Pituitary (2012) 15:S81–S86
DOI 10.1007/s11102-012-0411-y

Unilateral agenesis of internal carotid artery associated with congenital combined pituitary hormone deficiency and pituitary stalk interruption without *HESX1*, *LHX4* or *OTX2* mutation: a case report

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Published online: 15 July 2012

Abstract Agenesis of internal carotid artery (ICA) is an unusual finding in subjects with congenital Combined Pituitary hormone deficiency (CPHD) with only nine cases being reported to date but to our best knowledge none of them was genetically investigated. A 10-years old girl presented with severe growth failure (height 103 cm) with substantial bone age delay (3 years). She had no history of perinatal insults or familial CPHD. There was no evidence of mental retardation or craniofacial dysmorphism or ophtalmological abnormalities. She was first diagnosed with GH and TSH deficiency. Cerebral magnetic resonance imaging (MRI) showed hypoplastic anterior pituitary, flat sella turcica, absent pituitary stalk with ectopic posterior pituitary as well as agenesis of the left ICA and the left carotid canal. Genomic analysis of pituitary transcription factor *HESX1, LHX4* and *OTX2* showed no mutations. Treatment with GH and thyroxine was started. The patient remained free of neurovascular symptoms for 5 years but she presented at the age of 15 years with delayed puberty related to an evolving gonadotropin deficiency. ICA agenesis associated with CPHD is unusual and is often asymptomatic in children. Since the CPHD with pituitary stalk interruption cannot be due to *HESX1*, *LHX4* or *OTX2* mutation in our case, other pathogenetic mechanisms may be responsible for CPHD associated with unilateral ICA agenesis.

Keywords Congenital combined pituitary hormone deficiency · Unilateral agenesis of internal carotid artery · Pituitary transcription factors

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Introduction

Congenital combined pituitary hormone deficiency (CPHD) defined as a deficiency in two or more pituitary hormones occurring in infants or children with no evidence of acquired causes is a rare etiology of postnatal growth failure [1, 2]. Congenital CPHD or hypopituitarism may be associated with several pituitary and extra pituitary abnormalities on cerebral magnetic resonance imaging (MRI) [3]. Agenesis of internal carotid artery (ICA) is a rare vascular anomaly and an unusual finding in subjects with congenital CPHD with only nine cases being reported to date [4–11]. Underlying mechanisms of CPHD in the setting of agenesis of ICA are still unclear. Previous reports suggested a possible developmental relationship between hypopituitarism and agenesis of ICA but to our best knowledge data on pituitary transcription factors genes mutations are not available. We report a case of CPHD and pituitary stalk interruption associated with an incidentally discovered congenital agenesis of the left ICA with no

mutation in pituitary transcription factors *HESX1*, *LHX4* or *OTX*.

Case history

A 10-years old Mediterranean girl presented with severe growth failure that started since she was 2 years old. She was born out of a consanguineous marriage. Familial history was unremarkable. She was born vaginally with no history of birth trauma. Her height was 103 cm (<−4 Standard Deviation [SD] according to Sempe height velocity chart), she was obese (BMI = 32.5 kg/m2, >97th percentile) and she had a so-called doll-like aspect. Tanner breast stage was B1. Neurological status was normal. There was no clinical evidence of diabetes insipidus or visual disturbances. Bone age was markedly delayed (3 years) based on published standards of Greulich and Pyle. Endocrine tests showed: severe GH deficiency with low Insulin-Like Growth Factor 1 level 25 ng/ml (normal values for age and sex: 127–903) and GH peak 0.1 µg/L on insulin tolerance test (ITT), (blood glucose nadir: 0.35 g/L), secondary hypothyroidism (low FT4 level 5.3 ng/L and normal TSH 0.42 mIU/L) and low prolactin level (3 ng/ml). Corticotroph function was normal on ITT (basal and peak cortisol response during ITT: 178 µg and 208 µg/L, respectively). Ophthalmological evaluation including visual acuity testing and examination of the optic discs was unremarkable. Metabolic analyses showed neither dyslipidemia nor glucose intolerance. Body mineral density (BMD) was normal on dual energy X-ray absorptiometry scan. Cerebral MRI was obtained (Fig. 1). T1 weighted sequence findings included: hypoplastic anterior pituitary, flat sella turcica, absent pituitary stalk with ectopic pituitary posterior lobe consistent with pituitary stalk interruption syndrome (PSIS) and agenesis of the left ICA. MR angiography showed no signal void corresponding to the left ICA, a collateral artery originating from the supraclinoidal segment of an enlarged right ICA reaching the left supraclinoid area with normal circle of Willis (Fig. 2). High resolution CT of the skull base confirmed the complete absence of the left carotid canal (Fig. 3). Caryotype was 46 XX. Within a multicenter study of genetic determinants of pituitary deficiencies (GENHYPOPIT Network launched as a multicentric study in both French and international pediatric and adult endocrinology centers including Argentina, Belgium, Egypt, Lebanon, Switzerland, Tunisia, and Turkey), the patient was screened for pituitary transcription factor *HESX1, LHX4* and *OTX2* mutations using previously described methods [12–14] after obtaining the consent of parents. However genomic analysis were entirely normal. The patient was put on thyroxine 50 µg daily and subcutaneous injections of biosynthetic GH (dose 35 µg/kg/day). Catch-up

