precision, enough to deliver a dose of radiation high enough to affect epileptogenesis while sparing critical normal structures at the same time. Regis at al have reported excellent result in 60% of children with complete seizure cessation in 40% and rare nondisabling seizures in 20%, often in association with dramatic behavioural and cognitive improvement.

Some reports emphasize the importance of the margin dose of radiation. Patients treated with doses exceeding 17 Gy to the margin of the HH have greater rates of seizure remission than those receiving less than 13 Gy. Duration since onset has been reported to be another factor predictive of outcomes with SRS. Patients with short durations are likely to enjoy better responses, whereas patients with long histories are likely to receive modest benefits even with high doses. The disadvantage of SRS is its delayed action, with maximal effect usually experienced after a period of about 6 months post treatment. Surgery may be preferred over radiosurgery among patients with very large lesions that could be causing symptoms do to mass effect, since surgery can accomplish immediate decompression. Overall, when the lesion is sufficiently small SRS offers a rate of seizure control comparable to microsurgery but with much lower risk.

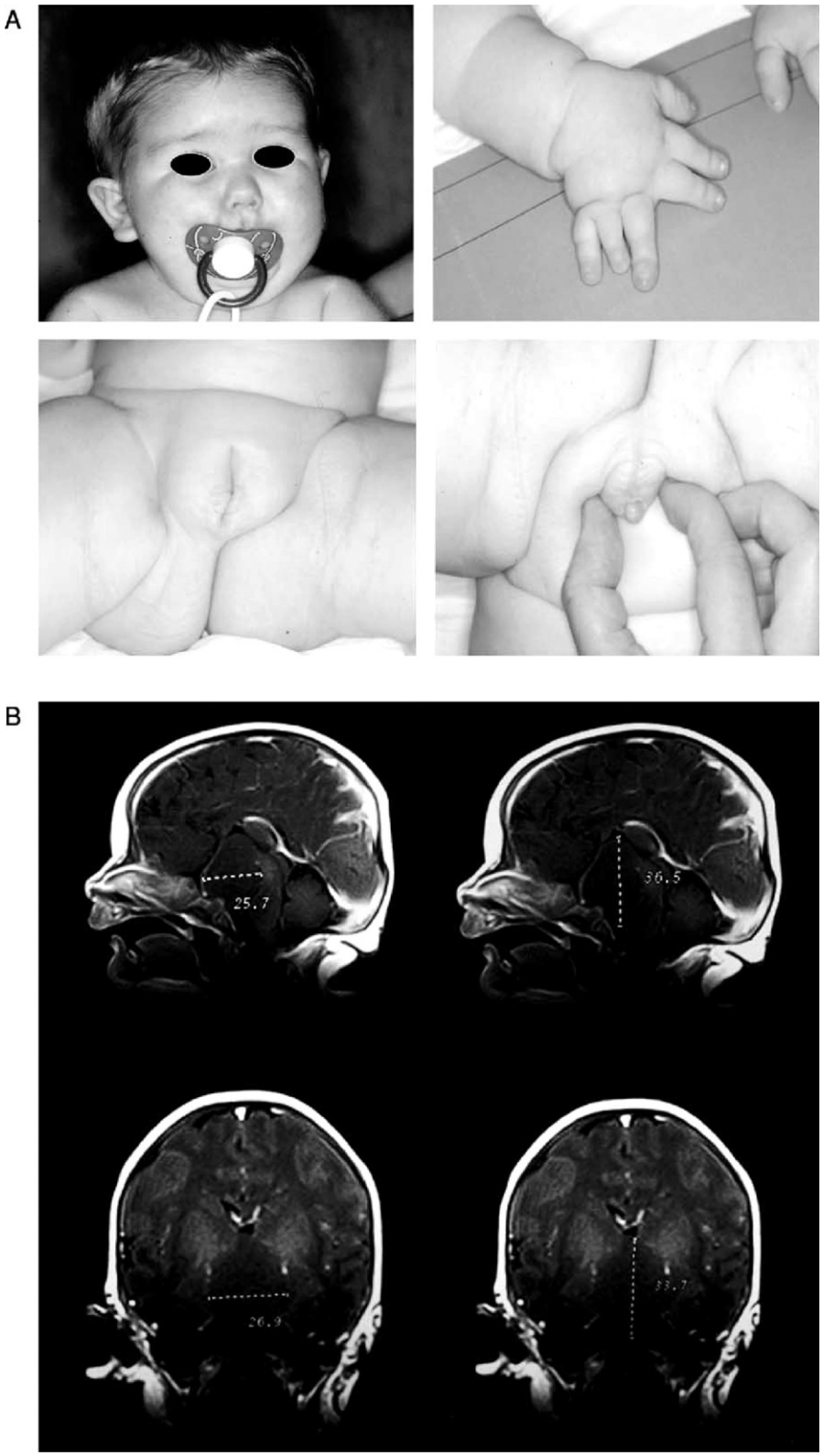

Fig. 3 (A) Frontal view showing a phenotype suggestive of congenital hypopituitarism. Note the hands with polydactyly; micropenis and cryptorchidism are associated with panhypopituitarism. (B) Sagittal and coronal T1-weighted MR images demonstrating the mass (dotted lines) compatible with hamartoblastoma and the absence of pituitary tissue.

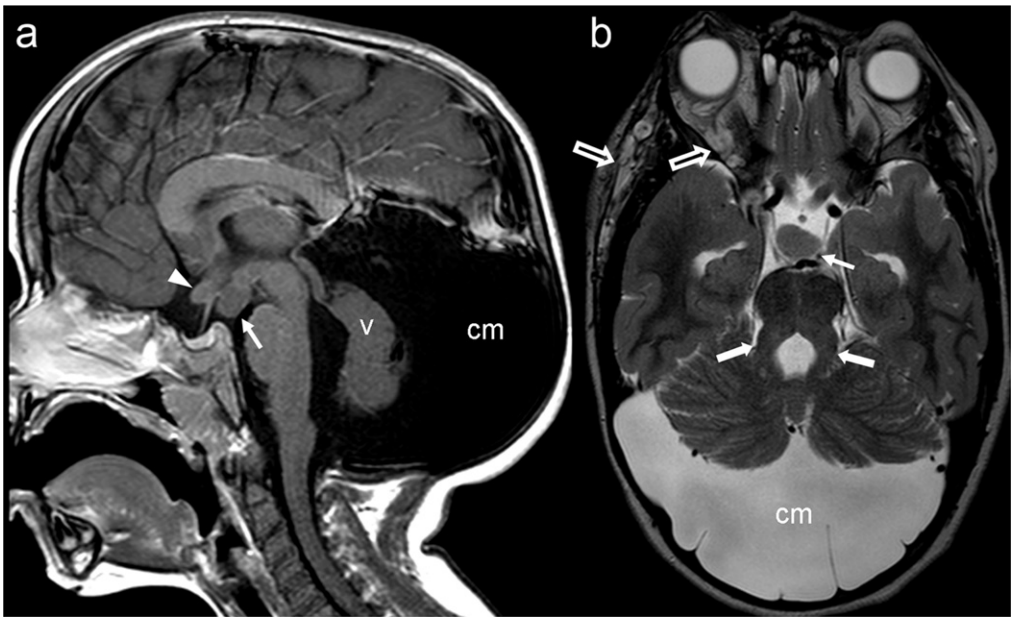

Fig. 4 Varadi–Papp syndrome and coexistent Neurofibromatosis type 1. (A) Gd-enhanced sagittal T1-weighted image; (B) Axial T2-weighted image. Hypothalamic hamartoma attached to the floor of the third ventricle and projecting into the interpeduncolar fossa (*thin arrow*, A, B). Pathologic thickening of the optic chiasm (*arrowhead*, A), without contrast enhancement, and small neurofibromas in the right orbit and temporal subcutaneous region (*open arrows*, B). Vermian hypoplasia (v), huge cystic dilatation of the cistern magna (cm) and molar tooth malformation (*thick arrows*, B).

