Neonatal hypothalamic hamartoma: a differentiating nonlethal hamartoblastoma

Case report

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The authors report on a patient with a large hypothalamic hamartoma with a cleft lip and palate and seizures. Neuroimaging revealed a large extraxial, intradural mass in the prepontine and interpeduncular cisterns with significant distortion of the brainstem. A stereotactic transfontanel needle biopsy revealed a cellular lesion that contained immature-appearing neuroepithelial cells consistent with prior descriptions of hypothalamic hamartoblastoma. While having a low level of proliferation by Ki67 (MIB-1) labeling, the lesion also contained evidence of neuronal maturation, with many cells expressing neuronal nuclear antigen as observed during immunohistochemical analysis. Further clinical evaluation revealed no other significant congenital abnormalities, and the patient was discharged home. Outpatient follow-up has continued for 2 years and the patient has been doing well, requiring no further treatment. This case illustrates that, despite its immature and proliferative histological appearance, this rare neonatal mass can be regarded as a “differentiating” hypothalamic hamartoma and can have a favorable prognosis.

KEY WORDS • hypothalamic hamartoblastoma • hamartoma • cleft palate • neonate • pediatric neurosurgery

Abbreviations used in this paper: FLAIR = fluid-attenuated inversion recovery; MR = magnetic resonance; Neu-N = neuronal nuclear antigen.
occasional tonic–clonic movements of his extremities. Evaluation of blood, urine, cerebrospinal fluid, blood glucose, and electrolytes revealed no obvious cause for the seizures. Phenobarbital was initiated and electroencephalography demonstrated a mild abnormality in the form of disorganization/slowing of the background (but without epileptiform discharges or electrographic seizures). Magnetic resonance imaging revealed a well-delineated, largely extraaxial mass located mainly in the prepubertal cistern but apparently exophytic from the tuber cinereum. The mass was 27 mm in maximum length and it dorsally displaced the basilar artery and the rostral brainstem (Fig. 1). No other brain malformations were evident. Magnetic resonance imaging before and after administration of Gd revealed no significant enhancement (Fig. 2). The T₂-weighted and FLAIR sequences revealed an increase in free water relative to brain, whereas the mass was isointense to the brain on the diffusion sequences (Fig. 3). This combination of findings on MR imaging is indicative of a mass exhibiting features of low aggressiveness.

Pathological Examination. A stereotactic transfontanel needle biopsy was performed by immobilizing the child’s head with bolsters and tape. A frameless stereotactic workstation (StealthStation; Medtronic, Inc., Memphis, TN) with a trackable Nashold biopsy needle was used. Accurate localization was confirmed using three-dimensional ultrasonography. The biopsy specimen revealed a lesion of variable cellularity with a tendency of groups of cells to form loose clusters. These clusters were dispersed within a delicate neuropil and included immature-appearing cells with hypocromatic nuclei and little discernible cytoplasm, along with a few larger cells with prominent nucleoli and a small amount of amphophilic cytoplasm that were consistent with neurons (Fig. 4A). Astrocyte-like cells were also observed. Immunohistochemical studies were performed on the formalin-fixed, paraffin-embedded tissue by an automated immunoperoxidase method (Ventana, Tuscon, AZ). Both the immature-appearing cells and the neuronlike cells were

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Fig. 1. Sagittal T₁-weighted MR sequence demonstrating the mass (m) in long axis. It is located anterior to the basilar artery and rostral brainstem. Both are displaced posteriorly without being invaded. The mass is attached to the caudal surface of the tuber cinereum (arrow), as would also be expected in a hypothalamic hamartoma.

Fig. 2. Composite axial T₁-weighted MR imaging sequences. Left: Unenhanced image. Right: Contrast-enhanced image obtained using Gd-dithylenetriamine (0.1 mg/ml). It is apparent that the mass does not enhance but remains the same intensity as adjacent brain tissue.
immunoreactive for neurofilament protein (RMdO20; Zy-
med Laboratories, Inc., San Francisco, CA) and Neu-N
(Fig. 4B; MAB377; Chemicon International, Inc., Temecu-
la, CA). Synaptophysin (S38; Dako Corp., Carpen
teria, CA) was diffusely positive in the neuropil. Scattered astro-
cytes with prominent cell processes strongly reactive to gli-
al fibrillary acidic protein (polyclonal; Dako) were distrib-
uted throughout the lesion but were especially associated
with cell clusters (Fig. 4C). Mitoses were not observed;
however, the overall Ki67 labeling index (MIB-1; Dako
Corp.) as evaluated by image analysis (Chromovision Sys-
tem; Berchtold Corp., Charleston, SC), was 3 to 4%. By
manual counts, this labeling index was not significantly in-
creased in the more cellular foci and supports a low level of
proliferation (Fig. 4D).

Postbiopsy Evaluation. Endocrine evaluation revealed de-
creased concentration of luteinizing hormone and follicle-
stimulating hormone and elevated prolactin and growth-
hormone concentrations; however, no therapy was required.
The boy’s seizures were well controlled with phenobarbital,
and no other events occurred during his hospital stay. The
patient was discharged home with neurosurgical, neurolog-
ical, and craniofacial follow up and no plans for immediate
resection.