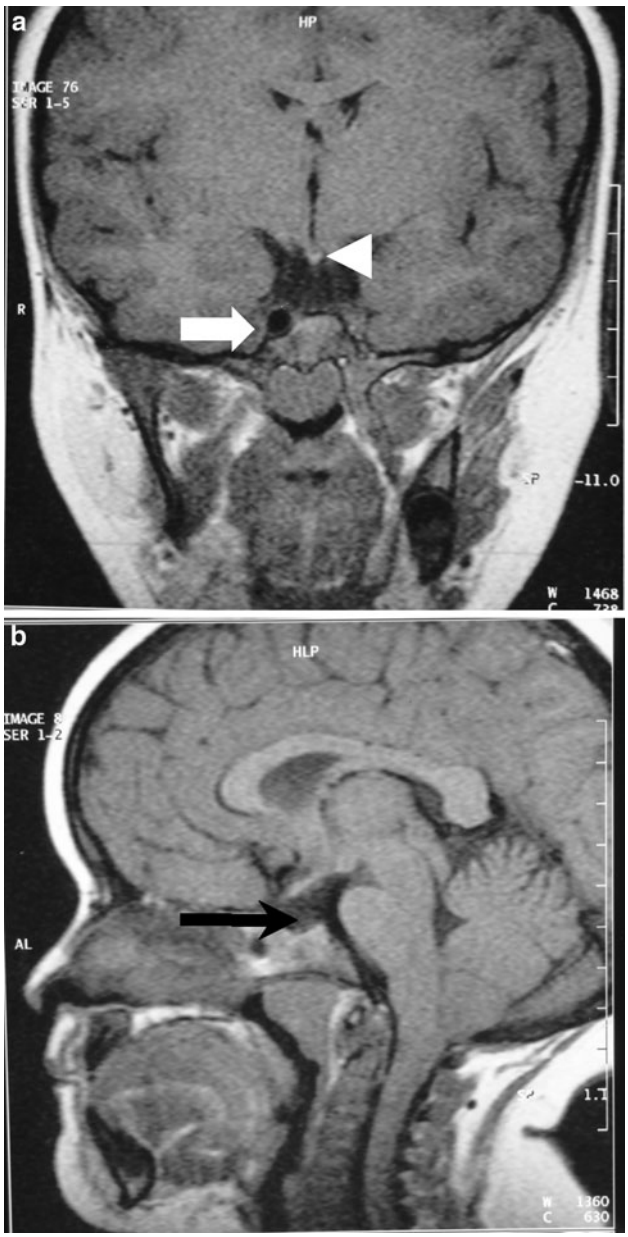

Fig. 1 **a** a coronal T1-weighted image shows ectopic posterior lobe pituitary as a small hyperintense nodule in the median eminence (*arrowhead*). The left internal carotid artery (ICA) is absent while the right internal carotid artery is normal (*bold arrow*). **b** A sagittal T1-weighted image shows the absence of the anterior pituitary in the flat sella turcica as well as the absence of pituitary stalk (*arrow*)

growth was 14 cm during the first year and then decreased to 6 cm during the second year despite increasing GH dosage to 50 µg/kg/day. Because the patient came from a remote rural area, she discontinued GH treatment and was lost to follow-up for 3 years. She remained free of neurological symptoms but she presented at the age of 15 years with delayed puberty related to gonadotropin deficiency (FSH 0.89 UI/L and LH 1.97 UI/L). GH treatment was restarted as height was 130 cm (<−4DS).

