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High Proportion of Pituitary Abnormalities and Other Congenital Defects in Children with Congenital Nasal Pyriform Aperture Stenosis

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ABSTRACT: We aimed to determine the occurrence of pituitary dysfunction and additional malformations in patients with congenital nasal pyriform aperture stenosis (CNPAS) and to predict which patients are at risk of pituitary dysfunction. Among the 40 studied patients, hypothalamo-pituitary (HP) axis abnormalities were found in 16 patients (40%), with endocrine dysfunction ($n = 9$) and/or abnormal HP MRI findings ($n = 15$). A normal HP axis on MRI was highly predictive of normal endocrine function. Of the 40 patients, 31 had additional abnormalities in the cranio-facial area ($n = 26$), the brain ($n = 12$), the vertebrae ($n = 5$), the limbs ($n = 4$), the heart ($n = 7$) and the kidney ($n = 3$). Six patients had syndromic associations: VACTERL ($n = 4$), CHARGE ($n = 1$) and RHYNS ($n = 1$) syndromes. Craniofacial and brain malformations were more common in patients with HP axis abnormalities than in patients with normal HP axis. Familial history of midline defects and/or consanguinity were found in 30% of patients.

In conclusion, HP axis abnormalities are frequent in patients with CNPAS and justify MRI of the brain early in life and clinical evaluation to screen for patients with pituitary insufficiency. CNPAS may be a genetically heterogeneous condition with a large phenotypic variability that shares common etiological mechanisms with the various forms of the holoprosencephaly phenotype. **(*Pediatr Res* 60: 478–484, 2006)**

Congenital nasal pyriform aperture stenosis (CNPAS) is a rare condition that causes airway obstruction in newborn children, which was first described in 1989 (1). It is caused by an overgrowth of the nasal process of the maxillar, reducing the anterior part of the nasal cavity. It can be diagnosed by physical examination and computed tomography scan. Surgical intervention early in life is usually needed (2–4). CNPAS must be distinguished to choanal atresia, which causes a reduction of the posterior part of the nasal cavity (1,3).

There is limited clinical data concerning this syndrome and the disorder is considered as a mild form of holoprosencephaly (5–9). In patients with CNPAS, familial history of holoprosencephaly, cleft palate and ocular coloboma and/or consanguinity have occasionally been reported. An autosomal recessive inheritance of the disorder has been suspected (3,8,10,11). CNPAS occurs as an isolated condition or in association with other midline defects (3–7,9–14). Solitary median maxillary central incisor (SMMCI) (3–6,12–14) and/or pituitary deficiencies (3,7,10,12,15) have been reported. The clinical symptoms of pituitary dysfunction are not always obvious in early childhood and can be potentially severe. Without early diagnosis and appropriate hormonal treatment, morbidity and mortality is high (3,10,11,16). Therefore, the study of additional congenital abnormalities is important for the management and prognosis of the patients. A systematic analysis of the whole phenotypic spectrum associated with CNPAS has not been carried out in previous studies. Therefore, we aimed to investigate the occurrence of pituitary abnormalities and additional malformations in patients with CNPAS and to predict those patients at risk of pituitary dysfunction.

SUBJECTS AND METHODS

The study population comprised 40 prepubertal children (23 girls, 17 boys) with CNPAS. They had a mean age of 3 ± 3.3 y (0.1–10.9 yrs) at the time of evaluation. All had been consecutively managed neonatally in the ORL department at the Robert Debré hospital from 1991–2004.

The subjects were examined by a pediatric endocrinologist, geneticist, ophthalmologist and stomatologist. Pituitary function was completely evaluated and magnetic resonance imaging (MRI) of the brain was carried out. Heart, renal, vertebral, dental and chromosomal abnormalities were sought through ultrasonography, radiography and karyotype respectively. Familial history of malformations and/or consanguinity was also recorded.

