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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.

An ectopic posterior pituitary lobe presents a distinctive appearance on MR images, with the hyperintense posterior lobe characteristically seen at the median eminence in the floor of the third ventricle on unenhanced T1-weighted images (1, 2). Ectopic posterior pituitary lobe is found in many cases of growth hormone deficiency (3–8) and also occurs in some cases of septo-optic dysplasia, which classically has features of optic nerve hypoplasia, hypothalamic-pituitary dysfunction, and agenesis of the septum pellucidum (9). We present four cases of ectopic posterior pituitary lobe with varying clinical presentations and pituitary appearances without other features of septo-optic dysplasia. An interesting feature present in all four cases was coexistent periventricular heterotopia, suggesting that ectopic posterior pituitary lobe and periventricular heterotopia share a common underlying causative mechanism, even though pituitary development occurs earlier in fetal life than does neuronal migration. We reviewed the current understanding of pituitary development and its genetic control to consider the basis of these lesions.

Methods

Four cases of ectopic posterior pituitary lobe with incidental periventricular heterotopia presented at our institution be-

TABLE 1: Summary of clinical and hormonal abnormalities

Clinical Feature	Case 1	Case 2	Case 3	Case 4
Age at presentation	2 yr	14 mo	5 yr 9 mo	3 yr 11 mo
Sex	M	M	M	F
Presenting symptoms	Short stature, poor growth	Short stature, poor growth, episodes suggesting hypoglycemia	Short stature, poor growth	Short stature, poor growth
Height	On 1st centile	<1st centile	<1st centile	<1st centile
Antenatal/perinatal events	IUGR at 34 wk gestation, neonatal hypoglycemia	Breech presentation, elective CS	Neonatal hypoglycemia	Maternal hypertension, forceps delivery for fetal distress
Seizures	0	1 Generalized seizure	0	0
Family history	0	Cousin with epilepsy, maternal GM with anosmia	0	0
Vision/fundi	Asymptomatic, n/t	N	Asymptomatic, n/t	N
Other examination findings	Micropenis, small nasal dimple	Micropenis	0	0
Maximum GH response to glucagon (normal >20 mI U/L)	19	27	3	3
Free thyroxine (normal range, 10–25 pmol/L)	7.2	Total T4 = 110 nmol/L (normal range, 70–155 nmol/L), TSH = 2.1 mIU/L (normal range, <5 mIU/L)	6.3	12.1
Plasma cortisol (8:30 AM) (normal range, 200–750 nmol/L)	330	546	200	n/t
Prolactin (normal range, 50–500 mIU/L)	n/t	n/t	40	76
Response to GH treatment	On 15th centile	>1st centile after 6 mo	On 3rd centile (on GH, thyroxine, hydrocortisone)	>25th centile
HESX1 mutation	0	n/t	n/t	+ (father and sister also have mutation)

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.

tween 1998 and 2001. Of 5800 brain MR examinations performed in a tertiary pediatric center between 1998 and 2001, 20 were identified with ectopic posterior pituitary lobe. Among the 20 cases, periventricular heterotopia was found in four (20%) cases. Ectopic posterior pituitary lobe was diagnosed if there was a hyperintense focus at the median eminence on T1-weighted images; periventricular heterotopia was diagnosed on the basis of periventricular nodules that were isointense to gray matter on all pulse sequences. The clinical histories and MR imaging appearances of the four cases were reviewed.

Clinical details were noted, including patient age at time of presentation, sex, presenting symptoms, height, presence of visual disturbances, and other dysmorphic features. Histories were reviewed for available data regarding abnormal antenatal events, epilepsy, and relevant family history, including growth or hormonal disturbance and epilepsy. The results of hormonal testing and response to hormone replacement or therapy were noted.

MR images were obtained on a 1.5-T system (Signa Echospeed; GE Medical System, Milwaukee, WI), and the following series were obtained for all patients: sagittal and coronal spin-echo T1-weighted images (625/13/4 [TR/TE/NEX]) of the pituitary region, with a 14-cm field of view, 3-mm section thickness, and 0.3-mm section gap; axial fast spin-echo T2-weighted images (5200/102/3) and sagittal or coronal fast spin-echo T2-weighted images (5240/100/3). Case 4 included an additional unenhanced sagittal spin-echo T1-weighted series (650/9/2) with a fat-suppression pulse, and contrast-enhanced sagittal and coronal fat-suppressed T1-weighted MR images were obtained. Cases 1 and 2 included an additional spoiled gradient-recalled volume acquisition, with imaging parameters as

follows: 17.7/3.4 (TR/minimum TE), inversion time of 300 ms, 128 partitions, 1.5-mm section thickness, acquired in a sagittal plane with a 512 × 192 matrix.