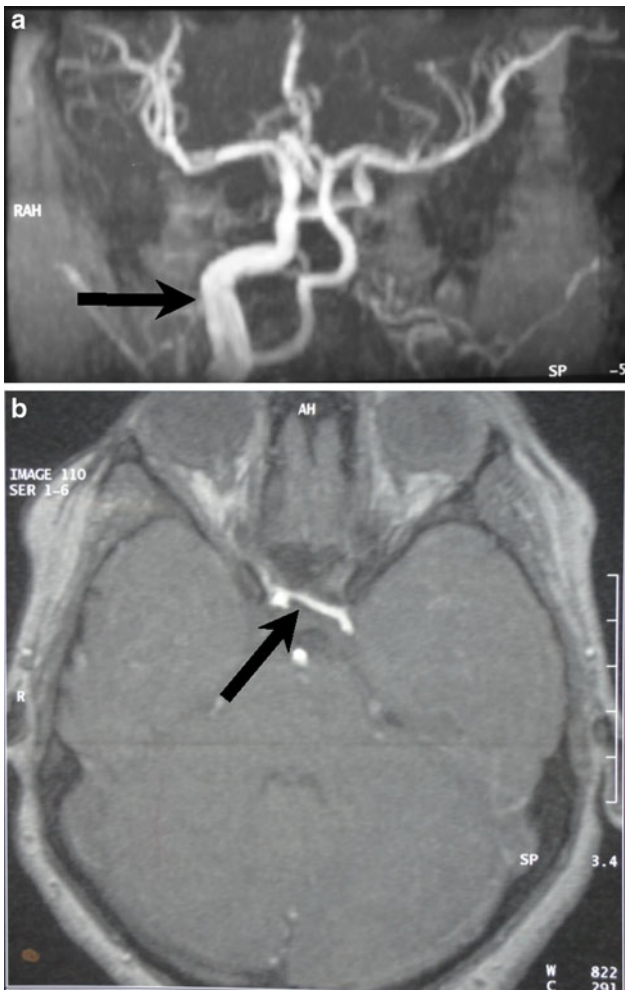

Fig. 2 **a** MR angiography showing no signal void corresponding to the left ICA. The right ICA is seen (*arrow*). **b** a collateral artery originating from the supraclinoidal segment of an enlarged right ICA reaching the left supraclinoidal area with normal circle of Willis (*black arrow*)

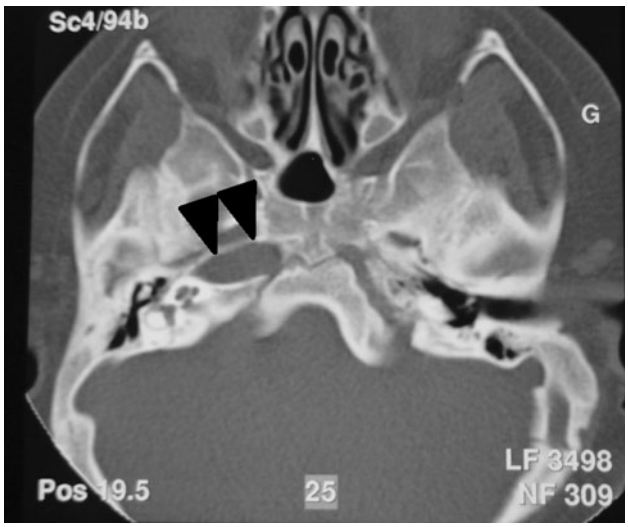

Fig. 3 High-resolution CT scan of the skull base. The left carotid canal is completely absent. The right carotid canal can be clearly seen (*arrowhead*)

Discussion

Our patient presented with characteristic clinical phenotype of congenital CPHD with severe and early childhood onset growth failure secondary to GH and TSH deficiencies and without evidence of pituitary tumors, infectious, infiltrative or inflammatory causes on MRI or history of perinatal insults such as breech delivery which may lead to hypopituitarism by mechanical traumatic transection of the pituitary stalk [9]. FSH and LH deficiency resulted in delayed puberty. Corticotroph function was normal at the time of initial diagnosis but regular adrenal tests are recommended because occurrence of evolving secondary adrenal deficiency has been described in congenital CPHD [1].

