CASE REPORT

Ectopic posterior pituitary tissue and paracentric inversion of the short arm of chromosome 1 in twins

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Ectopic location of posterior pituitary tissue has been associated with abnormal anterior pituitary function without diabetes insipidus (1, 2). We report twin boys who both had hypopituitarism, hypoplasia of the anterior pituitary gland, ectopic posterior pituitary tissue and paracentric inversion of the short arm of chromosome 1, 46,XY,inv(1)(p22p34). While subnormal growth velocity, short stature and delayed puberty have been reported in patients carrying abnormalities of chromosome 1, specific associations of endocrine disorders with a gene(s) on chromosome 1 are lacking (3–5).

Clinical histories

Twins A and B were the 2105-g and 2160-g male products of a 35-week gestation to a 32-year-old woman. The pregnancy, apart from the twin gestation and preterm labor, was uncomplicated. Delivery was vaginal vertex without any traumatic injuries to the fetuses. Physical examinations were similar for both boys. Specifically, there were no dysmorphic features. Each boy had a normal penis (> 2.5 cm) and bilaterally descended testes. For both, the echocardiograms showed atrial septal defects with a common A–V valve, pulmonary hypertension, and mild right ventricular dilatation. Their karyotypes were identical, 46,XY,inv(1)(p22p34) (Fig. 1). Karyotypes of their parents were normal.

Twin A, after a hospital course complicated by clinical features consistent with sepsis, jaundice, pulmonary hypertension, edema, disseminated intra-vascular coagulation (DIC) and hypoglycemia, died at 17 days of age.

Twin B developed signs of respiratory distress within minutes of birth. Phototherapy was initiated on day 3 of life for hyperbilirubinemia. Pneumatoses intestinalis was noted on day 4 of life. Subsequently, a chest X-ray was consistent with pulmonary edema/obstructive pneumonia. On the 22nd day of life, his extremities were edematous and an echocardiogram showed atroventricular valve regurgitation and right-to-left ductal shunting. He had poor bowel function; an abdominal ultrasound showed multiple fluid-filled loops of bowel. Following the observation of a small anterior pituitary and the absence of posterior pituitary tissue within the sella (ectopic posterior pituitary tissue) on his brother’s autopsy, endocrine studies were obtained. His T₄ level was < 19.31 nmol/l (< 1.5 μg/dl), free T₄ was 6.56 pmol/l (0.51 ng/dl), TSH was 2.3 μU/l (2.3 μU/ml) and cortisol was 44.14 nmol/l (1.6 μg/dl). Thyroid hormone and cortisol replacement therapies were initiated, but he continued to deteriorate and died at 7 weeks of age.

Subjects and material

Autopsies were performed on both twins shortly after death. Absence of the pituitary stalks were noted on gross examination. The anterior pituitary glands were removed. For twin A the anterior pituitary gland was weighed. For twin B, the bony sella was removed “en bloc” with the pituitary gland embedded in it to obtain serial sections in order to search for possible ectopic ductal structures within the bone. The tissues were fixed
Sections were incubated for 30 min at room temperature with a specific antisera. The bridge antibody (swine anti-rabbit IgG) and PAP complex were also purchased from DAKO. The stained sections were examined with the light microscope for the presence and intensity of staining for each of the hormone antibodies used.

Routine chromosomal analysis was performed from peripheral blood lymphocytes. Chromosomes were prepared using ethidium bromide and GTG-banded (6).

Results

The post-mortem examination of each infant revealed that the anterior pituitary gland was small and located within the sella. It weighed 50 mg in twin A (normal is 200 mg for a mature newborn infant). No posterior pituitary tissue was present within the sella of either infant. The base of the median eminence was smooth and no hypothalamic–pituitary connection was apparent (Fig. 2). There was no remnant of a pituitary stalk, no portal blood vessels, no hemorrhage, no fibrosis and no evidence of any other reaction to traumatic interruption of the stalk. A small nodular proliferation of capillary vessels and astrocytes within the median eminence resembled the architecture of posterior pituitary tissue. No specific staining was attempted. Hypothalamic architecture was normal. There were no other associated cerebral malformations. Anterior pituitary hormones were detected in the hypoplastic anterior pituitary with the use of immunohistochemical stains (Fig. 3). In both twins, immunohistochemical stains illustrated the presence of ACTH, TSH, PRL, FSH, LH and GH within the anterior pituitary tissue. There was no predominance of any one of the hormonal secretions or total absence of a single hormone secretion.

Additional findings in both infants consisted of a hypoplastic thyroid gland, small adrenal glands, large atrioventricular septal defect and bifid epiglottis.

Fig. 1. Cartoon of chromosome 1. Genes mapped to the region of the paracentric inversion are indicated to the right of the cartoon (19, 20).

Fig. 2. (Left) Pituitary gland of twin B. sectioned within the bony sella turcica. Note the small size of the anterior pituitary lobe and the absence of posterior pituitary tissue within the sella (hematoxylin and eosin stained section, magnification ×15). (Right) Normal control newborn infant pituitary gland with the sella turcica (hematoxylin and eosin stained section, magnification ×15).
Discussion

