# Endocrinopathies associated with midline cerebral and cranial malformations

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We systematically reviewed a series of patients (n = 85) with midline cerebral and cranial malformations to correlate the endocrinopathy with the neuroanatomic defect. Midline cleft lip and palate was associated not only with growth hormone deficiency (GHD) but also with diabetes insipidus (DI); holoprosencephaly and optic nerve hypoplasia with absence of the septum pellucidum had a similar incidence of GHD and DI. Optic nerve hypoplasia with absence of the septum pellucidum had the highest incidence of multiple pituitary endocrinopathies and of neonatal hypoglycaemia. Unilateral, although more commonly bilateral, optic nerve hypoplasia was associated with GHD. (J Pediatr 2002;140:252-5)

By the seventh week of intrauterine life, the cerebral gray matter undergoes a complex but orderly developmental process, with the production of neuronal and glial precursors and migration to their final destinations. Although Rathke's pouch has formed at the fourth week of gestation, it is only by 15 to 20 weeks' gestation that the adult form of the hypothalamus and the pituitary are capable of function. The main disorder of neuronal migration is schizencephaly (closed lip [type I] and open lip [type II]),[1,2] a symmetric gray matter-lined cleft in the cerebral hemispheres.[3] Holoprosencephaly (HO) is a condition in which the early forebrain fails to diverticulate and develops instead into a single, unpaired forebrain termed the holoprosencephalon.[4] It can be lobar (almost complete lobar and interhemispheric fissure formation), semilobar (incomplete, partial formation of the interhemispheric fissure), variant (heterotopic gray matter), or alobar (with a large holoventricle). Optic nerve hypoplasia (ONH), unilateral or bilateral, is a congenital anomaly and is characterized by the absence of ganglion cells at about 6 weeks' gestation,[5-7] also by different frequency, size, and morphology of the optic nerve, optic disc, and retinal vessels (with the typical "double ring sign").[8] When there is an association between ONH and cerebral hemispheric abnormality, 2 distinct pathogenic mechanisms (involving neuronal migration and axonal degeneration) coexist.[9] De Morsier[10] described the association between ONH and the absence of septum pellucidum (ASP), calling it septo-optic dysplasia (SOD). Hoyt et al[11] reported the association between SOD and hypopituitarism. Blethen and Weldon[12] coined the term septooptic pituitary anomaly. SOD is defined as a combination of two of these features: ONH, ASP, and hypopituitarism. The condition is considered to be sporadic, but in one family, an abnormality in the pituitary development gene *HESX1* (possibly its involvement in the regulation of axon growth during neural development) has been described.[13] We have attempted to correlate the anatomic lesion in children having midline cerebral and cranial defects with the pattern of endocrinopathy.

| | |
|---|---|
| ACC | Absence of corpus callosum |
| ASP | Absence of septum pellucidum |
| BNH | Bilateral optic nerve hypoplasia |
| CLAP | Cleft lip and palate |
| DI | Diabetes insipidus |
| GHD | Growth hormone deficiency |
| HH | Hypogonadatrophic hypogonadism |
| HOL | Holoprosencephaly |
| MPHD | Multiple pituitary hormone deficiency (two or more deficiencies out of GH, TSH, ACTH, HH) |
| NH | Neonatal hypoglycemia |
| ONH | Optic nerve hypoplasia |
| SOD | Septo-optic dysplasia |
| UNH | Unilateral optic nerve hypoplasia |

## Patients and Methods

We have performed a retrospective study of 85 patients (50 boys and 35 girls) with midline cerebral defects who were referred to a pediatric endocrine clinic. The reasons for referral are

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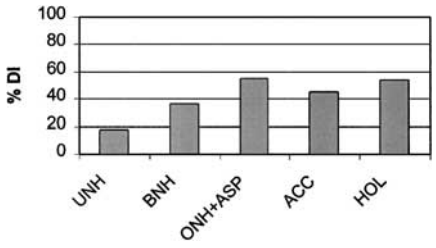


*Fig 1.* Percentage of patients with midline cerebral malformations having DI.

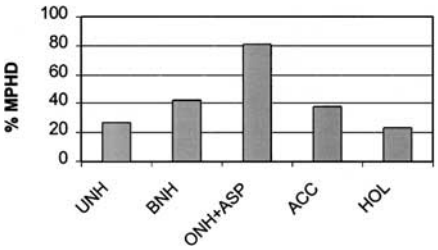


*Fig 2.* Percentage of patients with midline cerebral malformations having MPHD.