Congenital CPHD patients may harbor several structural defects including hypothalamo–pituitary (H–P) defects and extra pituitary anomalies which can be detected with current sensitive cerebral MRI techniques [2]. H–P MRI defects in our patient i.e. pituitary hypoplasia, pituitary stalk interruption and ectopic posterior pituitary are among the most commonly reported neuroradiological anormalies in congenital CPHD [3].

Extra pituitary anomalies have been reported in patients with syndromic CPHD, usually in structures sharing a common embryological origin, such as the eye and forebrain [15]. In our case, careful clinical examination and MRI analysis ruled out septo-optic dysplasia (SOD) [15]. Other clinical and radiological defects in extra pituitary structures found in patients with congenital CPHD include: variable craniofacial abnormalities such as single central incisor and cleft lip and palate, neck abnormalities, absent or hypoplastic corpus callosum as well as cerebellar tonsils herniation.

Agenesis or dysgenesis of ICA is an unusual finding in congenital CPHD with only nine cases being reported to date [4–11] (see Table 1). A malformative spectrum including coloboma and transsphenoidal encephalocele as well as single central maxillary incisor was reported in three patients with hypopituitarism and agenesis or dysgenesis of ICA [7, 11]. The left ICA is reported to be affected by dysgenesis three times more often than the right one [16]. In all previously reported CPHD and unilateral ICA agenesis cases as well as in our case agenesis of ICA was incidentally discovered on pituitary MRI. Sufficient collateral pathways and enlargement of normal vessels may explain the absence of neurovascular symptoms in our case and previous reported cases [8, 9]. However, vascular symptoms such as hemiplegia, seizures, strokes and intracranial hemorrhage may occur later in life secondary either to mass effect from the enlarged collaterals and associated

Table 1 Profiles of patients with agenesis of internal carotid artery and congenital combined pituitary hormone deficiency reported in the literature

	Gender/age (years) at the time of AICA discovery	Clinical and endocrinological features	MRI features	Reference
Case 1	NA	NA	Absence of ICA and carotid canal	[4]
Case 2	M 8	GH, TSH, ACTH, FSH and LH deficiencies.	Anterior pituitary hypoplasia, Ectopic posterior pituitary Congenital absence of the left ICA	[5]
Case 3	M 1	GH, ACTH, TSH, PRL, FSH and LH deficiencies.	Anterior pituitary hypoplasia Anomaly of the right ICA	[6]
Case 4	M 23	Panhypopituitarism Microphthalmia, Hypertelorism.	Ectopic posterior pituitary No identifiable anterior pituitary transsphenoidal encephalocele Dysgenesis of the right ICA	[7]
Case 5	M 37	Panhypopituitarism Optic nerve Coloboma, Hypertelorism.	Pituitary transsphenoidal encephalocele No identifiable anterior pituitary Dysgenesis of the right ICA	[7]
Case 6	F 29	GH, TSH, PRL, ACTH, FSH and LH deficiencies.	Anterior pituitary hypoplasia, Ectopic posterior pituitary Chiari I malformation Agenesis of right ICA	[8]
Case 7	M 5	GH, TSH and ACTH deficiencies.	Anterior pituitary hypoplasia, Mildly enlarged sella turcica Ectopic posterior pituitary, Absence of left ICA	[9]
Case 8	M 1	GH, ACTH, TSH, PRL, FSH and LH deficiencies, Microphallus.	Anterior pituitary hypoplasia. Absence of left ICA. No cerebral aneurysm. Slight decrease in left hemisphere blood flow.	[10]
Case 9	F 1	GH, ACTH, TSH -deficiencies, A single central maxillary incisor.	Anterior pituitary hypoplasia Absence of pituitary stalk and posterior pituitary spot. Absence of the right common carotid artery. Absence of the right ICA. Nasal pyriform aperture stenosis.	[11]

Panhypopituitarism: GH, TSH, LH and FSH, ACTH, PRL as well as ADH deficiency

AICA agenesis of internal carotid artery, *M* male, *F* female, *NA* not available, *GH* growth hormone, *TSH* thyroid stimulating hormone, *LH* luteinising hormone, *FSH* follicle stimulating hormone, *ACTH* corticotropin hormone, *PRL* prolactin, *ADH* antidiuretic hormone

cerebral aneurysms or to cerebrovascular insufficiency [9]. The documented increased frequency of aneurysm in the setting of agenesis of ICA (24–34 %) is an indication for long- term clinical and radiological follow-up [9].