Growth hormone deficiency (GHD) was diagnosed by auxological data and/or symptoms of endocrine dysfunction (hypoglycemia and/or micropenis), low IGF1 level (<50 ng/ml) and a growth hormone (GH) peak of less than 10 ng/ml after provocative testing. Thyroid stimulating hormone (TSH) deficiency was diagnosed by a plasma-free thyroxine (T4) level below 10 pmol/L and/or abnormal TSH stimulation after administration of TSH releasing hormone (TRH) (normal values for TSH were, respectively, 0.5–6 mU/L

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Abbreviations: CNPAS, congenital nasal pyriform aperture stenosis; **CPHD,** combined pituitary hormone deficiency; **GHD,** growth hormone deficiency; **HP,** hypothalamo-pituitary; **PPHS,** posterior pituitary hyperintense signal; **SMMCI,** solitary median maxillary central incisor

for basal, 14 ± 7 mU/L for peak and <8 mU/L for 120 min post-TRH administration). Hyperprolactinemia was defined as basal plasma prolactin levels above 25 ng/mL in children older than 3 mo. Adrenocorticotropic hormone (ACTH) deficiency was diagnosed by morning basal plasma cortisol values below 180 nmol/L and/or below 450 nmol/L during insulin-induced hypoglycemia. Gonadotropin function was not evaluated because all the subjects were prepubertal. Diabetes insipidus was excluded by a 12-h water deprivation test. Combined pituitary hormone deficiency (CPHD) was defined as GHD associated with abnormality of at least one other anterior pituitary hormone. Height was expressed as the SD score (SDS) for sex and chronological age (17).

All MRI images (1.5 Tesla Magnet Philips Intera, Philips Medical Systems, The Netherlands) were reviewed by the same investigator (CG) who was not aware of the endocrinological data. Sagittal and coronal thin (1.5 mm) slices of the pituitary area were acquired using a gradient echo T1-weighted sequence and coronal slices of the brain were acquired using T2-weighted sequence. If pituitary stalk was not visible gadolinium injection was used. The height and aspect of the anterior pituitary were recorded and judged to be either normal, hypoplastic (< -2 SD for age) according to normative data for children (18,19) or absent (not seen). The presence or absence of the pituitary stalk and the location of the posterior pituitary hyperintense signal (PPHS) were recorded. Associated brain abnormalities were also described.

All investigations since the year 2000 were part of a routine clinical management during the neonatal period. Patients born between 1991 and 1999 were evaluated during either the neonatal period ($n = 6$) or after ($n = 15$). Ethic committee approval was not required for this review study, according to French law. Informed consent for the evaluation was obtained from the parents at the time they were performed.

Statistical analysis. Results are expressed as the mean ± SD. The Mann-Whitney *U*-test was used for comparison between groups. The percentages within group were compared by the χ^2 test.

RESULTS

HP axis abnormalities. The 40 subjects with CNPAS (Fig. 1) were divided into two groups according to the presence (group 1, $n = 16$, 40%) or the absence (group 2, $n = 24$, 60%) of hypothalamo-pituitary (HP) axis abnormalities. As expected, group 1 subjects were significantly smaller than group 2 subjects (height at −1.4 ± 1.4 *versus* 0.3 ± 1.5 SDS, respectively; $p = 0.003$).

Group 1 patients were classified into two subgroups: group 1a, as having HP axis abnormalities with anterior pituitary insufficiency ($n = 9$, 22%) with or without visible anatomical abnormalitiy of HP area on MRI findings; and group 1b, as having morphologic abnormality of the HP area with normal pituitary function ($n = 7$, 17%) (Table 1). Group 1a patients showed either CPHD ($n = 6$) or isolated GHD ($n = 3$). All but one of these patients (patient 9) were diagnosed during the first weeks of life and showed HP axis abnormalities by MRI. Among these patients, eight had symptoms of endocrine dysfunction (hypoglycemia $n = 5$, micropenis and cryptorchidism $n = 1$, decreased growth velocity $n = 3$). None of the structure of the HP area was visible in two children, and ectopic PPHS was found in six children (at the median eminence $n = 5$, and with a double ectopic PPHS in the proximal and distal levels of the stalk $n = 1$) (Fig. 2). Interestingly, among subjects without pituitary insufficiency, seven patients had positive MRI for HP area (group 1b patients): Five patients had ectopic PPHS, either located at the distal end of the stalk ($n = 2$) or located along the stalk toward the distal end, communicating with an intrasellar location on the upper side of the anterior pituitary ($n = 3$) (Fig. 2*C*). Two patients had a hypoplastic anterior pituitary (height = 3.2 mm at 7 y of age and 2.5 mm during the neonatal period, respectively).

