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Clinical Research Article

Diagnosis and Incidence of Congenital Combined Pituitary Hormone Deficiency in Denmark—A National Observational Study

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Abstract

Context: Congenital combined pituitary hormone deficiency (cCPHD) is the loss of ≥2 pituitary hormones caused by congenital factors.

Objective: We aimed to estimate the national incidence of cCPHD diagnosed before age 18 years and in subgroups.

Methods: Patients with cCPHD were identified in the Danish National Patient Registry and Danish hospital registries in the period 1996-2020. Hospital files were reviewed and incidences calculated using background population data. Incidence was the main outcome measure.

Results: We identified 128 patients with cCPHD; 88 (68.8%) were males. The median (range) age at diagnosis was 6.2 (0.01-19.0) years. The median (25th;75th percentile) number of hormone deficiencies at diagnosis was 3 (3; 4) at <1 year vs 2 (2; 2) at 1-17 years, $P < .0001$. Abnormal pituitary magnetic resonance imaging findings were seen in 70.3% (83/118). For those born in Denmark aged <18 years at diagnosis (n = 116/128) the estimated national incidence (95% CI) of cCPHD was 10.34 (7.79-13.72) per 100 000 births, with an annual incidence rate of 5.74 (4.33-7.62) per million. In subgroup analysis (diagnosis <1 vs 1-17 years), the incidence was highest in the 1-17 years subgroup, 7.97 (5.77-11.00) vs 1.98 (1.39-2.84) per 100 000 births, whereas the annual incidence rate was highest at <1 year, 19.8 (13.9-28.4) vs 4.69 (3.39-6.47) per million births.

Conclusion: cCPHD had the highest incidence rate and the most hormone deficiencies in those diagnosed at <1 year. The incidence was highest in the 1-17 years age group, underscoring the need for multiple pituitary hormone investigations throughout childhood and adolescence in children with only 1 hormone deficiency.

Key Words: congenital hypopituitarism, congenital combined pituitary hormone deficiency, cCPHD, cMPHD, diagnosis of hypopituitarism, incidence

Abbreviations: cCPHD, congenital combined pituitary hormone deficiency; DNPR, Danish National Patient Registry; FSH, follicle-stimulating hormone; GH, growth hormone; GHD, growth hormone deficiency; LH, luteinizing hormone; MRI, magnetic resonance imaging; PHD, pituitary hormone deficiency; TSH, thyroid-stimulating hormone.

Pituitary hormone deficiency (PHD) may be isolated with only 1 hormone deficiency or combined (CPHD) with ≥2 hormone deficiencies (1, 2). CPHD may be acquired or congenital (cCPHD), the latter defined as partial or complete loss of ≥2 hormones secreted from the pituitary gland caused by genetic factors or malformation (2–4). CPHD is considered congenital in the absence of identified acquired causes such as cerebral tumors, surgery, infection, radiotherapy, hemorrhage, infarction, and infiltrative or granulomatous disease in the hypothalamic–pituitary region (5, 6).

cCPHD may be caused by genetic variants of genes involved in the embryological development of the midbrain and pituitary, including *HESX1*, *LHX3*, *LHX4*, *POU1F1*, *PROP1*, *SIX6*, *OTX2*, *PITX2*, *GLI2*, and *SOX3*. However, despite increasing knowledge, most patients remain genetically unexplained when screened for genetic mutations (2, 7, 8). Disruption of early-acting transcription factors of pituitary organogenesis may lead to extrapituitary abnormalities such as septo-optic dysplasia, holoprosencephaly, or aplasia/hypoplasia of other brain structures, especially in the midline. In contrast, disruption of later-acting transcription factors leads to a more pituitary-specific phenotype with hormone deficiencies alone (9, 10).

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Table 1. Search strategy for cCPHD by ICD-10 diagnosis codes

ICD-10 code	Diagnoses
Inclusion criteria diagnosis codes	
E23.0-E23.9	Hypofunction and other disorders of pituitary
Q89.2G	Congenital malformation of pituitary
Q04.0-Q04.9[a]	Other congenital malformations of brain
Exclusion criteria diagnosis codes	
C69.0-C69.9	Malignant neoplasm of eye and adnexa
C70.0-C70.9	Malignant neoplasm of meninges
C71.0-C71.9	Malignant neoplasm of brain
C72.0-C72.9	Malignant neoplasm of spinal cord, cranial nerves, and other parts of central nervous system
C75.1-C75.3	Malignant neoplasm of pituitary gland, craniopharyngeal duct, and pineal gland
D33.0-D33.9	Benign neoplasm of brain and other parts of central nervous system
D35.2-D35.4	Benign neoplasm of pituitary gland, craniopharyngeal duct, and pineal gland
A80.0-A89.9	Viral infections of the central nervous system
I60.0-I60.9[b]	Subarachnoid hemorrhage
I61.0-I61.9[b]	Intracerebral hemorrhage
I62.0-I62.9[b]	Other nontraumatic intracranial hemorrhage
I63.0-I63.9[b]	Cerebral infarction
I64[a]	Stroke, not specified as hemorrhage or infarction

[a]A search on these ICD-10 diagnosis codes was performed at each the 4 tertiary hospitals as a spot sample (n = 80).
[b]These ICD-10 diagnosis codes were only used as an exclusion criterion if the registration occurred prior to registration of E23.0-E23.9 and/or Q89.2G ICD-10 codes.

cCPHD has a broad clinical spectrum from potentially life-threatening multiple hormone deficiencies in the neonate to a late-onset gradual presentation in childhood or adolescence (1, 4, 6, 11, 12). A wide variation occurs in both age of onset, presence of cerebral malformations, and composition of hormone deficiencies, even within the same family (3, 13).

Neonates with clinical overt cCPHD may present with micropenis and other features of hypovirilization (boys), hypoglycemia, electrolyte abnormalities, prolonged jaundice, failure to thrive, and severe hypernatremic dehydration due to central diabetes insipidus (3, 6). Onset of cCPHD in later infancy or childhood may occur as a gradual process with the hormone deficiencies developing consecutively with symptoms and signs of growth retardation, constipation, fatigue, developmental delay, polyuria, intense thirst, and/or delayed puberty (13, 14).