Underlying mechanisms of CPHD and PSIS associated with ICA agenesis are still unclear. In our case H–P MRI defects and agenesis of both carotid canal and ICA strongly suggest a disordered embryogenesis [17]. As the skull base, carotid arteries and H–P axis develop around the 4–8th weeks of gestation, mechanical, vascular and/or genetic insults during this period may have disturbed their normal development [5, 7, 8, 11]. A common embryogenetic defect seems unlikely because pituitary axis and internal carotid arteries originate from different tissues: the ICA is formed from the terminal segments of the dorsal aorta and the 3rd aortic arch arteries while anterior pituitary and neurohypophysis originate from Rathke's pouch, a diverticulum of the primitive oral cavity (stomodeal ectoderm) and the neural ectoderm of the floor of the forebrain, respectively [18]. As the blood supply of the anterior and

posterior pituitary gland is from the superior and inferior hypophyseal arteries, respectively, which arise from the ICAs we hypothesized that unilateral agenesis of ICA could result in pituitary vascular insufficiency, pituitary hypoplasia and hypopituitarism [9]. However the normal structure of the brain suggests good blood supply from the opposite ICA. Moreover partial disruption of ICA perfusion could explain pituitary hypoplasia and hypopituitarism but not pituitary stalk interruption and ectopic posterior pituitary. Finally, MR angiography is not consistent with the hypothesis of a continuous pituitary compression by an enlarged collateral vessel [9].

Beyond vascular disturbance, we suspected a genetic mechanism of CPHD. Less than 5–20 % of hypopituitarisms are secondary to mutations in pituitary transcription factors genes operating in pituitary development [1]. *PROP1* (prophet of Pit1) mutations are the most common cause of congenital CPHD, including GH, TSH, PRL gonadotropin, and evolving ACTH deficiencies. *POU1F1* (previously termed PIT1) mutations are associated with GH, PRL, and TSH deficiencies. *LHX3* mutations are characterized by CPHD with sparing of ACTH in the majority of cases, a short rigid neck and variable sensorineural hearing loss [19]. Recent studies strongly suggested that both clinical phenotype and MRI findings may be predictive of the involved pituitary transcription gene mutation [3]. Genetic data were not referred in previously reported cases of CPHD and agenesis of ICA. In our case, *PROP1*, *POU1F1* and *LHX3* screening was not indicated because pituitary stalk interruption and ectopic posterior pituitary practically may exclude *PROP1*, *POU1F1* and *LHX3* defects [1]. We screened our patient for mutations in *HESX1, LHX4* and *OTX2* which are the most frequently mutations found in syndromic CPHD with pituitary stalk interruption [13, 15, 19–22]. Patients with *HESX1, LHX4* or *OTX2* may harbor several extra pituitary anomalies such as corpus callosum hypoplasia (HESX1) or ocular defects (OTX2). Unsuccessful genetic analysis in our patient who had neither familiar history of CPHD nor dysmorphism was consistent with the literature data as the majority of cases of hypopituitarism are idiopathic in origin [15]. Moreover, Reynaud et al. [1] found that the most significantly predictive features in finding a genetic defect was family history of CPHD.

Conclusion

Unilateral agenesis of ICA associated with congenital CPHD is a rare condition and is often asymptomatic in children but clinical and radiological follow-up are mandatory because the possibility of future occurrence of cerebral aneurysms and subsequent complications. Underlying mechanisms of CPHD associated with ICA agenesis are still unclear. This vascular insult could lead to pituitary hypoperfusion and hypoplasia but could not explain pituitary stalk interruption. Further genetic investigation may improve our understanding of the pathophysiology of CPHD with PSIS in the setting of ICA agenesis as our investigation suggest that the underlying mechanism(s) may be different from those involved in CPHD and PSIS without ICA agenesis.

Acknowledgments The GENHYPOPIT network for the study of genetic determinants of hypopituitarism, coordinated by Thierry Brue (thierry.brue@mail.ap-hm.fr), was funded by the Groupement d'Intérêt Scientifique Institut des Maladies Rares (GISMR0201) and the Programme Hospitalier de Recherche Clinique (PHRC 25/2003, French Ministry of Health).

Conflict of interest The authors declare that there is no conflict of interest that could be perceived as prejudicing the impartiality of the research reported.

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