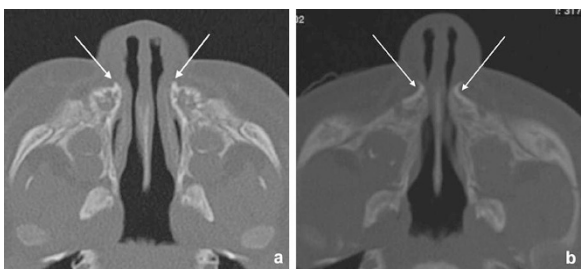

Figure 1. Axial Computed Tomography slice at the level of the maxillary bone (*A*) Normal pattern with a wide bilateral nasal pyriform aperture (*arrows*). (*B*) Congenital nasal pyriform aperture stenosis (*arrows*).

Other additional congenital malformations. The additional congenital malformations in patients with CNPAS according to the presence or absence of HP axis abnormalities are reported in Table 2. Overall, 31 (78%) of the 40 patients displayed other additional abnormalities, being all group 1 patients ($n = 16$) and 15 out of the 24 (62%) group 2 patients ($p = 0.005$). The malformations affected the craniofacial area ($n = 26$): shallow sella turcica, craniopharyngeal canal, solitary median maxillary central incisor (Fig. 3), microcoria, cataract, ptosis; the brain ($n = 12$): optic nerve hypoplasia, Arnold Chiari malformation, olfactory bulbs agenesis, nystagmus, strabismus, coloboma, micophthalmia; the vertebrae ($n = 5$): intervertebral synostosis; the limbs ($n = 4$): hexadactyly, radial hypoplasia; the heart ($n = 7$): infundibular pulmonary stenosis, interventricular or interauricular septal defect, atrio-ventricular communication, tetralogy of Fallot; or the kidney ($n = 3$): renal dysplasia, sigmoid kidney, duplication of the pelvis and calices. Patients with HP axis abnormalities had a higher frequency of craniofacial and brain malformations ($n = 16$, 100%) than patients with a normal HP axis ($n = 13$, 54%); $p = 0.002$. A SMMCI was the most frequently observed malformation ($n = 22$, 55% of cases) and was found significantly more often in children with HP axis abnormalities than in children with a normal HP axis (81% *versus* 37%; $p = 0.006$).

In the studied population, we identified three known associations in six patients (15% of cases): four cases of VACTERL syndrome (vertebral defects, anal atresia, cardiac defects, tracheo-esophageal fistula, renal anomaly, limb defect); one case of CHARGE syndrome (Coloboma, heart defect, atresia of the choanae, retardation of growth and development, genital anomalies), and one case of RHYNS syndrome (retinis pigmentosa, hypopituitarism, nephronophtisis, mild skeletal dyplasia). There was no difference in the proportion of these anomalies between group 1 and group 2 patients. Moreover, only two of the patients had chromosomal anomalies (46XX, del(X) (p11) and 22q11 deletion, respectively).

Familial history. A familial component was suspected in 12 patients (30% of cases), with a similar proportion between group 1 and group 2 patients. Parental consanguinity ($n = 9$) and/or familial history of midline malformation ($n = 5$) and/or anterior pituitary deficiency ($n = 1$) were found (table 2).

Table 1. *Clinical, radiological and hormonal evaluation of the subjects with CNPAS and hypothalamo-pituitary axis abnormalities (group 1, n = 16), with (group 1a, n = 9) or without (group 1b, n = 7) anterior pituitary insufficiency*

