Presentation and diagnosis of childhood-onset combined pituitary hormone deficiency. A single center experience from over 30 years

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Introduction

Timely diagnosis of combined pituitary hormone deficiency (CPHD) is challenging due to its rarity, and the variable manifestations and multiple etiologies of the disease (1-3). However, prompt diagnosis is extremely important to assure the child's normal growth and development, and to avoid the possibly life-threatening consequences of the cortisol-secretion stimulating ACTH deficiency (1). We investigated the diagnostic spectrum of childhood-onset CPHD in Finland's largest pediatric tertiary center between the years 1985 and 2018.

Results

Of the 125 CPHD patients (69 boys and 56 girls), 62% had an acquired disease with intracranial tumors as the major cause of pituitary insufficiency. One third of the patients had an intrinsic disease. There were four families with more than one member with intrinsic hypopituitarism. Seven patients had a molecular genetic diagnosis (*PROP1, OTX2, SOX3, TBC1D32*). One patient with genetically defined hypopituitarism had died at the age of three years despite adequate hormonal treatment.

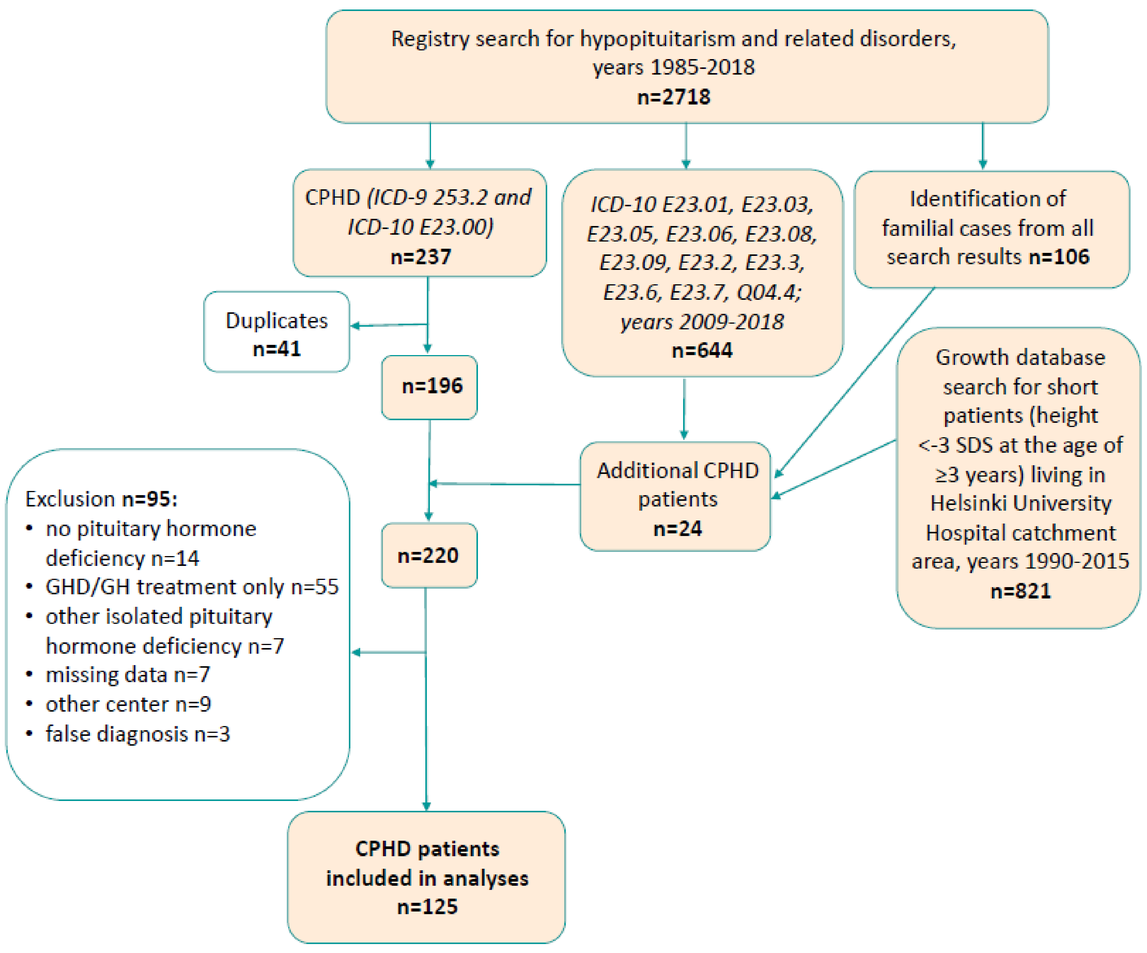

Figure 1. Identification of the CPHD patient cohort

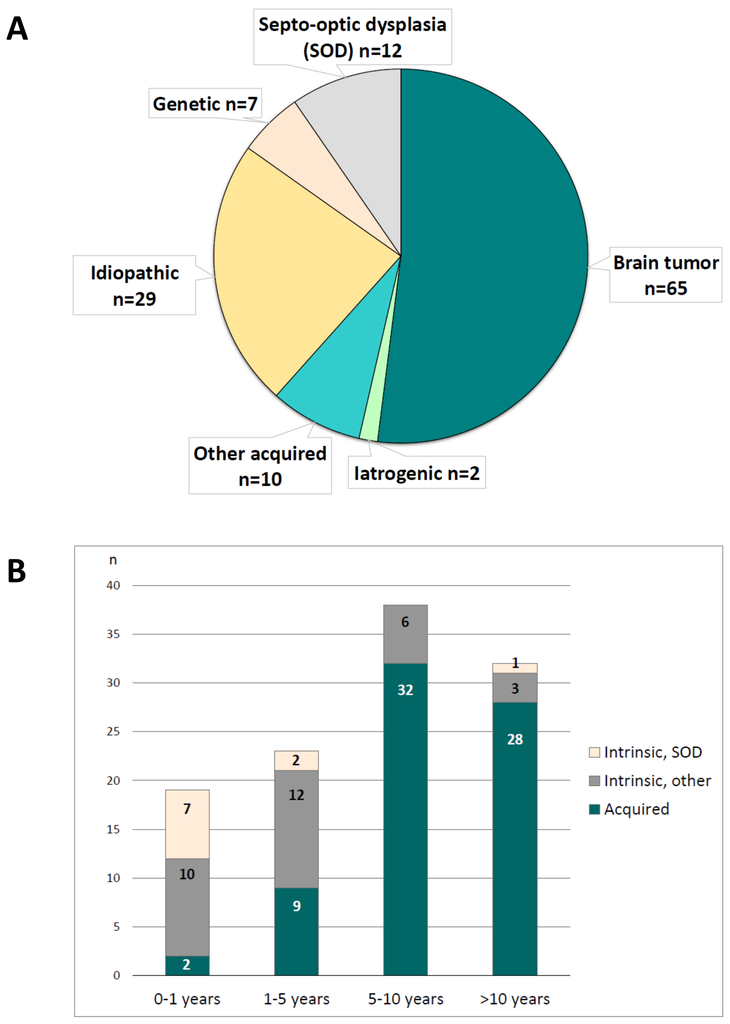

Figure 2. The etiologies (n) of childhood-onset CPHD, n total = 125 (A) and the age at presentation of CPHD patients by etiology, n total = 112 (B)

Phenotypic features of the patients with intrinsic CPHD