Stereotactic radiofrequency thermocoagulation has also been used. It is a procedure during which a monopolar needle, under stereotactic guidance, is inserted into the surgical target. Current at high frequency (above 250 Khz) is injected, resulting in heating of the tissue at the electrode tip. The effectiveness of stereotactic radiofrequency thermocoagulation in the treatment of epilepsy has been reported in small case series of HH. Kameyama et al. reported the largest group, consisting of 25 patients of whom 19 (76%) had seizure remission; improvement in behaviour also occurred. Complications in this group included evidence of hypothalamic dysfunction in more than 50% of patients (hyperphagia, hyponatremia, Horner's syndrome, all transient). Stereotactic radiofrequency thermocoagulation has the advantage over SRS of earlier postoperative treatment effects.

Associated Conditions

Pallister–Hall Syndrome

Pallisteral–Hall syndrome (PHS) was first described in 1980 as a lethal congenital malformation syndrome associated with hypothalamic hamartoblastomas, postaxial polydactyly, craniofacial malformations and imperforated anus. Additional abnormalities include developmental and postnatal retardation, holoprosencephaly, pituitary agenesis/dysgenesis with hormone dysfunction leading to micropenis, cryptorchidism, hypopituitarism or panhypopituitarism, laryngeal clefts, bifid epiglottis, buccal frenula, small nose/anteverted nares, low-set/posteriorly angulated ears and microphtalmia, limb/skeletal malformations such as short fourth metacarpals and nail dysplasia, involvement of other organs with abnormal lung lobulation, renal agenesis and/or dysplasia, and congenital heart defects (**Fig. 3**). The syndrome is now considered a clinical, variable "iceberg" disorder with wide phenotypic variability where adrenal insufficiency is the most common cause of perinatal death.

This disorder is inherited as an autosomal dominant trait and has been reported in association with unbalanced chromosome translocation between chromosomes 3 p and 7q and later mapped to chromosome 7p13. Mutations in the transcription regulator gene GLI3 have been identified in patients with PHS, but also in four other different autosomal dominant phenotypes: the Greig cephalopolysyndactyly syndrome, preaxial polydactyly type IV, postaxial polydactyly type A and postaxial polydactyly type A/B.

Consensus guidelines in 1996 developed diagnostic criteria for the delineation of familial Pallister–Hall syndrome, which include the presence of hypothalamic hamartoma, central polydactyly most commonly affecting the third or fourth digit, and, in the first degree relatives of an index case, hypothalamic hamartoma or similar digital abnormalities associated with an autosomal dominant. An association with endocrine dysfunction requires hormone substitutive treatment. Adult height above the target height has been reported in a patient treated with growth hormone for up to 7 years. Surgical correction of visceral abnormalities is mandatory.