		MRI of the Hypothalamo-pituitary axis			Hormonal evaluation								
									TSH response to TRH			Cortisol	
Patient no./sex	Age (yrs)	Pituitary	Pituitary stalk visibility	Localization of posterior pituitary hyperintense signal	Pituitary function	GH peak 1 (ng/ml)	GH peak 2 (ng/ml)	IGF1 (ng/ml)	Free T4 (pmol/L)	Basal mUI/L	Peak mUI/L	120 mUI/L	8 h (nmol/L)	Hypoglycemia (nmol/l)
Group 1a: with pituitary insufficiency														
1§/F	0.2	absent	no	not seen	CPHD†	**<0.2**	-	**26**	**1.9**	**2.6**	**3.5**	**-**	**52**	**34**
2§/M	0.1	absent	no	not seen	CPHD†	**<0.2**	**0.2**	-	**6.1**	**2.7**	**-**	**-**	-	**<27**
3/F	0.1	hypoplastic	no	median eminence	GHD	**4.1**	**3.4**	**34**	14.4	0.5	6.8	4	650	
4§/F	0.2	hypoplastic	no	median eminence	CPHD†	**<0.2**	**1.4**	**29**	**5.8**	**3.1**	**8.4**	8.4	-	**32**
5§/F	0.1	hypoplastic	no	median eminence	CPHD‡	**4.3**	**2.4**	**-**	11.9	**4.9**	24.4	10.1	299	560
6§/F	0.1	normal	yes	median eminence	GHD	**7.1**	-	**23**	17.6	2.7	23.4	4.5	221	-
7§/F	0.1	hypoplastic	yes	median eminence	GHD	**6**	-	**48**	15.5	3.69	-	-	197	-
8§/M	0.1	hypoplastic	yes	along the stalk : double signal proximal and distal	CPHD†	**<0.2**	-	**11**	*	**0**	-	-	-	**<20**
9§/M	3	normal	yes	normal	CPHD¶	**8**	**10**	**48**	16.5	**6.7**	**68.1**	**13.3**	603	783
Group 1b: without pituitary insufficiency														
10/F	0.5	normal	yes	along the stalk (distal)	normal	34.1	-	113	-	-	-	-	-	-
11/M	6.1	normal	yes	along the stalk (distal)	normal	17	-	107	15.3	11.8	-	-	532	426
12/M	10.9	normal	yes	along the stalk (distal and intrasellar)	normal	15	-	204	19.1	1.7	-	-	704	756
13/M	7.3	normal	yes	along the stalk(distal and intrasellar)	normal	31.6	-	73	20.8	1.7	-	-	440	397
14/F	5.7	normal	yes	along the stalk (distal and intrasellar)	normal	25.2	-	114	16.1	1.9	-	-	360	594
15/M	0.1	hypoplastic	yes	normal	normal	19.7	-	**35**	22.3	3.15	-	-	818	-
16/M	7	hypoplastic	yes	normal	normal	19.2	-	236	18	4.1	-	-	694	794

Abnormal biochemical results in **bold**.

GHD, isolated growth hormone deficiency; CPHD, combined pituitary hormone.

* Free T4 = 12 pmol/l after treatment by L-tyroxine 20 μg/day for 1 month.

† GH + TSH + ACTH deficiencies; ‡ GH + TSH deficiencies; ¶ GH + compensed TSH deficiencies + hyperprolactinemia (37 μg/ml).

§ Hypopituitarism symptomatology: micropenis (11mm) and bilateral cryptorchidism (n = 1; Patient 8); hypoglycemia (n = 5; Patients 1,2,4,5,8), low growth velocity (n = 3; patients 6,7,9)

None had neurohypophysis dysfunction.