A recent Finnish study from 1 tertiary hospital estimated the incidence of cCPHD to 1 in 16 000 live-born children (6). In Denmark, all patients are registered in the Danish National Patient Registry (DNPR) with information on their ICD-10 diagnoses. Treatment of cCPHD in children is only approved in 4 tertiary hospitals. Given these unique possibilities, we performed a nationwide registry and hospital file study, aiming to estimate the national incidence of cCPHD diagnosed before age 18 years and in subgroups, including hormone deficiency characteristics and brain magnetic resonance imaging (MRI) abnormalities in the patients.

Table 2. Hospitals included in the tertiary hospital registry search and the secondary hospital spot sample

Hospitals	Search period
Tertiary hospitals	
Department of Pediatrics, Aalborg University Hospital	January 1, 1996-December 31, 2020
Department of Pediatrics and Adolescent Medicine, Aarhus University Hospital	January 1, 2000-December 31, 2020
Hans Christian Andersen Children's Hospital, Odense University Hospital	January 1, 2016-December 31, 2020
Department of Growth and Reproduction, Rigshospitalet	November 6, 2016-December 31, 2020
Secondary hospital, spot sample	
Department of Pediatrics, Kolding Hospital	January 1, 1996-December 31, 2020

Materials and Methods

Study Population

The study included all patients with cCPHD in Denmark born between January 1, 1996, and December 31, 2020, identified through ICD-10 diagnosis code searches in the DNPR and locally at the 4 Danish tertiary hospitals.

The DNPR contains all inpatients in Denmark since 1977 and all outpatients since 1995, with ICD-10 diagnosis codes since 1994. Whenever a patient is in contact with a Danish hospital, 1 primary and an optional number of secondary ICD-10 diagnosis codes are registered as the reason for the contact, along with codes identifying the reporting hospital and department. The DNPR identifies patients based on a central person registrations number, which is a unique personal identification number, including information on date of birth, given to all Danish citizens since 1968. The validity and completeness of the DNPR ICD-10 diagnosis code registration allow for national incidence estimations according to a systematic review (15).

The DNPR search identified all Danish patients with relevant diagnoses before age 15 years from January 1, 1996, to December 31, 2020. As cCPHD does not have a specific ICD-10 diagnosis code, we had to search the DNPR for broader pituitary-related ICD-10 diagnosis codes E23.0-E23.9 (hypofunction and other disorders of pituitary) and Q89.2G (congenital malformation of pituitary), thus including both isolated PHD and acquired CPHD. A number of additional ICD-10 diagnosis codes indicating an acquired etiology of PHD were used as exclusion criteria, as detailed in Table 1. Furthermore, identified patients who were not treated at a tertiary hospital were excluded. To detect failure of referral of patients with cCPHD to a tertiary hospital, we reviewed the hospital files of all patients registered at 1 secondary hospital in the DNPR data set as a spot sample (Table 2). This was done to examine the frequency of referral failure and, through that, the validity of the method used to identify patients with cCPHD.

For validation, supplementary ICD-10 diagnosis code searches on E23.0-E23.9, Q89.2G, and Q04.0-Q04.9 (other congenital malformations of brain) were performed locally at the 4 tertiary hospitals for variable periods according to the possibilities of the individual hospital registries (Table 2).

Table 3. Criteria used for validation of secondary and tertiary hormone deficiency

Pituitary hormone	Criteria for validation of secondary and tertiary hormone deficiency
Growth hormone (GH)	Two pathological GH stimulation tests and concomitantly relevant clinical features. One pathological GH stimulation test, low/normal levels of IGF-1, low/normal levels of IGF-BP3 if measured, concomitantly relevant clinical features, and validated secondary/tertiary deficiency of ≥1 hormone (this criterion was solely considered valid if only 1 GH stimulation test was performed). Low/normal levels of IGF-1, low/normal levels of IGF-BP3 if measured, concomitantly relevant clinical features, and validated secondary/tertiary deficiency of ≥1 hormone (this criterion was solely considered valid if no GH stimulation tests were performed).
Thyrotropin (TSH)	Low levels of thyroxine/free thyroxine, concomitantly low/normal/inadequately high levels of TSH, and concomitantly relevant clinical features.
Follicle-stimulating hormone/luteinizing hormone (FSH/LH)	One pathological relevant stimulation test, low levels of estradiol/testosterone, concomitantly low/normal levels of LH and FSH[a], and concomitantly relevant clinical features. Low levels of estradiol/testosterone, concomitantly low/normal levels of LH and FSH[a], concomitantly relevant clinical features, and validated secondary/tertiary deficiency of ≥1 hormone (this criterion was solely considered valid if no stimulation test was performed). Relevant clinical features, initiation of sex hormone replacement treatment, and validated secondary/tertiary deficiency of ≥1 hormone (this criterion was solely considered valid if no stimulation test or blood samples were performed). Persistently low levels of testosterone/estradiol, concomitantly low/normal levels of FSH and LH, 1 GnRH stimulation test showing normal pituitary function[a], no indication of peripheral hormone deficiency, and ≥1 validated secondary/tertiary hormone deficiency.
Adrenocorticotropin (ACTH)	One pathological relevant stimulation test and concomitantly relevant clinical features.
Antidiuretic hormone (ADH)	One pathological relevant stimulations test and relevant clinical features. High serum osmolality/high serum sodium, low urine osmolality, concomitantly relevant clinical features, and validated secondary/tertiary deficiency of ≥1 hormone (this criterion was solely considered valid if no stimulation test was performed).

Abbreviations: GnRH, gonadotropin-releasing hormone; IGF-1, insulin-like growth factor-1; IGF-BP3, insulin-like growth factor binding protein 3.
[a]Stimulation tests and blood samples must be performed at an appropriate age: age 0 to 6 months (minipuberty), age >11 years (girls)/>12 years (boys) if secondary/tertiary deficiency of ≥1 other hormone has been validated, or age >9 years (girls)/>10 years (boys), if secondary/tertiary deficiency of ≥2 others has been validated.

