Ectopic Posterior Pituitary Lobe and Periventricular Heterotopia: Cerebral Malformations with the Same Underlying Mechanism?

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BACKGROUND AND PURPOSE: Ectopic posterior pituitary lobe often occurs in children with growth hormone deficiency and is part of the spectrum associated with septo-optic dysplasia. Some cases of septo-optic dysplasia are caused by homozygous mutations in the homeobox gene HESX1, whereas heterozygous mutations are associated with milder phenotypes. To date, HESX1 is the only gene associated with ectopic posterior pituitary lobe. We describe an association between ectopic posterior pituitary lobe and periventricular heterotopia in four children without classic features of septo-optic dysplasia and suggest possible mechanisms on the basis of a review of pituitary embryology and recent molecular genetic advances.

METHODS: Among 20 children with ectopic posterior pituitary lobe, four had associated periventricular heterotopia. We herein review the clinical and MR imaging findings of these four children. Mutation screening of HESX1 was performed in two.

RESULTS: All four children had growth hormone deficiency. None had visual or neurologic disturbances. MR images showed a range of pituitary appearances, with scattered discrete periventricular heterotopia in each case. Other abnormalities were limited to small suprasellar lipomas and callosal dysgenesis. A heterozygous HESX1 mutation was present in one case.

CONCLUSION: The coexistence of ectopic posterior pituitary lobe and periventricular heterotopia suggests they have a common underlying genetic basis that is due to gene expression at different locations and stages of development. The presence of a heterozygous HESX1 mutation in one case suggests this gene is important in the development of both ectopic posterior pituitary lobe and periventricular heterotopia and supports their place in the spectrum of septo-optic dysplasia. Further analysis of HESX1 and other genes in related developmental pathways will elucidate their roles in the development of both malformations.
**TABLE 1: Summary of clinical and hormonal abnormalities**

<table>
<thead>
<tr>
<th>Clinical Feature</th>
<th>Case 1</th>
<th>Case 2</th>
<th>Case 3</th>
<th>Case 4</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age at presentation</td>
<td>2 yr</td>
<td>14 mo</td>
<td>5 yr 9 mo</td>
<td>3 yr 11 mo</td>
</tr>
<tr>
<td>Sex</td>
<td>M</td>
<td>M</td>
<td>M</td>
<td>F</td>
</tr>
<tr>
<td>Presenting symptoms</td>
<td>Short stature, poor growth</td>
<td>Short stature, poor growth,</td>
<td>Short stature, poor growth</td>
<td>Short stature, poor growth</td>
</tr>
<tr>
<td></td>
<td></td>
<td>episodes suggesting</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>hyperglycemia</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Height</td>
<td>On 1st centile</td>
<td>&lt;1st centile</td>
<td>&lt;1st centile</td>
<td>&lt;1st centile</td>
</tr>
<tr>
<td>Antenatal/perinatal events</td>
<td>IUGR at 34 wk gestation,</td>
<td>Breech presentation, elective</td>
<td>Neonatal hypoglycemia</td>
<td>Maternal hypertension, forceps delivery for fetal distress</td>
</tr>
<tr>
<td></td>
<td>neonatal hypoglycemia</td>
<td>CS</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Seizures</td>
<td>0</td>
<td>1 Generalized seizure</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Family history</td>
<td></td>
<td>Cousin with epilepsy, maternal</td>
<td></td>
<td>0</td>
</tr>
<tr>
<td></td>
<td>0</td>
<td>GM with anosmia</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>Vision/fundal</td>
<td>Asymptomatic, n/t</td>
<td>N</td>
<td>Asymptomatic, n/t</td>
<td>N</td>
</tr>
<tr>
<td>Other examination findings</td>
<td>Micropenis, small nasal dimple</td>
<td>Micropenis</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Maximum GH response to glucagon (normal &gt;20 mU/L)</td>
<td>19</td>
<td>27</td>
<td>3</td>
<td>3</td>
</tr>
<tr>
<td>Free thyroxine (normal range, 10–25 pmol/L)</td>
<td>7.2</td>
<td>Total T4 = 110 nmol/L</td>
<td>6.3</td>
<td>12.1</td>
</tr>
<tr>
<td></td>
<td></td>
<td>(normal range, 70–155 nmol/L), TSH = 2.1 mIU/L</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>(normal range, &lt;5 mIU/L)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Plasma cortisol (8:30 AM) (normal range, 200–750 nmol/L)</td>
<td>330</td>
<td>546</td>
<td>200</td>
<td>n/t</td>
</tr>
<tr>
<td>Prolactin (normal range, 50–500 mIU/L)</td>
<td>n/t</td>
<td>n/t</td>
<td>40</td>
<td>76</td>
</tr>
<tr>
<td>Response to GH treatment</td>
<td>On 15th centile</td>
<td>&gt;1st centile after 6 mo</td>
<td>On 3rd centile (on GH, thyroxine, hydrocortisone)</td>
<td>&gt;25th centile</td>
</tr>
<tr>
<td>HESXI mutation</td>
<td>0</td>
<td>n/t</td>
<td>n/t</td>
<td>+ (father and sister also have mutation)</td>
</tr>
</tbody>
</table>