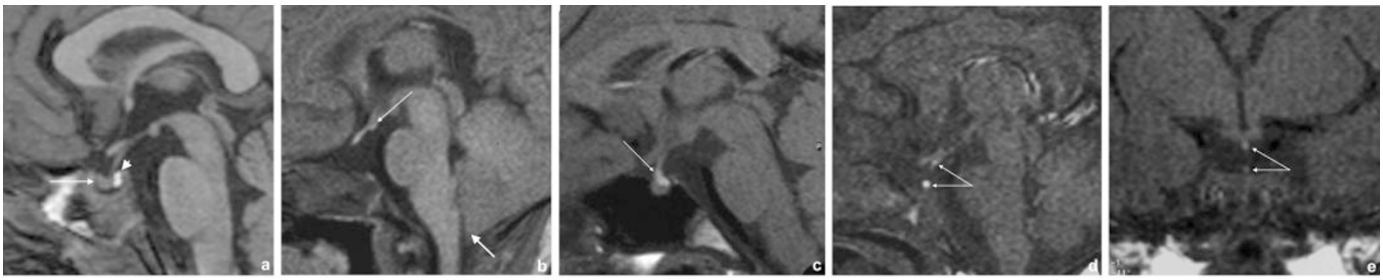

Figure 2. Variable location of the ectopic neurohypophysis on MRI. (*A*) Normal appearance of pituitary gland in a 7-y-old child. Anterior pituitary gland (*arrow*) Hyperintense posterior pituitary gland (*arrowhead*) (*B*) Patient 4, T1 weighted sagittal slice. Hypoplastic anterior pituitary, no pituitary stalk being visible (even after gadolinium injection). The hyperintensity of the ectopic pituitary is at the median eminence (*arrow*). Associated abnormalities were shallow sella turcica and Arnold Chiari malformation (*large arrow*). (*C*) Patient 12, T1 weighted sagittal slice. The hyperintensity of the ectopic neurohypophysis is visible in the distal portion of the pituitary stalk and communicates with an intrasellar neurohypophysis (*arrow*). The anterior pituitary and the pituitary stalk have a normal appearance. (*D,E*) Patient 8, T1 weighted sagittal and coronal slices. Double ectopic hypersignal of the neurohypophysis in the distal and the proximal portions of the pituitary stalk.

DISCUSSION

In this study, we found important associations between CNPAS, midline craniofacial and brain lesions, pituitary abnormalities and other additional congenital defects. Only nine patients (22% of cases) showed isolated CNPAS with no other congenital malformations or HP axis abnormality. Previous studies on reported associated malformations in CNPAS were conducted in the form of case reports or small series and none of them have systematically screened patients for pituitary insufficiency and/or associated malformations. The present study conducted on a cohort of clinically well characterized patients with CNPAS demonstrated that CNPAS rarely appears isolated and expand the spectrum of phenotype in these patients.

SMMCI and HP axis abnormalities were the most common associated disorders, which were found in 55% and 40% of cases, respectively. For patients with HP axis abnormalities, we found endocrine dysfunction in 56% of the cases. A normal HP axis on MRI was highly predictive of normal endocrine function. Only one of our patients with a normal HP axis on MRI showed an endocrinopathy. Ectopic neurohypophysis was the most frequent HP axis abnormality. This finding is consistent with several reports demonstrating that ectopic neurohypophysis is commonly associated with midline craniofacial and/or brain malformation (20–24). Ectopic neurohypophysis was located either at the median eminence or at different areas along the pituitary stalk. Surprisingly, one patient showed a double ectopic PPHS, at both the proximal and distal areas of the pituitary stalk. Three patients with normal endocrine function demonstrated a variant of ectopic PPHS, with the hyperintense signal of the neurohypophysis being visible in the distal portion of the pituitary stalk that communicates with an intrasellar neurohypophysis. Location of ectopic PPHS along the stalk has been shown to predict a less severe form of the disease (25,26). To our knowledge, these aspects in the location of the posterior pituitary hyperintense signal have not been previously described. It remains to be seen whether group 1b patients will develop endocrine dysfunction later in life.

All patients with CNPAS and HP axis abnormalities showed at least one other craniofacial or brain anomaly. The most frequent was SMMCI, which occurred in all but one group 1 patient. Although previously less frequently observed, craniofacial and brain findings are primarily consistent with those of previous reports (3,4,12). The relatively high incidence of olfactory bulbs agenesis in the present study was also found to occur most frequently in patients with HP axis abnormalities. As SMMCI, CNPAS has long been reported as a mild form of holoprosencephaly (5–9). The association of holoprosencephaly with a wide variety of craniofacial and extracranial anomalies is well recognized and individuals with holoprosencephaly have been ascribed to a variety of syndromes with multiple congenital anomaly (27,28). Our study showed that extracranial anomalies also frequently occurred in patients with CNPAS. These findings have not been addressed in previous studies apart in four cases with VACTERL syndrome (29), with a ring chromosome 18 (6) and with multiple congenital malformations including cardiovascular, gastrointestinal and limbs anomalies (7), respectively. Although choanal atresia is a clinical feature of CHARGE syndrome (30), CHARGE and RHYNS syndromes have not been previously reported as associated with CNPAS.