The hospital registry searches, which included patients with an above-mentioned diagnosis code given at the age of 0-17 years, were followed by hospital file examinations to exclude patients born outside the study period 1996-2020 and patients with ICD-10 diagnosis codes indicating acquired PHD. Next, the DNPR and hospital registry searches were merged by central person registration numbers to disallow patient duplets, followed by a retrospective review of all available hospital files of the remaining patients to validate the cCPHD diagnosis and exclude patients with fewer than 2 documented secondary/tertiary hormone deficiencies or acquired CPHD.

Data Collection

Hospital file data were collected from March 1, 2021, to June 30, 2022. For the finally included patients, the following data were included: date of birth, sex as indicated by the presence of male/female genitals (male/female), born in Denmark (yes/no), date and results of blood samples and stimulation tests of interest (low/normal/inadequately high/high), date and result of urine osmolality measurement (low/normal/high), abnormalities of the adenohypophysis, neurohypophysis, pituitary stalk, midline, and cerebrum by the latest MRI (aplasia/hypoplasia/ectopic/normal or yes/no), and clinical signs of hormone deficiencies (yes/no).

Validation of Hormone Deficiencies

All hormone deficiencies were retrospectively validated using the criteria in Table 3. The criteria were defined by 5 experienced pediatric endocrinologists, including a representative from each of the tertiary hospitals and were based on clinical practice and national as well as international literature and guidelines (1, 3, 16–20). We chose to also include validated congenital deficiency of thyrotropin-releasing hormone and gonadotropin-releasing hormone. Blood sample and stimulation test results were categorized as low/normal/inadequately high/high based on the clinical assessment in the hospital file and the existing reference values at the given time and hospital.

Transient hormone deficiencies were excluded. We included children diagnosed with childhood growth hormone deficiency (GHD) without requiring retesting in the transition phase for adult GHD, where lower GH cut-offs are used. Patients with birth asphyxia or infant brain hemorrhage were considered having cCPHD only if structural pituitary abnormalities were described by MRI. In cases of central hypothyroidism where hormone replacement treatment had not been initiated, thyroid stimulating hormone (TSH) deficiency was retrospectively judged present when at least 2 consecutive and latest blood samples met our defined criteria. To distinguish central hypogonadism from constitutional delay in puberty, we additionally reviewed the patient files for inadequate treatment of TSH or GH deficiency, which can cause a delay in puberty, and for mentions of familial predisposition to constitutional delay in puberty. If any of these conditions were detected, the patients were not considered to have central hypogonadism after validation.

Every validated hormone deficiency was assigned a date of diagnosis, which we defined as the date of the blood sample or stimulation test that led to the diagnosis by clinicians. If the date of the blood sample/stimulation test was unavailable,

we instead used the date of the hospital file note commenting on the result. The age at diagnosis of cCPHD was defined as the age at diagnosis of the second hormone deficiency.

Data Analysis

All validated cases of cCPHD made up the national cCPHD cohort. The national cCPHD incidence cohort was formed by excluding patients born outside Denmark and patients diagnosed with cCPHD after age 17 years. The incidence was calculated using the birth year of patients with cCPHD, dividing the number of patients with cCPHD born in a period with the number of live births in Denmark in the same period. Data on the annual birth counts were obtained from Statistics Denmark. Subgroup incidences were calculated by dividing patients into 2 groups according to their age at diagnosis: <1 year and 1-17 years.

Incidence rates were calculated by dividing the number of patients with cCPHD born in a period with the corresponding person-time of the birth cohorts. The person-time was determined by multiplying the birth counts with a factor of 1 (subgroup <1 year); 17 (subgroup 1-17 years); and 18 (the national incidence cohort).

The incidence calculations were subjected to right truncation from 2003 to 2020, as children born in this period did not reach age 18 years in the observation period. To eliminate the influence of right truncation, we calculated the overall incidence in the period 1996-2002. For the subgroup diagnosed before age 1 year, the incidence was calculated in the period 1996-2019. For completeness, we also calculated the incidence of cCPHD diagnosed at all ages (0-19 years) and the incidence of cCPHD diagnosed before age 18 years for the whole period 1996-2020.

The SE and the 95% CI were calculated using the formulas $1/\mathrm{SE}(\ln \mathrm{IR}) = \sqrt{1/a}$, $2/95\%\ \mathrm{CI}(\ln \mathrm{IR}) = \ln \mathrm{IR} \pm 1.96 * SE(ln\,\mathrm{IR})$, and $3/e^{95\%\mathrm{CI}(\ln \mathrm{I})}$. In the formulas, "a" represents the number of clinical events, "IR" the incidence rate, and "e" the exponential constant.

Statistical calculations were performed using Stata/IC 16.1, Microsoft Excel version 16.57, and Maple 2020.2. Pearson's chi-square goodness-of-fit test was used to analyze differences in the sex distribution. The background population sex distribution from 1996 to 2020 served as reference (Statistics Denmark). Fisher's exact test was performed to explore associations between the number of hormone deficiencies and MRI abnormalities and age at diagnosis. $P < .05$ was considered to be statistically significant.

Ethics

This study was approved by the region of Southern Denmark (j.no. 20/58158). To ensure compliance with the General Data Protection Regulation and the Danish Data Protection Act, data were collected and managed in collaboration with the Open Patient data Explorative Network (OPEN) using Microsoft SharePoint and REDCap (Research Electronic Data Capture) (21, 22).

Results

Through the ICD-10 diagnosis code searches and the subsequent hospital file reviews, we identified 114 patients through the DNPR search and 14 patients through the tertiary hospital registries, resulting in a national cCPHD cohort of 128 patients (Table S1 (23)). Of these, 116 were born in Denmark and diagnosed before age 18 years, representing the national incidence cohort of cCPHD diagnosed <18 years (Fig. 1).

Clinical Data

Males were overrepresented in the national cCPHD cohort (88/128; 68.8%), and in both subgroups (Table 4); however, they were only statistically significant in the subgroup of patients diagnosed aged 1-17 years (chi-square $P < .0001$). The median age (range and 25th;75th percentile) at cCPHD diagnosis was 6.2 (0.01-19.0 and 0.6; 11.9) years (Fig. 2 and Table 4). Age at diagnosis was not available in 5 patients, however diagnosed with cCPHD at some point before age 18 years. Of the remainer, thirty-two patients (26.2%) were diagnosed aged <1 year and 90 patients (73.8%) between 1 and 17 years of age. The median (range) patient age at last follow-up was 15.6 (1.0-24.8) years, and 51 patients (39.8%) had reached 18 years of age at last follow-up.