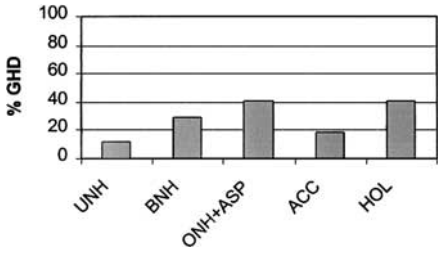


*Fig 3.* Percentage of patients with midline cerebral malformations having GHD.

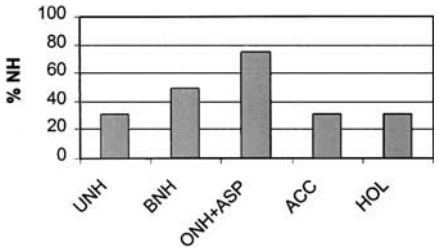


*Fig 4.* Percentage of patients with midline cerebral malformations having had persistent NH.

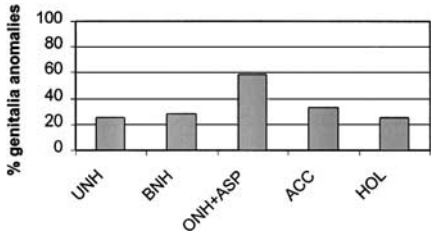


*Fig 5.* Percentage of patients with midline cerebral malformations having genitalia anomalies because of HH.

shown in the Table in *The Journal of Pediatrics Online* (Available at: *http://www.mosby.com/jpeds*). We recorded the height, expressed as standard deviation score according to the UK growth references.[14] Patients were classified as having ≥1 midline brain and cranial defect, ONH (unilateral and bilateral), ONH plus absence of septum pellucidum (ASP), absence of corpus callosum (ACC), holoprosencephaly (HOL), or cleft lip and palate (CLAP) with or without pituitary dysfunction. Data analyzed included ophthalmologic examination, computed tomography or magnetic resonance imaging, presence of neonatal hypoglycemia (level of blood sugar <2.6 mmol/L, asymptomatic or symptomatic), abnormalities of genitalia (micropenis, cryptorchidism, hypospadias) in boys, indicative of congenital gonadotrophin deficiency, and dynamic endocrine function testing. We only investigated patients who had symptoms or signs of endocrine disease. Somatotrophic, thyrotrophic, gonadotrophic function, and corticotrophic reserve were assessed by using spontaneous responses and stimulation test with glucagon or insulin, luteinizing hormone-releasing hormone, and thyrotropin-releasing hormone; these protocols were according to Hughes,[15] age-appropriate normal ranges for stimulated luteinizing hormone levels were those cited by Roger et al[16] and thyroid-stimulating hormone responses were assessed according to Vanderschueren-Lodeweyckx.[17] Patients 12, 59, and 64 were investigated because of persistent hypoglycemia. Patients 81 and 83 had a normal growth velocity and were not investigated. Patient 30 died at 5 months of age, before endocrine testing could be arranged. Patients 19, 37, 38, 67, and 70 were investigated and found to have no endocrinopathy. Posterior pituitary function was defined according to the presence or absence of central diabetes insipidus (DI). All patients with polyuria and polydipsia underwent a water deprivation test to confirm deficient vasopressin secretion; patients who were asymptomatic were tested with an early morning paired serum and urine osmolality. Statistical measurements were performed with the $\chi^2$ test.