Note.—M indicates male; F, female; IUGR, intrauterine growth; CS, caesarian section; GM, grandmother; n/t, not tested; N, normal; 0, absent; GH, growth hormone; TSH, thyroid-stimulating hormone.

**Results**

The major clinical findings and hormonal abnormalities are summarized in Table 1. The four children (three boys and one girl) presented during early childhood with short stature and growth disorders. There were no symptomatic visual defects in any case, although the results of fundal examination were available for only two cases. No patient had epilepsy. An A541G heterozygous HESXI mutation was found in case 4. No mutation was found in case 1.

The MR imaging appearances are summarized in Table 2. All patients had small anterior pituitary lobes and pituitary stalks. Case 1 showed typical findings of ectopic posterior pituitary lobe, with hyperintensity at the median eminence, a thin truncated infundibulum, and a small sella turcica containing a tiny anterior pituitary lobe (Fig 1). Case 2 showed a variation of this, with the hyperintensity at the median eminence extending down into the thin infundibulum, slightly lower than in case 1 (Fig 2). In case 3, in addition to
ectopic posterior pituitary lobe at the median eminence, a thin linear focus of hyperintensity on the posterosuperior aspect of the pituitary gland was seen and was thought to also represent abnormally located posterior pituitary tissue; the anterior sella was dysplastic (Fig 3). In case 4, a small hyperintensity was present at the median eminence, corresponding to ectopic posterior pituitary lobe, which did not suppress on fat-saturated T1-weighted MR images. The infundibulum was best seen on the contrast-enhanced images, angling posterosuperiorly toward the median eminence, which could also be identified by its enhancement (Fig 4). These appearances remained stable for 5 years after initial presentation.

The periventricular heterotopia consisted of several nodules only, located at various sites along the lateral ventricular walls. Periventricular heterotopia was unilateral in two cases and bilateral in two (Table 2). The septum pellucidum and optic nerves were normal in all cases. Other MR imaging abnormalities were limited to small suprasellar lipomas involving the mamillary bodies and interpeduncular cistern in case 4 (Fig 4) and a short corpus callosum with a small splenium in case 2 (Fig 2). No periventricular leukomalacia or other cerebral abnormality was present to account for the callosal appearances in case 2.

**Discussion**

**Ectopic Posterior Pituitary Lobe and Associated Abnormalities**

The MR imaging appearances and differential diagnoses associated with ectopic posterior pituitary lobe have been described previously (2–6, 11–13). The patterns of hormonal disturbance found in association with ectopic posterior pituitary lobe are also well recognized (1–7, 12, 14). Various midline brain malformations have been associated with ectopic pos-
terior pituitary lobe, including Chiari 1 malformation, optic nerve hypoplasia, septo-optic dysplasia, agenesis of the corpus callosum, persistent cranio-pharyngeal canal, Kallmann syndrome, basilar impression, medial deviation of the carotid arteries, microcephaly, cerebellar atrophy, and vermian dysplasia (5, 7–9, 12, 15). Associated ophthalmic and midline facial abnormalities, including cardiac and musculoskeletal abnormalities, have been described (4, 5, 12, 14). Breech presentation and neonatal hypoglycemia are also common (3–5, 8). The association of ectopic posterior pituitary lobe and periventricular heterotopia raises interesting questions regarding the relationship of these focal abnormalities.

Development of the Pituitary

To consider mechanisms for ectopic posterior pituitary lobe development, it is necessary to understand the multiple steps in pituitary formation. The pituitary gland consists of two portions: the adenohypophysis and the neurohypophysis. The neurohypophysis comprises the posterior pituitary lobe, the infundibulum, and the median eminence of the hypothalamus. The adenohypophysis and neurohypophysis develop from a out-pouching of ectoderm at the roof of the oral cavity (Rathke’s pouch) and from the neuroectodermal floor of the forebrain (diencephalon), respectively. In human embryos, the primordium of the adenohypophysis can be distinguished as early as 22 days (16) and probably contains cells committed to form the adenohypophysis, even at this very early stage (17). Work in other species has shown that both pituitary lobes originate from an ill-defined population of surface and neural ectoderm precursors; cells of the future adenohypophysis lie at the anterior margin of the neural ridge and grow ventrally to line the primitive oral cavity (18). Before this occurs, these cells lie adjacent to other primitive forebrain structures, such as the future hypothalamus and nasal ectoderm that are thought to influence cell commitment within the future adenohypophysis (19). The importance of these nearby forebrain structures has also been shown in humans (20, 21), although the origin of the adenohypophysis remains controversial. A number of homeobox genes, including HESX1 and