The number of recorded hormone deficiencies was 2 in 66 patients (51.6%), 3 in 21 patients (16.4%), 4 in 39 patients (30.5%), and 5 in 2 patients (1.6%). GHD was the most common deficiency, succeeded by deficiency of TSH, follicle-stimulating hormone (FSH)/luteinizing hormone (LH), adrenocorticotropic hormone, and antidiuretic hormone. However, deficiency of TSH was more common than GHD in patients diagnosed <1 year of age. Patients with cCPHD diagnosed at <1 year of age had the highest number of hormone deficiencies, both at diagnosis and at last follow-up (Fisher's $P < .0001$ vs subgroup 1-17 years). In the 1-17 years subgroup, 58 (64.4%) patients were diagnosed with only 2 hormone deficiencies. The most prevalent combination was GHD and TSH deficiency (n = 37), followed by GHD and FSH/LH deficiency (n = 11).

Abnormal pituitary gland or stalk MRI findings was seen in 83.3% (n = 25/30) for those diagnosed at <1 year of age, decreasing to 63.4% (n = 53/82) in the 1-17 years subgroup (missing data, n = 10). Hypoplastic, absent, or ectopic neurohypophysis was the most common solitary abnormality, followed by hypoplastic or absent adenohypophysis, the category "other cerebral abnormality," pituitary stalk abnormality, and midline malformation. Fifty-seven patients (48.3%) had additional midline or other cerebral abnormalities. As the only significant difference between the age subgroups, hypoplastic or absent pituitary stalk was more frequent <1 vs 1-17 years (17/30 vs 28/82, $P = .049$).

The National Incidence of cCPHD

The national incidence (95% CI) of cCPHD diagnosed before age 18 was calculated to be 10.34 (7.79-13.72) per 100 000 live births in the period 1996-2002, giving an incidence rate of 5.74 (4.33-7.62) per million live births per year. No trend in the incidence through this observation period was observed (Figs. 3 and 4). The incidence estimate including all patients diagnosed in the whole observation period 1996-2020 was somewhat, yet nonsignificantly lower, probably owing to right truncation (Table 5). The incidence and annual incidence rate were by far highest for patients diagnosed before age 1 year, 19.8 (13.9-28.4) per million live births per year, compared with the later ages. Incidences split by age 1-8 years and 9-17 years are shown elsewhere (Table S2 (23)).