## RESULTS

Clinical and auxologic data are presented in the Table (see *The Journal of Pediatrics Online*); 16 patients had neonatal hypoglycemia. Varying anatomic abnormalities could be associated with specific endocrinopathies. Patients with CLAP were distributed in all midline anatomic groups, with the exception of ONH with ASP (normal 48%; multiple defects of cerebral anomalies 26%; HOL 21%; ACC 5%). Midline CLAP was associated not only with GHD but also with DI. Patients with HOL had a greater percentage of combined anterior and posterior hormone defects (with an increasing percentage having DI and a decreasing percentage having anterior pituitary defects). Despite the fact that patients with HOL had a high incidence of DI ($P < .01$; Fig 1), they did not have such a high incidence of multiple pituitary hormone deficiency (MPHD) (≥2 deficiencies of GH, thyroid- stimulating hormone, adrenocorticotropic hormone, and hypogonadatrophic hypogonadism (HH), Fig 2). By definition, all children with ONH with ASP had SOD, but SOD also included those with unilateral optic nerve hypoplasia (UNH) and bilateral optic nerve hypoplasia (BNH) having an endocrinopathy. Fifty-nine percent had anterior pituitary hormone deficiency (28% isolated; 31% multiple or MPHD), 13% had DI (2% isolated, 11% associated with anterior pituitary abnormalities). Adrenocorticotropic hormone and gonadotrophin insufficiency was probably

associated with the higher incidence of neonatal hypoglycemia and high genitalia abnormalities, respectively, in the patients with ONH plus ASP. Although there was a spectrum of neuroanatomic defects, the deficiency most commonly associated in patients with ONH with ASP was MPHD ($P < .01$). In addition, these patients commonly had DI. The majority of patients with ASP had hormonal deficiency ($P < .01$). Patients with ONH with ASP and ONH with intact septum (both unilateral and bilateral) had the same percentage of endocrine dysfunction.

In children with single malformations, we observed that GH was the most frequent pituitary hormone affected; our patients with ONH, HOL, and ACC had the same percentage of genital abnormalities and GHD, which was predominantly in patients with ASP. In the patients with GHD (Fig 3), the majority had ONH with ASP or HOL (42% each). However, MPHD was much more common in patients with ONH combined with ASP (81%, Fig 2), and this explains why neonatal hypoglycemia (Fig 4), as well as genital abnormality from HH (Fig 5), were more common in this group. In the patients with isolated GHD, there was almost an equal proportion between unilateral and bilateral ONH (UNH 21%; BNH 25%). However, the group with BNH more commonly had MPHD (UNH 27%; BNH 42%). The most common radiologic abnormality in the patients with DI was ONH with ASP (55%) and HOL (54%) (Fig 1), although the incidence of DI in UNH was 18%. Evolving endocrinopathies were common and occurred in 48% of the patients (Table, *The Journal of Pediatrics Online*).

## DISCUSSION

We have reviewed a series of patients with midline cranial and intracranial defects and correlated the neuroanatomy with the endocrinopathy. Our study confirms previous reports that posterior pituitary ectopia is a sensitive and specific neuroradiologic marker for anterior pituitary hormone deficiency.[18] Because SOD implies the likelihood of an endocrinopathy as part of its definition (2 features of ONH, ASP, and pituitary endocrinopathy), we have not used this term to describe anatomic abnormalities. The septum pellucidum is frequently present in SOD. Huseman et al[19] indicated that the presence or ASP gave no indication of possible endocrine dysfunction,[19] which is in contrast with our data. Thinning of the corpus callosum predicted the clinical finding of neurodevelopmental deficits only in patients who had associated cerebral hemispheric abnormalities on magnetic resonance imaging,[18] but we were unable to comment on the endocrine outcome because only 2 of 22 patients with ACC had this as an isolated finding. The finding of hypothalamic pituitary dysfunction is probably a manifestation of a midline defect that involves the anterior hypothalamus.[20] Varying morphologic defects could produce any endocrine abnormality but our patients were selected because they were referred to an endocrinologist.

DI is usually secondary to a structural abnormality. The mechanism of osmotic regulation may be related to a failure of hypothalamic function affecting osmoreception, as well as a deficiency of vasopressin.[21,22] We found that CLAP were associated not just with GHD but also with DI. Unilateral ONH was associated with the development of GHD, whereas bilateral ONH was more likely to be associated with panhypopituitarism.

Children with SOD have a different pattern of endocrinopathy, depending on whether the septum pellucidum is present or absent. Although children with ONH combined with ASP and children with HOL had an equal incidence of having GHD plus DI, children with ONH with ASP had the highest incidence of combined anterior and posterior pituitary failure, which may account for the high mortality rate in children with SOD compared with children with GHD.[23] It probably explains why ONH with ASP has a high incidence of neonatal hypoglycaemia and hypogonadotrophic hypogonadism. It also explains why the only midline intracranial malformation to be defined as a combination of anatomic and endocrine abnormalities is SOD.