Fig 2. Images from case 2.
A, Unenhanced midline sagittal spin-echo T1-weighted image (625/13/4) shows a small hyperintensity at the median eminence typical of ectopic posterior pituitary lobe, with a second small hyperintensity extending downward into the upper infundibulum (arrows). The infundibulum is thinned, with a small pituitary gland and sella turcica. The splenium of the corpus callosum is small.
B, Axial fast spin-echo T2-weighted images (5200/102/3) show small heterotopic nodules isointense to gray matter, above the frontal horns (arrowheads).

Fig 3. Image from case 3. Unenhanced midline sagittal view spin-echo T1-weighted image (625/13/4) shows hyperintensity at the median eminence, typical for ectopic posterior pituitary lobe (short arrow). A small hyperintense focus can also be seen lying posterosuperiorly on the superior aspect of the small pituitary gland (curved arrow), which probably also represents ectopic pituitary tissue. The sella has an abnormal morphology, with a sloping anterior wall. It contains a thin layer of soft tissue lining the floor of the dysplastic anterior sella and more recognizable pituitary tissue in the base of the sella. The infundibulum is difficult to definitely identify because it is markedly thinned but may lie more anteriorly than usual (long arrow).
genes that encode signaling molecules are implicated in this early development (22).

Rathke’s pouch begins to invaginate upward from the oral cavity toward the diencephalon around 28 days. It then thickens and elongates, developing direct contact with the diencephalon in the midline, with only a thin intervening basement membrane (20, 23). Cells in the floor of the diencephalon have been found to be relatively quiescent, with few mitoses (20). Therefore, the neurohypophysis may form as a result of adherence to Rathke’s pouch (20), with growth of Rathke’s pouch and surrounding structures determining its eventual morphology (20, 24). Many factors from Rathke’s pouch, the diencephalon, and surrounding tissues are thought to control this stage of development. Reciprocal inductive signals between the diencephalon and Rathke’s pouch affect growth (19, 25, 26), and induction probably requires direct contact between these two structures (26).

Pituitary anatomic development is largely complete by 49 days and is followed by functional specialization with formation of the portal circulatory system and differentiation of hormone-secreting cells. Cell differentiation probably requires direct contact with the hypothalamus (26), and cases of growth hormone deficiency with an absent infundibulum tend to have more severe hormonal deficits than cases with a visible stalk (6, 12, 13). Numerous homeobox transcription factors from both the adenohypophysis and neighboring structures control cell differentiation, including such genes as \textit{POU1F1} and \textit{PROP1} (22). Mutations affecting these are not associated with ectopic posterior pituitary lobe (14, 27, 28), as might be expected, because overall pituitary morphology is already determined by the time these genes are expressed.

**Causes of Ectopic Posterior Pituitary Lobe**

Although early descriptions of ectopic posterior pituitary lobe postulated a traumatic cause (1, 2), more recent studies favor a genetic basis (4–8, 14, 29), supported by rare familial cases of ectopic posterior pituitary lobe (4, 12, 14, 30–33). The focal nature of the lesions observed in our cases is also an argument for a genetic abnormality with effects at different sites and developmental stages, because a vascular injury affecting such disparate structures as the pituitary and the periventricular germinal matrix could be expected to produce more widespread damage.

On the basis of developmental processes described above, we postulate that ectopic posterior pituitary lobe could occur if abnormal formation of Rathke’s pouch or its surrounding structures precluded contact between the diencephalon and Rathke’s pouch. Alternatively, if the mechanisms for intercellular adherence between the diencephalon and Rathke’s pouch were faulty, proper contact might not be maintained. In view of the complex chain of intercellular events needed for pituitary formation, the effect of an early abnormality would probably become amplified during subsequent development. The association of ectopic posterior pituitary lobe with a range of pituitary and midline lesions suggests that there are many early developmental steps that can be disrupted, with anterior pituitary hypoplasia and ectopic posterior pituitary lobe as an end product.