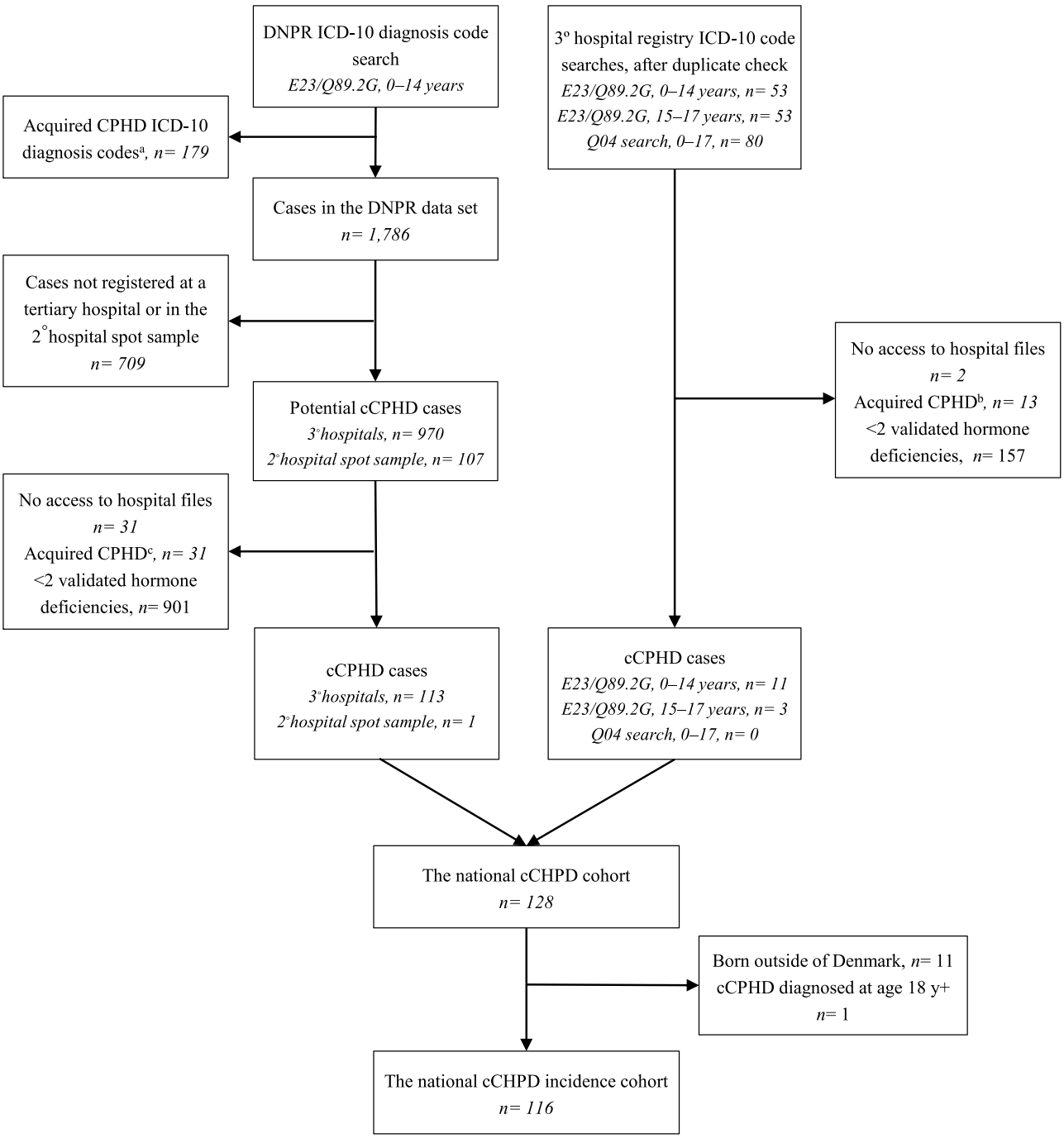

Figure 1. Flow chart of the identification of the national congenital combined pituitary hormone deficiency (cCPHD) cohort and the national cCPHD incidence cohort. Patients at risk of cCPHD were identified through searches on ICD-10 diagnosis codes E23.0-E23.9 (hypofunction and other disorders of pituitary), Q89.2G (congenital malformation of pituitary), and Q04.0-Q04.9 (other congenital malformations of brain). All potential cCPHD cases were examined through retrospective hospital file reviews to validate the cCPHD diagnosis from uniform criteria. DNPR, Danish National Registry; CPHD, combined pituitary hormone deficiency.
[a]C69.0-C72.9; n = 69, C75.1-C75.3; n = 4, D33.0-D33.9; n = 53, D35.2-D35.4; n = 41, A80.0-A89.9; n = 8, I60.0-I64.9; n = 4.
[b]Infections/autoimmunity; n = 1, brain neoplasm and treatment hereof; n = 8, leukemia/lymphoma and treatment hereof; n = 2, severe eating disorder; n = 1, birth asphyxia; n = 1.
[c]Infections/autoimmunity; n = 3, Langerhans cell histiocytosis; n = 6, transfusion-dependent thalassemia; n = 3, brain neoplasm and treatment hereof; n = 3, leukemia/lymphoma and treatment hereof; n = 6, other; n = 10.

Discussion

In this first of its kind national study, we identified 128 patients with cCPHD, of which nearly 50% were diagnosed before age 6 years. Above half of the patients had 2 hormone deficiencies, whereas deficiency of all 5 hormones were only seen in 2 patients. Cerebral abnormalities by MRI were seen in almost 90% of the patients.

The incidence of cCPHD diagnosed before age 18 years was calculated to be 10.34 (7.79-13.72) per 100 000 live births with an incidence rate of 5.74 (4.33-7.62) per million live

Table 4. Magnetic resonance imaging (MRI) and hormone deficiency characteristics of the 128 patients in the national cCPHD cohort

	Diagnosis at age <1 year	Diagnosis at age 1-17 years	Total
Number	32 (26.2)	90 (73.8)	128[a] (100)
Sex			
Male	20 (62.5)	65 (72.2)[d]	88 (68.8)[d]
Female	12 (37.5)	25 (27.8)	40 (31.2)
Age at observation period end	11.4 (5.9; 17.8)	16.5 (12.3; 20.1)	15.6 (10.7; 20.4)
Age at diagnosis of			
First hormone deficiency	0.06 (0.03; 0.2)	4.8 (3.0; 7.5)	3.6 (0.5; 6.5)
Second hormone deficiency	0.1 (0.04; 0.2)	8.3 (4.2; 13.1)	6.2 (0.6; 11.9)
Third hormone deficiency	0.08 (0.05; 0.2)	8.2 (6.0; 12.6)	3.1 (0.1; 10.0)
Fourth hormone deficiency	0.4 (0.08; 0.9)	13.0 (12.0; 14.0)	10.8 (0.4; 13.0)
Fifth hormone deficiency	12.2 (12.2; 12.2)	11.8 (11.8; 11.8)	12.0 (11.8; 12.2)
Number of hormone deficiencies			
At cCPHD diagnosis	3 (3; 4)[e]	2 (2; 2)	2 (2; 3)
At latest follow-up	4 (3; 4)[e]	2 (2; 3)	2 (2; 4)
Type of deficiencies at last follow-up			
Adrenocorticotropin (ACTH)	27 (24.1)	32 (13.9)	61 (16.9)
Growth hormone (GH)	30 (26.8)	83 (35.9)	119 (33.0)
Thyrotropin (TSH)	31 (27.7)	74 (32.0)	110 (30.5)
Follicle-stimulating/luteinizing hormone (FSH/LH)	19 (17.0)	40 (17.3)	63 (17.5)
Antidiuretic hormone (ADH)	5 (4.5)	2 (0.9)	8 (2.2)
Brain MRI findings[b]			
Abnormal brain MRI	29 (96.7)	70 (85.4)	105 (89.0)
Abnormal pituitary gland or stalk	25 (83.3)	52 (63.4)	83 (70.3)
Adenohypophysis hypoplastic or absent	18 (60.0)	42 (51.2)	66 (55.6)
Neurohypophysis hypoplastic, absent or ectopic	21 (70.0)	44 (53.7)	71 (60.2)
Pituitary stalk hypoplastic or absent	17 (56.7)[g]	28 (34.1)	48 (40.7)
Additional midline or other cerebral abnormalities	18 (60.0)	37 (45.1)	57 (48.3)
Cerebral midline malformations[c]	11 (36.7)	16 (19.5)	27 (22.9)
Other cerebral abnormalities	15 (50.0)	33 (40.2)	50 (42.4)
Normal brain MRI	1 (3.3)	12 (14.6)	13 (11.0)
Missing brain MRI	2 (6.2)	8 (8.9)	10 (7.8)
Combined brain MRI abnormalities[b]			
Pituitary abnormality only	11 (36.7)	33 (40.2)	48 (40.7)
Adeno- and neurohypophysis only	1 (3.3)	7 (8.5)	10 (8.5)
Pituitary stalk, adeno- and neurohypophysis	4 (13.3)	14 (17.1)	20 (16.9)
Pituitary and midline abnormalities only	3 (10.0)	2 (2.4)	5 (4.2)
Pituitary and other cerebral abnormalities only	6 (20.0)	11 (13.4)	19 (16.1)
Pituitary, midline, and other cerebral abnormalities	5 (16.7)	6 (7.3)	11 (9.3)

Data are presented as median (25th;75th percentile) or n (%).
All hormone deficiencies diagnosed within 6 months of the second hormone deficiency was considered present at the time of cCPHD diagnosis.
[a]Age at diagnosis was not available in 5 patients and 1 patient was diagnosed after age 17 years.
[b]The percentage distribution was calculated from the number of available brain MRI scan.
[c]Including Rathke's pouch cysts, incomplete Rathke's pouch closure, malformations of the optic chiasm, hypothalamus, third ventricle, corpus callosum and septum pellucidum.
[d]Fisher's $P < .0001$ vs female.
[e]Fisher's $P < .0001$ vs subgroup 1-17 years.
[g]Fisher's $P = .049$ vs subgroup 1-17 years.

births per year. A by far higher incidence (~1:50 000) was seen in patients diagnosed before age 1 year, who also presented with the highest incidence rates and highest number of hormone deficiencies.