The pathogenesis of CNPAS is still unknown. As in our study, features of holoprosencephaly ranging from severe to mild forms such as SMMCI or cleft palate, have been identified by studying first-degree relatives of patients with CNPAS and consanguinity has also been described through familial study (3,8,10,11). This suggests that genetic and/or environmental factors may play a role in the pathogenesis of the disease. A mutation in the sonic hedgehog (SHH) gene has been reported in one case with CNPAS and semilobar holoprosencephaly. This mutation was inherited from the father who had hypotelorism only (31). A mutation in the SHH gene has also been associated in one sporadic case with midnasal stenosis and SMMCI (31). A number of genes for holoprosencephaly have been identified. These were mostly SHH, TGIF, ZIC2 and SIX3 genes. Abnormalities in these genes have mostly been found in familial cases of holoprosencephaly spectrum (31). Half of the mutations have been found in the SHH gene, which is known to play a critical role in early forebrain and CNS development. However, as no anomaly to these genes were found in 80% of holoprosencephaly cases, other genes are likely to be involved (27,31). As reported in

Table 2. *Other additional congenital anomalies and familial history in subjects with CNPAS, according to the presence (group 1; n = 16) or absence (group 2; n = 24) of hypothalamo-pituitary axis abnormalities*

	Craniofacial anomalies	Cerebral anomalies (except HP axis)	Other anomalies	Polymalformative association	Familial history
Group 1					
1	shallow sella turcica	optic nerve hypoplasia, Arnold Chiari malformation, nystagmus, strabismus	Renal dysplasia, infundibular pulmonary stenosis	RHYNS	consanguinity
2	shallow sella turcica, SMMCI	olfactory bulbs agenesis, Arnold Chiari malformation	-	-	consanguinity, panhypopituitarism ‡
3	shallow sella turcica, SMMCI, micro corie, craniopharyngeal canal	-	-	-	-
4	shallow sella turcica, SMMCI	Arnold Chiari malformation	infundibular pulmonary stenosis	-	-
5	SMMCI	coloboma	-	-	consanguinity
6	SMMCI, posterior cataract	olfactory bulbs agenesis	-	-	-
7	SMMCI	-	-	-	-
8	SMMCI, craniopharyngeal canal	-	-	-	-
9	-	nystagmus	Interventricular septal defect	-	-
10	SMMCI	-	-	-	-
11	SMMCI, craniopharyngeal canal	-	Cervical intervertebral synostosis, right radial aplasia, left radial hypoplasia, atrioventricular communication	VACTERL	consanguinity
12	SMMCI	-	-	-	-
13	SMMCI	-	-	-	consanguinity
14	SMMCI	strabismus	Lumbar intervertebral synostosis, sacral agenesis, thumbs' triphalangism, hexadactylism, sigmoid kidney, tetralogy of Fallot	VACTERL	consanguinity, holoprosencephaly‡
15	-	olfactory bulbs agenesis	-	-	consanguinity
16	SMMCI	olfactory bulbs agenesis, coloboma	Cervico-thoracic intervertebral synostosis, asymetry of the ears	CHARGE	-
Group 2					
17	-	-	-	-	-
18	SMMCI	-	-	-	SMMCI†‡, cleft lip and palate‡
19	-	-	-	-	-
20	craniopharyngeal canal	-	-	-	-
21	-	-	-	-	-
22	SMMCI, craniopharyngeal canal	-	-	-	-
23	SMMCI	strabismus	-	-	-
24	-	-	-	-	-
25	-	-	Hexadactylism, interauricular septal defect	-	-
26	-	-	-	46XX, del(X) (p11)	-
27	-	-	-	-	-
28	SMMCI	-	-	-	consanguinity
29	-	olfactory bulbs agenesis	Lumbar and sacral intervertebral synostosis, oesophagus atresia, duplication pelvis and calices of the kidney	VACTERL	-
30	SMMCI	-	-	-	-
31	SMMCI	-	-	-	holoprosencephaly‡
32	-	-	Laryngeal atresia	22q11	-
33	-	-	-	-	-
34	SMMCI, left ptosis	-	-	-	-
35	-	-	-	-	-
36	craniopharyngeal canal	-	-	-	cleft lip and palate†
37	SMMCI	-	-	-	-
38	-	-	-	-	-
39	craniopharyngeal canal	microphthalmia	Cervical intervertebral synostosis, partial sacral agenesis, hexadactylism, hypospadias, interauricular septal defect	VACTERL	-
40	SMMCI	-	-	-	consanguinity, incisive tooth agenesis†

SMMCI, Solitary median maxillary central incisor.