The extent of the cerebral malformation does not always correlate with the severity of the endocrinopathy. Therefore, patients with midline cranial and intracranial malformations should be carefully assessed and followed from early childhood because of the risk of developing hormonal dysfunction. Hormone dysfunction may evolve with time, as indeed 48% of our patients were documented as having evolving endocrinopathies (79% of patients with an endocrinopathy).[24] Patients with CLAP or UNH should be assessed and followed in the same manner, although the risk of an associated endocrinopathy is less.

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***Table.*** Auxologic, clinical, and radiologic data

| Patients (N) | Age at dx (y) | Cause and age of referral (y) | Ht SDS at referral | Genitalia abnormality in boys |
|---|---|---|---|---|
| 1 | 0.05 | Polydipsia (0.05) | 3.86 | MP |
| 2 | 0.1 | Midline defect (0.9) | –1.37 | |
| 3 | 0.1 | Midline defect (7.5) | –0.77 | |
| 4 | 0.1 | Midline defect (1.3) | –2.08 | |
| 5 | 0.1 | Midline defect (0.1) | –4.24 | |
| 6 | 0.1 | Midline defect (6) | –1.27 | |
| 7 | 0.1 | Midline defect (2.3) | –1.30 | CR |
| 8 | 0.1 | Midline defect (5.3) | –0.70 | |
| 9 | 0.1 | Polydipsia, (0.1) | | |
| | | Midline defect | –2.18 | |
| 10 | 0.1 | Polydipsia (2.7) | –0.53 | |
| 11 | 0.1 | Polydipsia (1.2) | 0.59 | |
| 12 | 0.1 | Hypoglycemia (0.1) | 2.45 | |
| 13 | 0.1 | Hypoglycemia (0.1) | –1.23 | |
| 14 | 0.1 | Hypoglycemia (0.1) | –1.71 | |
| 15 | 0.1 | Hypoglycemia (0.8) | | |
| | | Midline defect | –3.15 | CR |
| 16 | 0.1 | Short stature (1) | –4.17 | |
| 17 | 0.1 | Short stature (4.1) | –2.77 | |
| 18 | 0.1 | Short stature (1) | 0.42 | |
| 19 | 0.1 | Short stature (7) | –3.25 | MP |
| 20 | 0.1 | Short stature (11) | –2.43 | |
| 21 | 0.1 | Short stature (13) | –1.37 | |
| 22 | 0.1 | Short stature (3) | –3.56 | MP,CR |
| 23 | 0.1 | Short stature (11) | | |
| | | Midline defect | –4.23 | |
| 24 | 0.1 | Congenital hypothyroidism (0.1) | –1.23 | |
| 25 | 0.2 | Polydipsia (0.2) | –3.50 | MP,CR,HS |
| 26 | 0.2 | Hypoglycemia (0.2) | –0.71 | |
| 27 | 0.2 | Hypoglycemia (0.2) | –3.50 | |
| 28 | 0.2 | Midline defect (1.7) | 1.15 | |
| 29 | 0.2 | Midline defect (0.8) | –0.02 | |
| 30 | 0.3 | Midline defect (0.3) | –3.56 | |
| 31 | 0.3 | Midline defect (0.3) | –2.47 | |
| 32 | 0.3 | Midline defect (4) | –1.48 | |
| 33 | 0.3 | Polydipsia (0.3) | –3.56 | |
| 34 | 0.3 | Polydipsia (3.8) | –1.75 | |
| 35 | 0.3 | Polydipsia (1) | –1.66 | |
| 36 | 0.4 | Midline defect (0.8) | –0.90 | |
| 37 | 0.5 | Short stature (5.2) | –2.02 | |
| 38 | 0.5 | Short stature (9.9) | –2.61 | |
| 39 | 0.5 | Short stature (9.8) | | |
| | | Genitalia anomalies | –0.94 | MP,CR |
| 40 | 0.5 | Midline defect (0.5) | –1.68 | |
| 41 | 0.5 | Hypoglycemia (0.5) | 0.004 | |
| 42 | 0.5 | Hypoglycemia (8) | –3.27 | MP |
| 43 | 0.6 | Short stature (3) | 0.19 | |