Published data on the incidence of hypopituitarism are scarce. The incidence rate of all-cause adult-onset hypopituitarism in northwestern Spain was estimated to be 4.21 per 100 000 inhabitants per year (19), whereas another study suggested that the incidence of all-cause CPHD during childhood is less than 3 per million per year (24). We identified a higher incidence rate, even when including only cCPHD and not all-cause CPHD. We primarily ascribe this to the unique

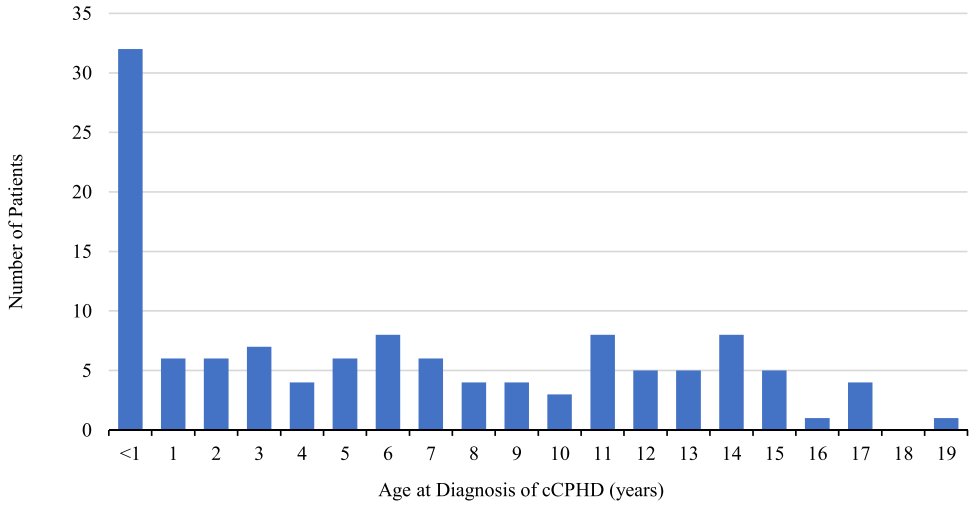

Figure 2. The age distribution at diagnosis of congenital combined pituitary hormone deficiency (cCPHD). The age at cCPHD diagnosis was defined as the age on the date of the second hormone deficiency diagnosis (n = 123).

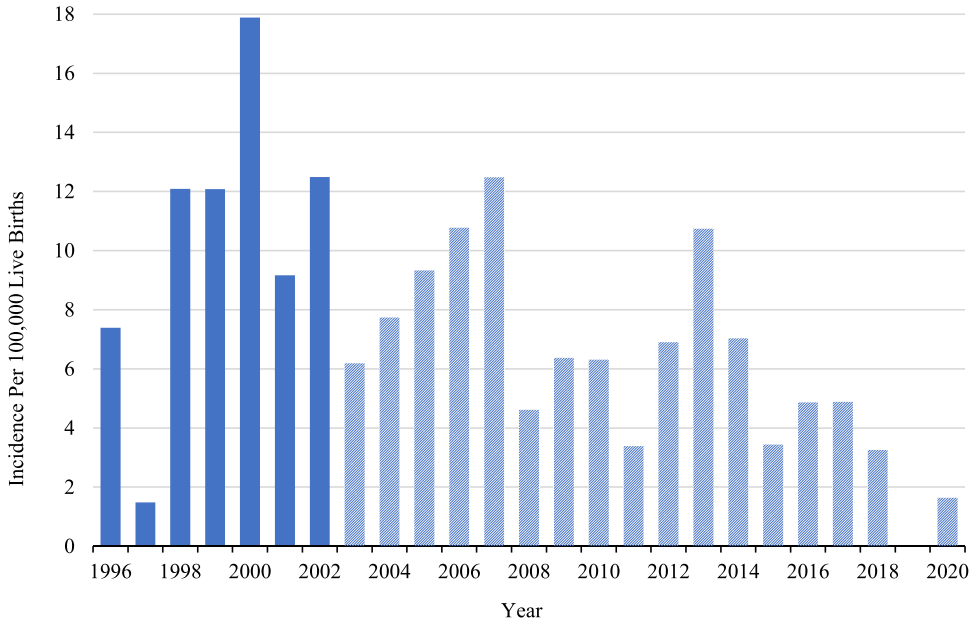

Figure 3. The incidence of congenital combined pituitary hormone deficiency (cCPHD) in Denmark diagnosed before age 18 years. The figure only includes patients with cCPHD who were born in Denmark and diagnosed before age 18 years (n = 116). Solid columns represent the incidence estimations that are not influenced by right truncation, as all patients born in the period 1996-2002 have turned 18 years old by the end of the observation period. Hatched columns represent incidence estimations that may be influenced by right truncation.

access to national and hospital registries in Denmark and detailed hospital file validation. The tertiary hospital registry searches and the secondary hospital spot sample identified 12 additional patients with cCPHD diagnosed before age 15 years, and 3 additional patients aged 15-19 years at diagnosis, indicating incomplete case identification from the national registry search strategy. On the contrary, the identified national cohort was regarded as complete or almost complete, providing high validity to the incidence estimates. The denominator, the annual birth counts in Denmark, was moreover accurate owing to Statistics Denmark, whose calculations were based on data from both the central person registrations and the DNPR registry. Recently, a Finnish study from 1 tertiary hospital estimated the incidence of cCPHD to be 1:16 000 (6.25:100 000) based on 26 identified patients in the period 2000-2018 (6). The lower incidence than our study may be attributed to right censoring, as a follow-up time of 18 years was not ensured. In our study, the importance of avoidance of right censoring was underscored, as the incidence was highest in 1-17 years at diagnosis. Furthermore, while the definition of cCPHD resembles ours, it is, however, not clear whether children diagnosed up to and including age 17 years were included in the Finnish study.