† father; ‡ brother.

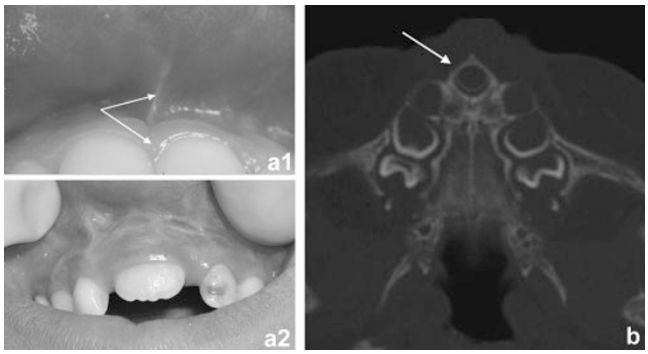

Figure 3. Solitary Median Maxillary Central Incisor (SMMCI) diagnosed by clinical and radiologic evaluation. (*a*1) Normal central dentition: note the frenulum labii superiosis and the intermaxillary suture (*arrows*) (*a*2) SMMCI, absence of the frenulum labii superioris and of the intermaxillary suture. (*b*) Axial Computed Tomography slice at the level of the maxillary bone demonstrating a SMMCI (*arrow*).

patients with features of holoprosencephaly spectrum (27,31), CNPAS may be a genetically heterogeneous condition with transmission occurring along various pattern (recessive or dominant mode of inheritance) and with a large phenotypic variability that shares common etiological mechanisms with the various form of holoprosencephaly phenotype. Mechanism by which the variable expressivity of the disorder may occur could be due to multigenic (32) or environmental influences (33) or as demonstrated for the SHH gene, may be due to a temporal disruption of a single molecular pathway during embryonic development (34). Recently, animal models have shown that a coordinated interaction between epithelial and mesenchymal cells is essential during the initial stages of palate development (35). Moreover, although half of all patients with CHARGE syndrome have CHD7 gene abnormalities (36), disruption to the epithelial-mesenchymal interaction has also been proposed to explain the pathogenesis of this affection, which includes multiple congenital anomalies involving different organs and tissues (37,38). These theories can explain the features of holoprosencephaly spectrum and as in our patients, the association of multiple congenital anomalies. The six hormone-producing cell types of the pituitary differentiate from a common population of ectodermal progenitors through the sequentially action of several transcription factors during pituitary development (39). However, it remains unclear how the developmental signaling systems interact during embryogenesis of the face, forebrain and pituitary.

In conclusion, CNPAS covers many features of the holoprosencephaly spectrum associated with craniofacial and extracranial anomalies. Long-term morbidity is related to the additional malformations. These patients should be carefully assessed during the neonatal period and a cerebral MRI is required before surgery. Patients with an abnormal HP axis are at a greater risk of endocrine dysfunction than those with a normal HP axis. These patients require prompt diagnosis and hormone replacement therapy to prevent a potentially life threatening and/or developmental delay due to hypoglycaemia, hypocortisolism and hypothyroidism and to ensure normal growth. Therefore, complete biochemical endocrine testing is justified during the neonatal period when an abnormal HP axis is seen by cerebral MRI, because ectopic PPHS or aplasia of the anterior pituitary are reliable indicators of endocrine dysfunction,. For other cases, the clinical features of pituitary deficiency should be detected during infancy to determine promptly those patients requiring a blood sample for determining plasma free T4, TSH, cortisol and IGF1 levels. Repeated investigations should be required for those patients who have abnormal HP axis on MRI but test normal initially or for those patients who develop clinical signs of endocrine dysfunction (*i.e.*, growth retardation) later in life. Careful assessment for other midline defects or physical findings should be done. Apart from SMMCI and HP axis abnormalities, most of the associated malformations are variable. They share considerable phenotypic overlap beyond craniofacial, heart, renal and limb anomalies. Therefore, counseling patients with CNPAS and their families is difficult for clinicians.

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