| Midline defect | Pituitary morphology on MRI | Type and age of dx of hormonal deficiency (age, y) |
|---|---|---|
| BNH, ASP, ACC | Ectopic posterior, no stalk | TSH (0.05), DI (0.05) |
| ACC, HOL | | |
| CLAP | | |
| CLAP | | |
| BNH, ASP, ACC, HOL | | TSH (0.4), ACTH (0.4) |
| CLAP | | |
| CLAP | | |
| HOL | | |
| ACC, HOL, CLAP | Small | TSH (0.1), ACTH (0.1), HH (12), DI (0.1) |
| HOL, CLAP | | DI (2.7) |
| UNH, ASP, ACC, CLAP | | |
| UNH, ASP | Absent, no stalk | GH (1.3), TSH (0.4), ACTH (0.2) |
| UNH, ASP | Ectopic posterior | GH (1.8), TSH (0.1), ACTH (0.1), HH (0.2) |
| | No stalk, small | |
| BNH, ASP | No stalk, small | GH (1.5), TSH (3.5), ACTH (0.1), HH (0.1) |
| UNH, ASP, CLAP | | GH (1.5) |
| CLAP | | GH (5) |
| CLAP | | GH (4.1) |
| ACC, HOL, CLAP | | GH (1) |
| CLAP | Small | GH (7) |
| HOL, CLAP | Ectopic posterior | |
| CLAP | | |
| ACC, CLAP | | GH (5.3) |
| CLAP | | HH (16.7) |
| UNH, ASP | | TSH (0.1) |
| ACC, HOL, CLAP | | HH (11), DI (0.2) |
| BNH, ASP | | GH (0.2), TSH (0.2), ACTH (0.2), PP (7) |
| BNH, ASP | Empty sella | GH (3), ACTH (0.2) |
| | No stalk, no posterior | |
| BNH, ASP | | |
| BNH, HOL | | |
| HOL, CLAP | Absent | |
| BNH, ASP | Small | |
| BNH, ASP | No stalk, small | GH (4.1) |
| ACC, HOL | Ectopic posterior | |
| BNH, ASP, ACC | No stalk, small | GH (3.8), TSH (3.8), ACTH (3.8), DI (3.8) |
| UNH, HOL | | |
| BNH, ASP | Ectopic posterior, no stalk | GH (1.9) |
| BNH, ASP, ACC | | |
| BNH | | |
| UNH, ASP | | GH (11), HH (11) |
| BNH | | |
| BNH | | |
| UNH, ASP, ACC | | GH (8), TSH (8), ACTH (8), DI (8) |
| BNH, ASP | | |

***Table—cont'd***

| Patients (N) | Age at dx (y) | Cause and age of referral (y) | Ht SDS at referral | Genitalia abnormality in boys |
|---|---|---|---|---|
| 44 | 0.7 | Midline defect (1.8) | –0.96 | |
| 45 | 0.7 | Midline defect (0.7) | 2.86 | CR |
| 46 | 0.7 | Short stature (2) | –2.19 | |
| 47 | 0.8 | Polydipsia (0.8) | 1.72 | |
| 48 | 0.8 | Polydipsia (0.8) | –3.58 | |
| 49 | 0.8 | Short stature (0.8) | –3.00 | |
| 50 | 0.8 | Hypoglycemia (0.8) | | |
| | | Midline defect | –1.61 | CR |
| 51 | 0.8 | Midline defect (0.8) | 1.73 | |
| 52 | 1 | Midline defect (9.6) | 1.08 | |
| 53 | 1 | Midline defect (1) | 0.30 | |
| 54 | 1 | Short stature (4) | –1.92 | |
| 55 | 1 | Short stature (5) | –2.44 | |
| 56 | 1 | Short stature (15) | –3.50 | |
| 57 | 1 | Short stature (9) | –0.55 | CR,HS |
| 58 | 1 | Polydipsia (1) | –2.49 | |
| 59 | 1 | Hypoglycemia (3.4) | 2.70 | |
| 60 | 1.1 | Midline defect (1.1) | –1.98 | |
| 61 | 1.3 | Short stature (4) | –4.31 | |
| 62 | 1.3 | Midline defect (7.8) | 0.63 | |
| 63 | 1.3 | Midline defect (1.3) | –0.98 | |
| 64 | 1.5 | Hypoglycemia (1.5) | 1.29 | |
| 65 | 1.5 | Polydipsia (1.5) | –1.75 | |
| 66 | 1.7 | Midline defect (1.7) | –0.32 | |
| 67 | 2 | Short stature (11) | –2.51 | |
| 68 | 2.4 | Midline defect (2.4) | 0.13 | MP |
| 69 | 2.5 | Midline defect (3) | –1.81 | HS |
| 70 | 2.6 | Short stature (2.6) | –2.38 | HS |
| 71 | 3 | Short stature (3) | 0.13 | |
| 72 | 3.5 | Short stature (3.5) | –0.86 | |
| 73 | 3.5 | Short stature (3.5) | –1.85 | |
| 74 | 4 | Midline defect (4.9) | 1.14 | |
| 75 | 4 | Hypoglycemia (4) | –2.40 | CR |
| 76 | 4.6 | Midline defect (4.6) | 0.22 | |
| 77 | 5 | Midline defect (5) | –1.02 | |
| 78 | 5 | Short stature (7.8) | –6.94 | |
| 79 | 6.2 | Midline defect (6.2) | 0.75 | |
| 80 | 6.6 | Midline defect (6.6) | 1.07 | |
| 81 | 8 | Short stature (8) | –2.23 | |
| 82 | 10 | Short stature (10) | –0.03 | |
| 83 | 13 | Short stature (13) | –2.30 | |
| 84 | 13 | Short stature (13) | –3.59 | |
| 85 | 13.1 | Short stature (13.1) | –3.21 | |