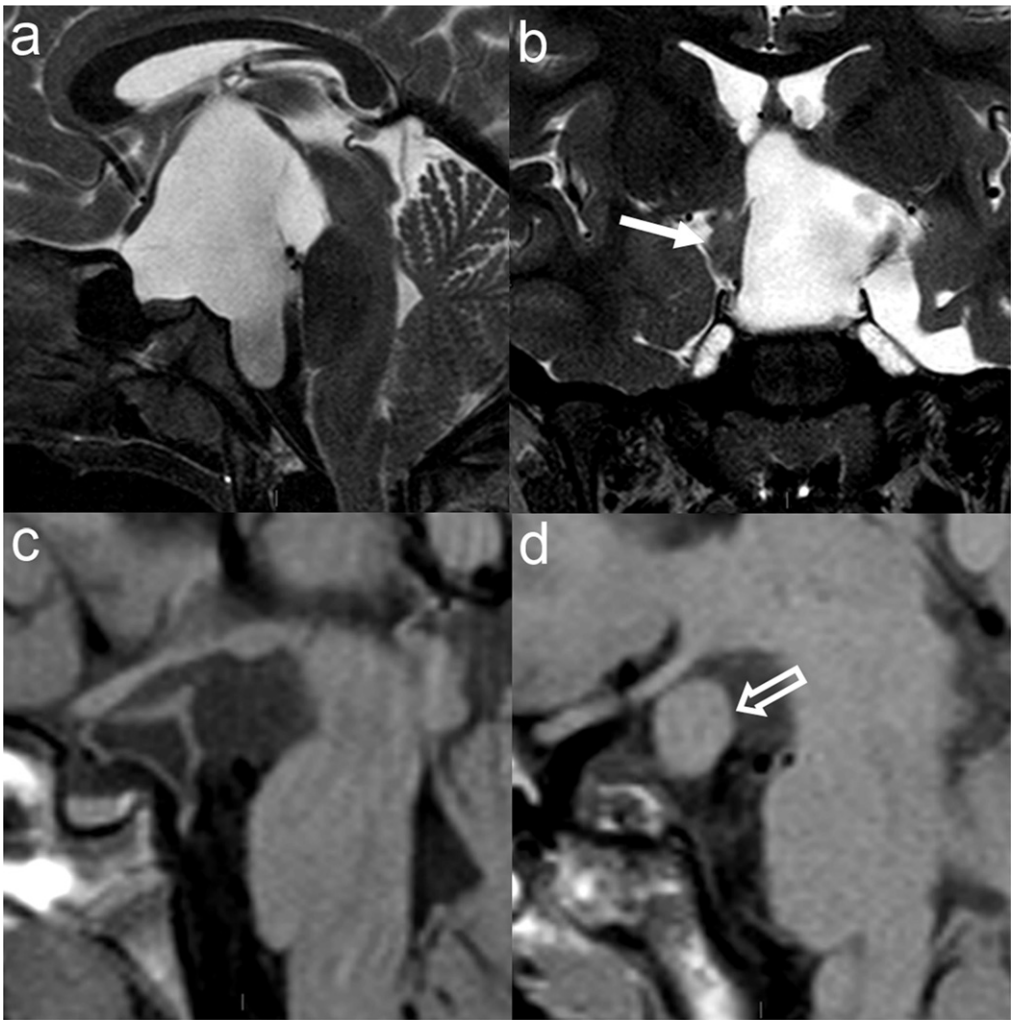

Fig. 5 Coexistent suprasellar arachnoid cyst and hypothalamic hamartoma in a 8-year-old boy with precocious puberty. (A) Sagittal T2-weighted image; (B) Coronal T2-weighted image; (C, D) Sagittal T1-weighted images. (A, B) Brain MRI at admission shows a huge suprasellar arachnoid cyst. Along the right wall of the cyst a solid mass, isointense to brain parenchyma, is demonstrated (*arrow*, B). (C, D) Brain MRI performed following surgical fenestration of the cyst better shows the peduncolated hamartoma, projecting into the interpeduncolar fossa (*open arrow*, D).

PHS patients usually have well controlled seizures and endocrine disturbances other than precocious puberty. Only a few PHS patients (those with the most frequent and difficult to control seizures) have marked behavioural or developmental problems. These data support previous reports of a strong effect of seizures on cognitive and behavioural problems in patients with HH.

Other Conditions

Hamartomas may be found in syndromes of midline defects such as oral-facial-digital syndrome type 6 (Varadi–Papp syndrome) (Fig. 4), Smith–Lemli–Opitz syndrome, solitary maxillary incisor, or in association with CNS malformations including agenesis of corpus callosum or holoprosencephaly. They have also been described in Laurence–Moon–Biedl syndrome, McKusick–Kaufman syndrome and Waardenburg syndrome. Syndromic HH have milder symptoms than isolated HH, but likely arise from similar pathogenic mechanisms.

HH have also been reported in association with a spectrum of cystic abnormalities (Fig. 5) which include intrahamartomatous cysts, arachnoid cysts that extend within the hamartoma, and arachnoid cysts that are adjacent to or remote from the hypothalamic hamartomas. The mechanism behind this association is not known. Different hypotheses advocate disruption of the prenatal subarachnoid space formation by the hamartoma, or inclusion of meningeal tissue within the hamartoma.

Acknowledgment

We thank Dr Luigi Gargantini (Clinica Pediatrica, Ospedale di Treviglio) for providing the case of Pallister–Hall syndrome illustrated in Fig. 2.

Further Reading

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