Our study revealed an overrepresentation of males with cCPHD, in agreement with some (6, 7, 9), but not all, studies (25). X-linked genetic factors have been suggested as an explanation of male predominance, but the sex disparity may also be attributed to ascertainment bias, as short stature in

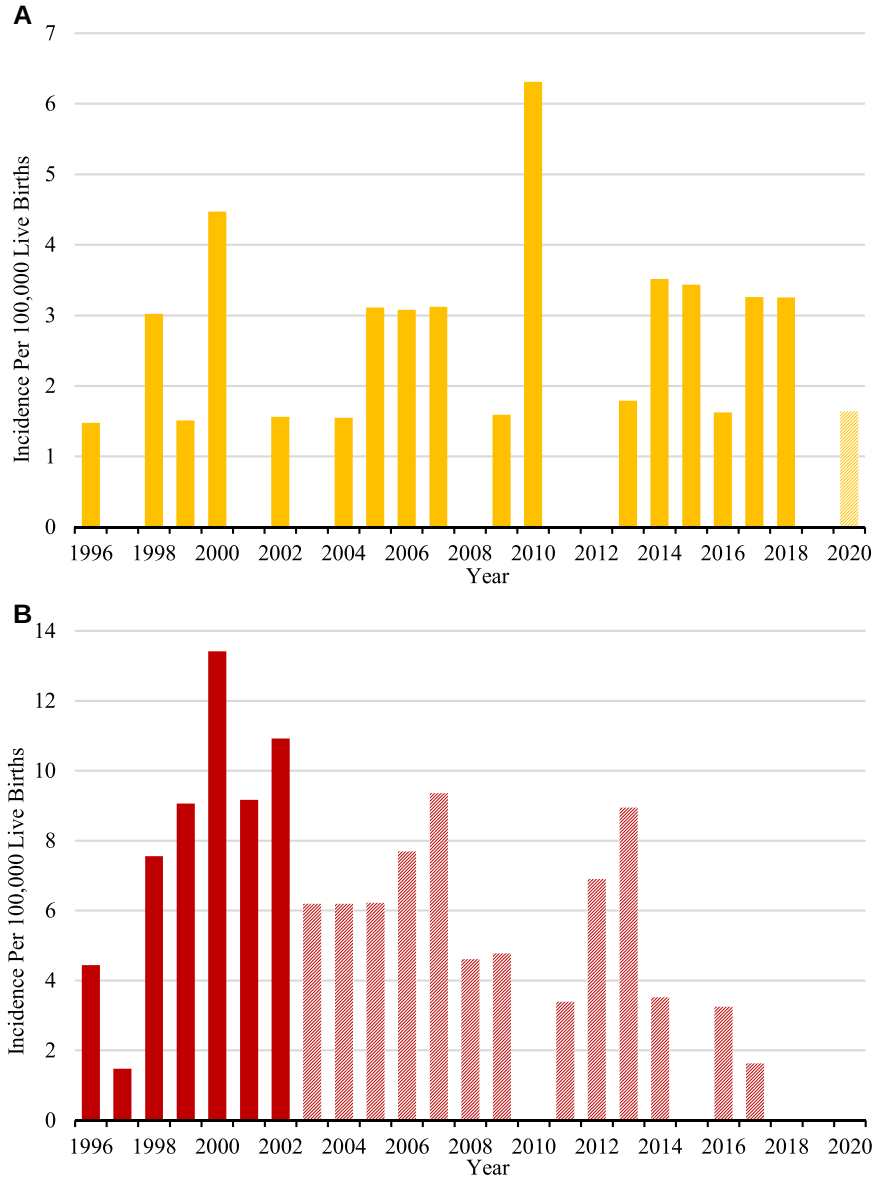

Figure 4. The incidence of congenital combined pituitary hormone deficiency (cCPHD) in Denmark diagnosed before age 1 year (A), and at age 1-17 years (B). Solid columns represent the incidence estimations that are not influenced by right truncation, as all patients born in these years had turned 1 year (A), or 18 years (B) by the end of the observation period. Hatched columns represent incidence estimations that may be influenced by right truncation.

boys tends to become a greater cause for concern and more often conveys hormonal investigations than in girls (9, 12). Furthermore, boys show early apparent clinical signs of hypovirilization, which could account for the male predominance, especially among patients diagnosed before 1 year of age.

We found GHD to be the most abundant hormone deficiency, followed by TSH deficiency. These findings are supported by several previous studies (7, 26). Conversely, other studies report FSH/LH deficiencies as the second most frequent (3, 9, 25). The discrepancy may be explained by differences in study design, hormone deficiency criteria, and follow-up period. Additionally, many studies are based on patients with GHD and 1 or more additional hormone deficiencies. Therefore, it was interesting to observe that deficiency of TSH was the most frequent deficiency in the patients diagnosed at age <1 year. Additionally, we identified 9 patients with cCPHD who did not have GHD. Such patients will be overlooked in studies based on the diagnosis of GHD, which fail to examine the full spectrum of cCPHD.

A diagnosis peak was seen at age <1 year, with smaller peaks at age 6, 11, and 14 years. This highlights the broad age spectrum of clinical onset of cCPHD. The early peak <1 year represented the diagnosis of the most severe cCPHD cases, as the median number of hormone deficiencies at diagnosis and at last follow-up was significantly higher in this subgroup. The highest incidence of cCPHD was seen in the 1-17 years subgroup, which underscores the need of testing all pituitary hormone axes through childhood and adolescence when 1 or more axes are deficient.