Recent work has identified some of the molecular
defects involved in such malformations. For instance, a disorder with anophthalmia and ectopic posterior pituitary lobe has been described (34) and is possibly due to abnormality of the BMP-4 gene, which is thought to promote growth in the primitive forebrain and may play a role in induction of Rathke's pouch (25). Ectopic posterior pituitary lobe is also part of the spectrum of abnormalities associated with septo-optic dysplasia, as are heterotopia and schizencephaly (9, 35). Familial septo-optic dysplasia is associated with homozygosity for an inactivating mutation in the homeobox gene HESX1/Hesx1 in both man and mouse, whereas mice with heterozygous Hesx1 mutations have a milder phenotype (36). Recent analysis of 228 patients with hypopituitarism and midline defects (including 105 with septo-optic dysplasia and milder phenotypes such as idiopathic growth hormone deficiency) found heterozygous mutations in the HESX1 gene in three cases (10). Ectopic posterior pituitary lobe was present in two of these (the patient in our case 4 is the same patient as “Individual II.1 in Pedigree 2” in the report presented by Thomas et al [10]). Mutational analysis of HESX1 has so far been performed in two of our cases (cases 1 and 4) and was positive in case 4. These findings indicate that HESX1 may play an important role in some cases of ectopic posterior pituitary lobe, with HESX1 heterozygosity resulting in a milder phenotype than classic septo-optic dysplasia. HESX1 is thought to control forebrain cell proliferation and the amount of tissue designated to form Rathke's pouch (36) and has a semi-dominant inheritance pattern with incomplete penetrance accounting for the range of observed abnormalities (10). Possible mechanisms for the development of associated periventricular heterotopia are unknown, but in mice, Hesx1 is not expressed in the brain during neuroblast migration (37). Therefore, if HESX1 does have a role in causing periventricular heterotopia, it would probably be an early effect, possibly on germinall matrix formation, before cell migration. Other recent work has found HESX1 mutations in only five of 93 patients with ectopic posterior pituitary lobe (38), indicating that other unrecognized genes or local environmental factors are likely to be involved in ectopic posterior pituitary lobe with periventricular heterotopia.

On the other hand, we can speculate that the limited abnormalities in our cases could be explained by an abnormality of intercellular adhesion. This could prevent adequate contact between Rathke's pouch and the diencephalon and subsequently affect neuronal migration in the developing cerebral hemispheres. Familial cases of periventricular heterotopia are the result of mutations in the FLN-1 gene, which are thought to affect intercellular adhesion by causing deficient cross-linking between neuronal membrane receptors and the actin cytoskeleton (39). Familial periventricular heterotopia is an X-linked dominant condition that is associated with epilepsy in affected female persons and lethality in male persons (40). MR images typically show multiple bilateral contiguous nodules lining the lateral ventricles (40, 41). Although our patients do not currently have epilepsy, even small solitary heterotopic nodules are associated with epilepsy, which can have a delayed onset in early adulthood (42). The periventricular heterotopia in our cases consists of several discrete nodules only (unilateral in two cases), which is different from periventricular heterotopia classically associated with FLN-1 mutations, suggesting that the mechanism for neuronal migration is virtually intact. Ectopic posterior pituitary lobe is not described in families with FLN-1 mutations (39, 41). Mutational analysis will elucidate whether the FLN-1 gene is relevant to the cerebral abnormalities of our cases.

The finding of two separate foci of ectopic posterior pituitary lobe in case 3 is unusual (Fig 3). We speculate that two ectopic posterior pituitary lobe foci might result, in the setting of a heterozygous HESX1 mutation, if the level of active HESX1 protein were sufficient to form some posterior pituitary tissue within the sella, with the rest in the typical ectopic location at the median eminence (10, 38). This could be analogous to the normal cerebral cortex overlying periventricular heterotopia in neuronal migration (39). The mechanism for the associated callosal abnormality in case 2 could be a mutation in HESX1 or a related gene causing abnormal patterning of either the presumptive corpus callosum or the surrounding neuroectoderm. Whether the lipomas in case 4 are related to the presumed genetic abnormality of the ectopic posterior pituitary lobe or local environmental factors is unclear (43).

Conclusion

Ectopic posterior pituitary lobe typically has a range of associated clinical and MR imaging abnormalities. The presence of ectopic posterior pituitary lobe should alert the radiologist to the possibility of associated cerebral malformations, even without evidence of septo-optic dysplasia. Both ectopic posterior pituitary lobe and periventricular heterotopia have distinctive MR imaging appearances and the important clinical consequences of hormone deficiencies and epilepsy. Further analysis of this interesting association and potential molecular defects may help to shed light on mechanisms of early pituitary development and neuronal cell migration.

References