Neonatal signs of hypopituitarism, including hypoglycaemia, jaundice, and micropenis, were seen in 68% of the patients with intrinsic CPHD. Altogether 75% of the patients exhibited extrapituitary phenotypes. Nearly all of the patients (40/41) with MRI investigated had an abnormal brain MRI.

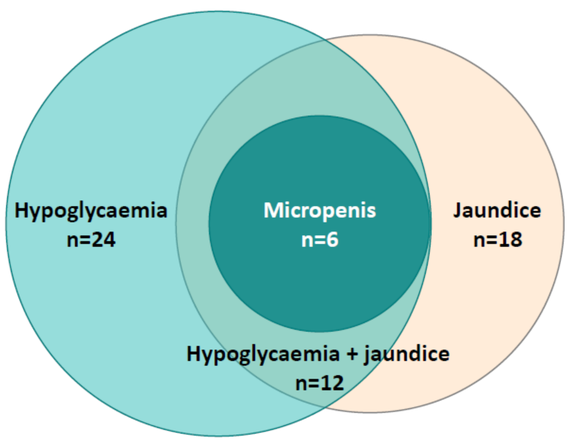

Figure 3. Neonatal features of intrinsic CPHD. Neonatal features were recorded in 30/44 patients (data not available n=4)

Table 1. Brain MRI findings in patients with intrinsic CPHD. The numbers denote n (%). MRI was available in 41/48 patients

Abnormalities in the pituitary and hypothalamus	**37 (90)**
Absent or hypoplastic anterior pituitary	30 (73)
Absent or ectopic posterior pituitary	30 (73)
Absent, hypoplastic, or interrupted pituitary stalk	29 (71)
Thick hypophysis	1 (2)
Thick to regressing infundibulum	1 (2)
Small hypothalamus	1 (2)
Other abnormal imaging findings	**28 (68)**
Optic nerve hypoplasia or atrophy	8 (20)
Corpus callosum hypoplasia or agenesis	6 (15)
Absent or anomal septum pellucidum	5 (12)
Olfactory bulb hypoplasia	3 (7)
Polymicrogyria	3 (7)
Schizencephaly	1 (2)
Sellar anomaly	9 (22)
Other	13 (32)

Conclusions

The diagnoses of intrinsic hypopituitarism predominate in younger patients with CPHD. Early signs of pituitary hormone deficiency were present in a significant proportion of patients with intrinsic CPHD, and should be recognized by all pediatricians, since congenital CPHD continues to be associated with significant mortality. Genetic investigations of the idiopathic and syndromic hypopituitarism patient cohorts are currently underway.

PEDIATRIC RESEARCH CENTER

References

1 Higham CE *et al.* Lancet 2016; 2 Cerbone M et Dattani MT Horm IGF Res. 2017; 3 Kurtoglu S *et al.* J Clin Res Pediatr Endocrinol 2019