Outpatient Evaluation. Since discharge from the hospital,
the patient has had one breakthrough seizure. Phenobarbital
therapy was discontinued at the age of 13 months. Follow-
up neuroimaging revealed no changes in the size of the
mass and no edema. He underwent successful repair of his
cleft lip and palate and continues to thrive and do well as
an outpatient. Currently, he is off all medications and only
receives intervention for developmental delay.

Discussion

Confusion surrounding the distinction between hypo-
thalamic hamartoblastomas and hamartomas stems from
the first descriptions of children with Pallister–Hall syn-
drome.3,6 The main features of this syndrome included
hypothalamic hamartoblastomas and various other malfor-
mations.15 Initial reports suggested that this tumor in a mid-
gestation fetus could be referred to as a hamartoma; how-
ever, the presence of undifferentiated germinal cells, the
large size of the lesion, and its apparent invasion of sur-
rounding tissue suggested that this lesion was neoplastic,3
and these features led to the term “hypothalamic hamarto-
blastoma.” Subsequent clinical follow up of neonates with
such tumors revealed lack of progressive growth or meta-
tasis, and patients tended to die of complications related to
other features of the syndrome. Consequently, these lesions
are currently viewed as neonatal hamartomas, and the pa-
tient’s prognosis is based on the presence or absence of
other congenital malformations.

The so-called “hypothalamic hamartoblastoma” is not
mentioned as a distinct neoplasm in the current (2000)
World Health Organization classification system.8 Our re-
port suggests that histologically immature-appearing hypo-
thalamic masses in infants may in fact mature into the more
familiar hypothalamic hamartomas of older children and adul-
ts. The hypothalamic hamartoma is also not considered
to be neoplastic in the conventional sense and is not includ-
ed in the World Health Organization brain tumor classifi-
cation.8

When considered in the context of normal brain develop-
ment, the primitive histological appearance of neonatal hy-
pothalamic hamartomas probably reflects the level of cen-
tral nervous system maturity at this early stage of life.3,12
Postnatal differentiation of the lesion most likely produces
the more mature neuronal phenotype and proliferatively
quiescent characteristics of the more typical adult form of
hypothalamic hamartoma. This supposition is supported by
our finding of positive immunoreactivity for neurofilament
protein and Neu-N in the immature-appearing cellular ele-
ments. In particular, Neu-N is developmentally expressed
in differentiating neurons and is considered to be a marker
of a more mature neuronal phenotype.10,16 Its expression in
the immature cells of neonatal hypothalamic hamartoma, which to our knowledge is described here for the first time, suggests that these cells have the potential to differentiate into more mature neurons. The presence of maturing neuronal and glial cells further suggests that infantile hypothalamic hamartomas have the potential to differentiate into the “nonneoplastic” hypothalamic hamartomas found in older individuals. The low Ki67 (MIB-1 antibody) labeling index of immature cells observed in the infantile lesion may reflect an overall immaturity of the neonatal nervous system instead of an intrinsic property of an expanding mass. This low level of proliferation would be expected to decline with further maturation of the child and subsequent differentiation of the lesion.

We have described the case of a full-term infant who presented with seizures and a cleft lip and palate and was found on MR imaging to have a large intracranial mass consistent with a hamartoma. Histological examination identified a tumor more closely resembling those described in the earlier reports of patients with Pallister–Hall syndrome; however, close follow up and monitoring over the subsequent 2 years has demonstrated a tumor consistent with a true hypothalamic hamartoma.

This case emphasizes the importance of accurately classifying this type of brain tumor. The majority of the literature reports that a diagnosis of a hypothalamic hamartoblastoma has a very poor prognosis, mainly attributable to other significant congenital malformations. In contrast, authors of more recent case reports of hypothalamic hamartomas report on children with a fair prognosis, even when associated with other congenital anomalies. In this case report, we discussed a neonate with a significant congenital anomaly and a lesion having pathological characteristics consistent with a hamartoblastoma whose clinical course has more clearly outlined that of a hamartoma. This finding supports the more recent argument that most of the lethal hamartoblastomas described in the literature were probably lesions similar to the one in our patient, but the patients died before repeated pathological studies could demonstrate maturation of the lesion.

Congenital hypothalamic hamartomas have been linked to other syndromes besides the Pallister–Hall syndrome, including Smith-Lemli-Opitz Type II, orofaciiodigital Type VI, and hydrolethalus syndrome. Features of these syndromes include holoprosencephaly, agenesis of the corpus callosum, facial abnormalities (including cleft lip and palate), and other skeletal abnormalities. A group of “nonsyndromal” infants with hypothalamic hamartoma and craniofacial anomalies have been reported. The cause of this association stems from the possibility that the tumor induces a disruptive pattern of anomalies early in fetal development. As mentioned earlier, our patient had a cleft lip and palate and a hypothalamic hamartoma, with no other anomalies present. It was felt that he represented another case of this associative pattern.

The patient continues to be followed as an outpatient, has been doing well, and is receiving treatment for his developmental delay. Close follow up is required for the develop-
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ment of precocious puberty and gelastic seizures commonly associated with these lesions. Improved surgical techniques will allow this patient’s prognosis to continue to be fair, even if these symptoms develop.5,7,9,13

References


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