Because the diagnosis of hypopituitarism was made post mortem in twin A, endocrine studies were only obtained for twin B. Hypothyroidism and hypocortisolism were the most prominent clinical features, the thyroid hormone levels—low T₄, low free T₄ and low TSH—are consistent with hypothalamic–anterior pituitary endocrine deficiencies. The diminutive sizes of the endocrine glands at autopsy reflected the lack of trophic hormone stimulation resulting from hypopituitarism, secondary to impaired transport of hypothalamic releasing factors due to the absence of a pituitary stalk. The presence of hormone secretion within anterior pituitary cells, as illustrated by immunocytochemical stains at autopsy, probably reflected “basal secretion” of differentiated cells without release of significant amounts of hormones within the blood, owing to the lack of trophic releasing factors from the hypothalamus. This is similar to the demonstration of minimal quantities of anterior pituitary hormone secretion in the pituitary glands of anencephalic infants with absence of the hypothalamus, or within anterior pituitary cells in organotypic cultures (7, 8). Experimental studies and observations on subjects with accidental section of the pituitary stalk have illustrated impaired transport of hypothalamic releasing factors from the hypothalamus to the anterior pituitary when the portal blood venous system is interrupted. No evidence of impaired vasopressin secretion is apparent whenever posterior pituitary tissue remains within the hypothalamus. In the presently reported cases, the babies were severely ill, but there was no clinical evidence of vasopressin deficiency. Although aggressive replacement therapy was initiated in twin B, the exact role of multiple endocrine deficiencies, especially glucocorticoid deficiency, in their deaths is unresolved.

With the advent of magnetic resonance imaging (MRI), posterior pituitary tissue can be identified as a “bright spot” or intense signal on T₁-weighted images (9). This technique has demonstrated the occasional finding of “ectopic” posterior pituitary tissue within the hypothalamic median eminence. This feature is uncommon in normal individuals. Further, the finding of such ectopic posterior pituitary tissue is associated with impaired anterior pituitary function in the absence of diabetes insipidus (10). The atypical location of posterior pituitary tissue at the base of the median eminence is usually attributed to developmental abnormalities or may be the result of accidental or acquired pituitary stalk section.

Two different pathophysiological mechanisms for ectopy of posterior pituitary tissue have been postulated. One theory is that this represents a developmental aberration with the lack of descent of the infundibulum, such that the anterior pituitary fails to consolidate with the posterior pituitary (10). The second hypothesis is that transection of the pituitary stalk, perhaps secondary to infarcts, hemorrhage or perinatal trauma, is followed by reorganization of the proximal neuronal tissue in the region of the median eminence (11). The smooth appearance of the base of the median eminence in these twin boys suggests that the failure of posterior pituitary tissue migration was a primary developmental dysgenesis with resulting anomalous neuroendocrine development. Hence, the absence of pituitary stalk tissue and ectopic position of posterior pituitary tissue in both twins presumably represents a congenital malformation in which the clinical manifestation (phenotype) is hypopituitarism.

The pathophysiological relationship of endocrine dysfunction associated with ectopy of the posterior pituitary and chromosome 1 abnormalities is unclear. Further, paracentric inversions are uncommon (12). The most frequently reported clinical findings associated with deletions of the short arm of chromosome 1 are low-set ears, congenital heart disease, microphthalmia, clinodactyly of the fifth finger, cryptorchidism and mental retardation (13). The location of such abnormalities on chromosome 1 in close proximity to genes implicated in early embryonal induction and organization (i.e. homeobox genes), and the involvement of adjacent pharyngeal and cardiac structures in this defect, opens the path to adventitous speculation. For example, protein products encoded by other genes in this region (Fig. 1)—PAGA and adenylate kinase-2—may have functions related to cell proliferation (14). Both our cases had similar congenital heart disease with large atrioventricular septal defects, but did not have additional dysmorphic features.

A 30-year-old woman was reported to have an interstitial deletion of chromosome 1 involving p22.1-p31.2, a deletion of the same chromosomal locus that was inverted in these twins. She had short stature, delayed puberty, bilateral microphthalmia with colobomas of the iris and developmental delay. Additional findings were a short neck, clinodactyly of the left fifth finger, subluxation of the left hip and bilateral equinovarus with severe valgus deformities of the great toes (5). While short stature and delayed puberty may be non-specific findings with chromosomal abnormalities, detailed endocrine evaluation is not available.

The relationship between our patients in whom the genetic anomaly was located on the short arm of chromosome 1 and the patient with growth hormone deficiency, hypothyroidism and an interstitial deletion of the long arm of chromosome 1 reported by Koivisto et al. (15) is unknown. Three siblings with congenital hypopituitarism were described recently for whom chromosomal analysis was not reported. Two had diabetes insipidus and absence of the posterior pituitary bright spot on MRI, while the third had partial diabetes insipidus and a bright spot on the median eminence consistent with ectopic posterior pituitary tissue (16).
Familial hypopituitarism has been described with mutations in Pit-1 (17). Pit-1 is a transcription factor that activates growth hormone and prolactin transcription and promotes differentiation of anterior pituitary cells (18). However, because the gene encoding Pit-1 has been mapped to chromosome 3, it is unlikely that mutations in the Pit-1 gene would be the basis of hypopituitarism in these twins. The normal differentiation of the anterior pituitary cells and the finding of pituitary hypoplasia at autopsy provide further evidence that abnormalities of the Pit-1 gene are unlikely in these twins.

The specific correlation between disturbed induction and dysgenesis of cardiac and cerebral ventral structures with anomalies of chromosome 1 remains to be elucidated. Hopefully, this report will encourage others to watch for this association in order to define better the precise relationship, if any, between these uncommon abnormalities. The finding of a causal relationship would benefit the search for candidate genes involved in both hypothalamic and cardiac differentiation.

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References

Fig. 3. Immunoperoxidase immunocytochemical staining of the anterior pituitary lobe of twin A (untreated twin) by a panel of antibodies to the different pituitary hormones (magnification ×75): (A) adrenocorticotropic (ACTH); (B) thyroid-stimulating hormone (TSH); (C) prolactin (PRL); (D) follicle-stimulating hormone (FSH); (E) luteinizing hormone (LH); (F) growth hormone (GH).

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