Mutation screening was performed by direct cycle sequencing of venous blood or buccal cell samples, as detailed by Thomas et al (10). Cases 1 and 4 were tested.

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 HESX1 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

TABLE 2: Summary of MR imaging findings

MR Imaging Finding	Case 1	Case 2	Case 3	Case 4
Posterior pituitary lobe	EPP	EPP	EPP Second EPP focus on posterosuperior aspect of gland	EPP
Anterior pituitary lobe	Small	Small	Small	Small
Infundibulum	Thin	Thin, hyperintensity at root of infundibulum	Markedly thin, anteriorly placed	Thin
Sella turcica	Small	Small	Small, dysplastic anterior sella	Small
Periventricular heterotopia	2 Nodules, unilateral, posterior body of lateral ventricle	Approximately 7 nodules, bilateral, frontal horns and bodies of lateral ventricles	2 Nodules, bilateral, right trigone, left temporal horn	1 Nodule, unilateral, left frontal horn
Septum pellucidum/ optic nerves	N	N	N	N
Other abnormalities	0	Mild callosal dysgenesis	0	2 suprasellar lipomas

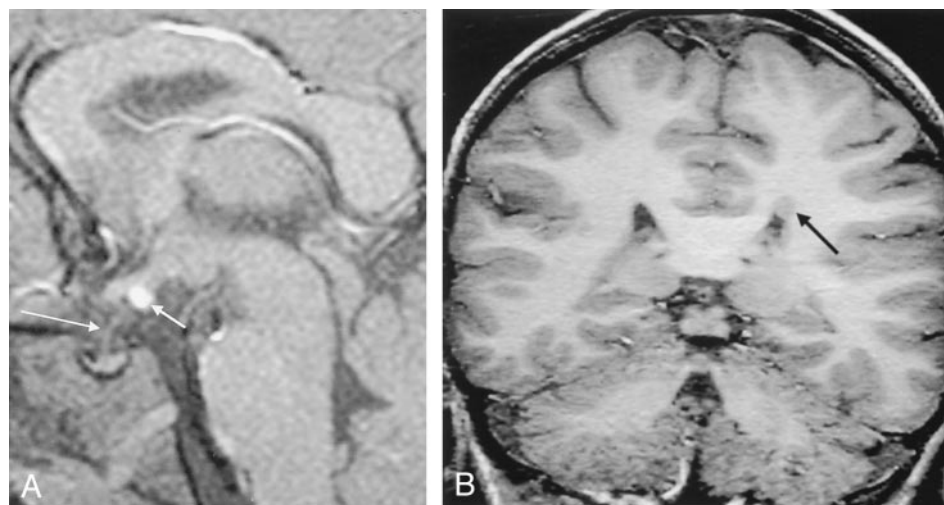Note.—EPP, ectopic posterior pituitary lobe; N, normal; 0, absent.

FIG 1.   Images from case 1, with typical findings of ectopic posterior pituitary lobe.
A, Unenhanced midline sagittal spin-echo T1-weighted image (625/13/4) shows hyperintensity corresponding to ectopic posterior pituitary lobe at the median eminence (*short arrow*). The pituitary gland and sella turcica are small, with a thin infundibulum (*long arrow*).
B, Coronal T1-weighted spoiled gradient-recalled image shows a small heterotopic nodule, isointense to gray matter, above the left trigone (*arrow*).

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 mammillary 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-
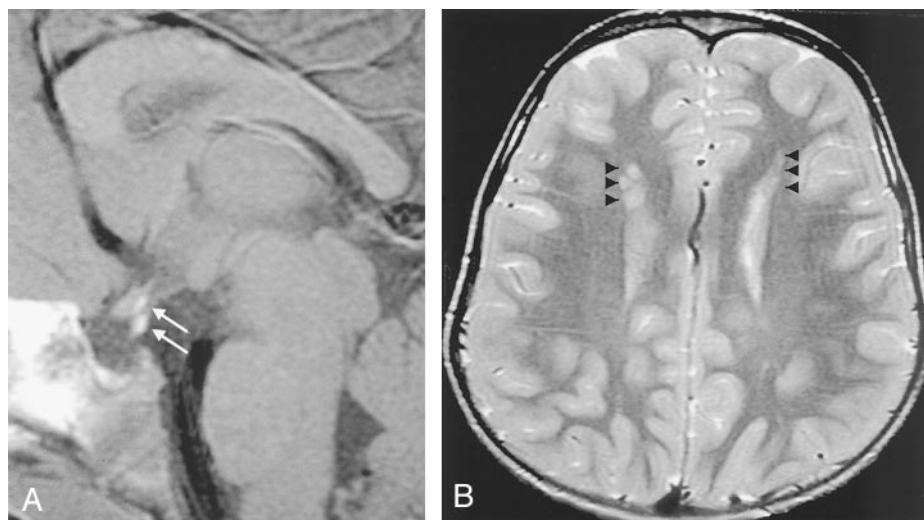
FIG 2.   Images from case 2.