In clinical practice and in the literature, the definition of PHD in childhood may be subject to variations. To minimize the risk of misclassification of late puberty as hypogonadotropic

Table 5. National incidences and incidence rates of congenital combined pituitary hormone deficiency from 1996 to 2020

Age at cCPHD diagnosis	Period[a]	Number of patients	Incidence per 100 000 live births	Incidence rates per million live births per year
0-17 years	1996-2002	48	10.34 (7.79-13.72)	5.74 (4.33-7.62)
0-17 years	1996-2020[b]	116	7.38 (6.15-8.85)	4.10 (3.42-4.92)
0-19 years	1996-2000	35	10.46 (7.51-14.56)	5.23 (3.76-7.28)
Subgroups				
<1 year	1996-2019	30	1.98 (1.39-2.84)	19.8 (13.9-28.4)
1-17 years	1996-2002	37	7.97 (5.77-11.00)	4.69 (3.39-6.47)

Incidences and incidence rates with 95% CI in brackets.
[a]To eliminate the influence of right truncation, incidences were calculated in various periods according to the included age ranges. This was done to ensure all patients reached 1/18/20 years of age in the observation period.
[b]For completeness, we calculated the incidence of cCPHD diagnosed before age 18 years for the whole period 1996-2020.

hypogonadism, we chose to define sex-specific age ranges, within which biochemical analyses of the hypothalamic–pituitary–gonadal axis should be performed. The risk of misclassification of hypogonadotropic hypogonadism increases with decreasing age of diagnosis, but with an increasing number of hormone deficiencies clinicians tended to investigate the gonadal hormone axes at an earlier age. The hormone deficiency criteria, therefore, had to reflect the clinical setting.

Furthermore, we chose to include patients who developed hypothyroidism during GH therapy even though evidence suggests that GH therapy may affect thyroid hormone levels per se. Some studies suggest that the changes in thyroid hormone levels during GH therapy are caused by increased peripheral thyroxine to triiodothyronine conversion (27, 28), whereas others suggest unmasking of latent central hypothyroidism (29–31). We included patients with GHD and TSH deficiency, as 2 recent studies on children with nonacquired isolated GHD support the latter mechanism (29, 30), and as our included patients had repeating levels of free thyroxine/thyroxine below the normal reference range.

The strengths of our study include the use of national registries with unique high completeness regarding patient diagnoses and birth counts, our supplementary tertiary hospital diagnosis code search, the method validation, the broadness of our diagnosis code searches for all-cause pituitary deficiency and pituitary malformation, and our hospital file validation of the cCPHD diagnosis by uniform criteria.

Our study also had limitations. A few children with cCPHD may have been overlooked due to incorrect diagnoses, lack of correct reporting to the DNPR, or lack of referral to a tertiary hospital. On the other hand, acquired causes of CPHD may have been undiagnosed in a few children.

The definition and validation of the hormonal deficiencies could be questioned, including inclusion of children with partly missing information and the potential of incorrect reference values for the hormone assays used in clinical practice. Despite our validation efforts, we had to rely on the diagnostic practice to some extent in this retrospective study. We were likewise unable to evaluate the extent of delay from disease onset to diagnosis.

The diagnosis of cCPHD may be challenging, especially in those with normal MRI findings. However, other studies have shown that normal anatomy of the pituitary gland does not exclude abnormal function and MRI findings are not included in the Danish or international diagnosis criteria guidelines (1, 3, 6, 16–20). A few patients did not have MRI performed, which could lead to minor underestimation or overestimation of the rate of pituitary, midline, and other cerebral abnormalities. Furthermore, as not all patients had reached 18 years' age at last follow-up, not all late-onset hormonal deficiencies may have been recorded. Lastly, the external validity of our incidence estimates may be limited due to differences in population characteristics such as ethnicity and the frequency of consanguinity and founder mutations (2, 9).

Conclusion

In this national registry study, the incidence of cCPHD diagnosed before age 18 years was calculated to be 10.34 (7.79-13.72) per 100 000 live births with an incidence rate of 5.74 (4.33-7.62) per million live births per year. cCPHD diagnosed before age 1 year had by far the highest incidence rate, with the highest number of hormonal deficiencies and with 96.7% having abnormal brain MRI findings. On the other hand, cCPHD diagnosed at age 1-17 years had the highest incidence, emphasizing the need for investigations of cCPHD throughout childhood and adolescence in children with isolated PHD. The data presented provide information that can be used to shape future screening programs for children at risk of developing cCPHD. Further research should be undertaken to investigate, for instance, the incidence of cCPHD in other populations, the genetics of cCPHD, genotype–phenotype relations, the management of cCPHD, and the correlation between the clinical signs and symptoms at onset and the disease course on follow-up.

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Author contributions

H.T.C. conceived the original idea and supervised the project. L.K.J. and H.T.C. performed the literature search and acquired the project funding. L.K.J. collected the data from the Danish National Patient Registry, Statistics Denmark, and the hospital files at the 4 tertiary hospitals. M.C.B. and L.K.J. collected the data from the hospital files at Kolding Hospital. L.K.J., H.T.C., R.B.J., D.H., N.B.H., and A.R.C. contributed to the study design and to the analysis and interpretation of data. L.K.J. and HTC both directly accessed and verified the underlying data. L.K.J. led the statistical analyses. L.K.J. and H.T.C. drafted the original manuscript. All authors contributed to the writing and revision of the final manuscript.

Disclosures

Authors have no financial or other conflicts of interest to declare. The Funders had no role in the design of this study, in the writing of this report, or in the decision to submit the manuscript for publication.

Data Availability

Restrictions apply to the availability of some or all data generated or analyzed during this study to preserve patient confidentiality or because they were used under license. The corresponding author will on request detail the restrictions and any conditions under which access to some data may be provided. The de-identified patient data that underlie this study are available to researchers upon approval by the Region of Southern Denmark. The full study protocol is available at https://portal.findresearcher.sdu.dk/en/publications/the-incidence-of-congenital-combined-pituitary-hormone-deficiency and the Stata do-files are available to anyone with a request. Proposals can be submitted up to 3 years following article publication and should be directed to henrik.christesen@rsyd.dk.

Clinical Trials Information

ClinicalTrials.gov ID:NCT05334563 (registered April 19, 2022).

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