*dx*, Diagnosis; *SDS*, standard deviation score; *MRI*, magnetic resonance imaging; *MP*, micropenis; *CR*, cryptorchidism; *HS*, hypospadias.

| Midline defect | Pituitary morphology on MRI | Type and age of dx of hormonal deficiency (age, y) |
|---|---|---|
| | Empty sella | GH (2) |
| UNH, ASP | | |
| ACC, HOL | | |
| HOL, CLAP | | GH (3.3), DI (0.8) |
| BNH, ASP | | GH (3.8), ACTH (3.8), HH (13), DI (0.8) |
| ACC, HOL | | GH (2) |
| | | |
| BNH, ASP, ACC | Small | GH (2.8), TSH (0.8), ACTH (0.8) |
| BNH, ASP | No stalk | |
| ASP, ACC, HOL | | HH (10) |
| BNH, ASP, HOL | No posterior | DI (4.2) |
| BNH, ASP, HOL | | GH (4) |
| UNH, ASP | Empty sella | GH (6.2), TSH (6.2), ACTH (6.2), HH (10.7), DI (6.2) |
| UNH, ASP | Ectopic posterior | GH (15), ACTH (15), DI (15) |
| | No stalk, small | |
| ACC | | GH (9), ACTH (9) on stress, HH (12.5) |
| BNH, ASP | | GH (1), TSH (3), ACTH (3) |
| BNH, ASP, HOL | | GH (4) |
| UNH, ASP | No stalk | GH (1.1) |
| UNH, HOL | | |
| UNH, ASP | | ACTH (7.8) |
| BNH | | |
| BNH, ASP , ACC | | GH (1.5), TSH (1.5), ACTH (1.5) |
| UNH, ASP, ACC, HOL | Absent, ectopic posterior | GH (2.2), ACTH (2.2) |
| UNH, ASP | | |
| HOL | | |
| UNH, ASP, HOL | | |
| HOL | Ectopic posterior | GH (5.5), TSH (3), ACTH (7), HH (8) |
| | No stalk, small | |
| UNH, ACC, HOL | Empty sella | |
| UNH, ASP, ACC, HOL | Ectopic posterior, no stalk | GH (4.6), TSH (3.6), ACTH (5.8) |
| UNH, ASP | | GH (6) |
| ACC, HOL | Empty sella | GH (4.1) |
| UNH | | |
| BNH, ASP | | GH (5), TSH (4), ACTH (4) |
| UNH, ASP | | |
| BNH | Small | |
| | No stalk, small | GH (7.8) |
| | No posterior | |
| BNH, ASP | | |
| UNH | | |
| UNH | | |
| UNH, ASP | Ectopic posterior | GH (10), TSH (10), ACTH (10), HH (10) |
| | No stalk, small | |
| ACC, HOL | | |
| BNH, ASP | | |
| ASP, HOL | Absent, ectopic posterior | GH (13.1), HH (13.1) |