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*).
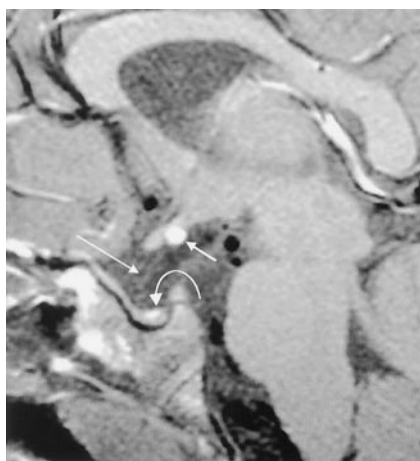

FIG 3.   Image from case 3. Unenhanced midline sagittal view spin-echo T1-weighted image (625/13/4) shows hyperintensity at the median eminence, typical for ectopic posterior pituitary lobe (*short arrow*). A small hyperintense focus can also be seen lying posterosuperiorly on the superior aspect of 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*).

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, such as a single central incisor tooth, are typical, and non-midline somatic conditions, 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 an 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
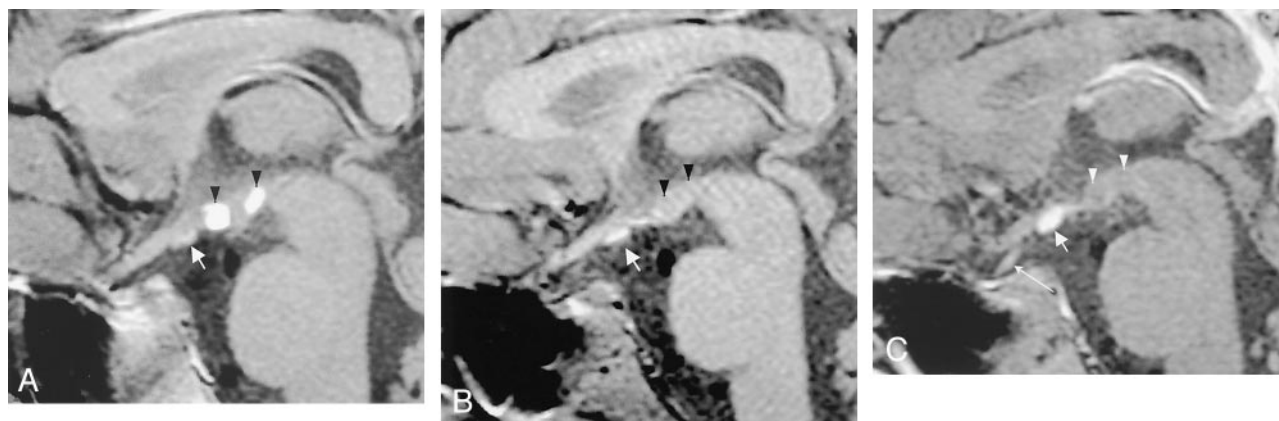
FIG 4. Images from case 4.

A, Unenhanced midline sagittal spin-echo T1-weighted image (625/13/4) shows two brightly hyperintense foci: one involving the mammillary bodies and the other in the interpeduncular cistern (*black arrowheads*). There is also a smaller less hyperintense focus located at the expected site of the median eminence, suggestive of ectopic posterior pituitary lobe (*white arrow*). The pituitary gland and sella are small, with a suggestion of a tiny posteriorly angled infundibulum.

B, Unenhanced sagittal spin-echo T1-weighted image (650/9/2) with fat suppression, obtained at the same position as the image shown in *A*, shows suppression of the two larger more posteriorly located hyperintensities (*black arrowheads*), indicating that these represent lipomas. The smaller anterior hyperintensity of ectopic posterior pituitary lobe does not suppress (*white arrow*). A little flow-related artifact is seen in the floor of the third ventricle between the median eminence and the mammillary bodies.

C, Contrast-enhanced sagittal spin-echo T1-weighted image (650/9/2) with fat suppression shows enhancement of the median eminence, confirming that the anterior hyperintensity lies at a typical location for ectopic posterior pituitary lobe (*short arrow*). Enhancement of the infundibulum can also be seen (*long arrow*). The two lipomas remain suppressed, with no enhancement (*arrowheads*).

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 *POU1F1* and *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 prob-

ably 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 germinal 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). Al-

though 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.

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