

Incidence of Congenital Combined Pituitary Hormone Deficiency in Denmark – a national observational study

Date of the document: March 20th 2022.

Background

Congenital combined pituitary hormone deficiency (cCPHD) is defined as the partial or complete loss of more than one hormone secreted from the pituitary gland, caused by genetic or prenatal factors. Combined pituitary hormone deficiency (CPHD) is a broader term covering both congenital and acquired forms (1-4).

The incidence and prevalence of cCPHD are not known.

Pituitary hormone deficiencies most commonly occur in the adenohypophysis involving growth hormone (GH), thyroid-stimulating hormone (TSH), corticotropin (ACTH), prolactin, luteinizing hormone (LH) and follicle-stimulating hormone (FSH). More rarely, the neurohypophysis is also affected, resulting in vasopressin deficiency (3, 5-7).

Symptoms and clinical features of cCPHD are variable, even within the same family, including the extent and severity of the hormone deficiencies, the age of clinical onset and the cerebral comorbidity. Moreover, delay inadequate treatment may affect the clinical outcome and prognosis (1, 4-6, 8-10).

Newborns with clinical overt cCPHD may present in the first days of life with hypoglycemia, electrolyte abnormalities, hypothermia, conjugated hyperbilirubinemia, poor appetite, vomiting, and failure to thrive. In boys, gonadotropin deficiency may present with hypogonadism including micropenis. Patients with vasopressin deficiency may have central diabetes insipidus from birth with polyuria and quickly develop severe hypernatremic dehydration (4, 11).

Delayed onset of cCHPD may occur as a gradual process, usually with growth hormone deficiency (GHD) as the first manifestation, followed by TSH deficiency and later other hormone deficiencies including FSH/LH deficiency (10, 12).

MRI of the brain and the pituitary region commonly, but not always, reveal anatomical abnormalities including aplasia or hypoplasia of the adenohypophysis and/or pituitary stalk. Aplasia, hypoplasia, or ectopic position of the neurohypophysis may be seen. Associated brain abnormalities may include septo-optic dysplasia (SOD) and aplasia/hypoplasia of other brain structures, especially in the midline(4, 13-15). Syndromes, including cCPHD with other brain or organ abnormalities, include heterotaxy syndrome, Worster-Drought Syndrome, congenital proprotein convertase 1/3 deficiency, FOXA2 mutation syndrome and many others (16-19).

Genetic testing can be helpful to understand the diverse phenotypic picture of cCPHD (20, 21). The development of the pituitary gland is dependent on the sequential temporal and spatial expression of transcription factors and signaling molecules and occurs in a well-defined sequence of events. Some of these factors include *HESX1*, *LHX3*, *LHX4*, *POU1F1*, *PROP1*, *SIX6*, *OTX2*, *PITX2*, *GLI2*, and *SOX3*, all of which have been shown to play a role in the development and maturation of the pituitary gland (22).

Disruption of this cascade due to mutations in any of these gene products affects the ontogeny of one or several of the pituitary cell types and ultimately leads to hormone deficiency with or without extra-pituitary abnormalities (3, 7, 23). Previous studies have shown a higher prevalence of genetic mutations in familial cases, where both dominant, recessive and X-linked inheritance has been demonstrated. Still, most patients with cCPHD have remained genetically unexplained (2, 6, 7).

The treatment of cCPHD consists of the substitution of the deficient pituitary hormones or their target hormones, including growth hormone, thyroid hormone, sex hormones, glucocorticoids, and vasopressin. Eventual other cerebral or other organ syndromal manifestations must be identified and managed.

Objectives

The aim of this study is to estimate the national incidence of cCPHD diagnosed before age 18 years, with reporting of separate incidences for patients diagnosed at age <1 year, 1–8 years, and 9–17 years, and hormone deficiency characteristics and brain MRI abnormalities in the patients.

Materials and methods

Method and design

This study is a national study based on ICD10 diagnosis codes from The Danish National Patient Registry (DNPR) and the four tertiary centers: Odense University Hospital, Aarhus University Hospital, Rigshospitalet, and Aalborg University Hospital. The DNPR contains a unique registration of all hospitalized patients in the country since 1977; with WHO ICD10 diagnosis codes since 1994. The registry identifies patients based on the unique personal identification number of each person living in Denmark. The diagnosis code searches at the four tertiary centers are made in addition to the DNPR search to provide a higher probability of identifying all patients with cCPHD in Denmark.

The DNPR and the four local hospital searches will be performed using the ICD10 codes E23.0-E23.9 (pituitary hormone deficiencies and other diseases in the pituitary gland), Q89.2G (congenital malformation of the pituitary), and Q04.0-Q04.9 (other congenital brain malformations) for the 25-year period: 1st of January 1996 – 31st of December 2020. Patients with the additional diagnoses C69.0-C72.9 (cancer in eyes, brain, other parts of the CNS), C75.1-C75.3 (cancer in the pituitary, corpus pinealis and craniopharyngeomas), D35.2 - D35.4 (benign tumours of the pituitary gland, corpus pineale, or ductus craniopharyngei) and D33.0-D33.9 (benign tumours in the brain and spinal cord) will be excluded. Patients with the ICD10 diagnosis codes A80.0-A89.9 (central nervous system infections) and/ or I60.0-I64.9 (nontraumatic subarachnoid hemorrhage, nontraumatic intracerebral hemorrhage, other and unspecified nontraumatic intracranial hemorrhage, cerebral infarction, stroke

not specified as haemorrhage or infarction) registered before the time of the E23.0-E23.9 diagnosis will also be excluded.

For the identified patients a retrospective hospital file review will be performed to confirm the cCPHD diagnosis and to exclude patients who meet one of the exclusion criteria listed below.

Exclusion criteria

The hospital file review will lead to exclusion of patients with

- 1) ICD-10 diagnosis code indicating acquired CPHD
- 2) No available hospital files
- 3) Less than two documented secondary/tertiary hormone deficiencies
- 4) Acquired CPHD secondary to cerebral infections, tumors, trauma, autoimmunity or other identified cause.

All hormone deficiencies will be retrospectively validated using a set of hormone deficiency criteria.

The criteria have been defined by five experienced pediatric endocrinologists, including a representative from each of the tertiary centers, and have been based on national and international endocrine guidelines, published literature, and the clinical practice at tertiary centers.

Study population

The study aims to include all patients in Denmark diagnosed with cCPHD in the 25-year period 1996-2020. The search will be restricted to only include children under the age of 15 years at the time of registration of the first ICD-10 diagnosis code E23.0-E23.9, Q89.2G, or Q04.0-Q04.9.

Data and data storage

The data used in this project are found in patient journals and include the following: birthdate, sex as indicated by the presence of male/female genitals (male/female), born in Denmark (yes/no), presence of ICD-10 diagnosis codes of interest (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 hospital file descriptions of clinical features of hormone deficiencies (yes/no).

The researchers do not have direct access to the patient journals. Data will therefore be passed on to the researchers by a doctor employed at the department responsible for the treatment of the patient. This differs in cases where the researcher is at the same time employed at the department and therefore have access to the data. The researcher will then pass on the information to this project directly. Data will not be passed on to third parties.

Data will be registered in RedCap and stored in Sharepoint in collaboration with Open Patient data Explorative Network (OPEN), https://open.rsyd.dk/index_en.html. The procedures at OPEN at Odense University Hospital ensures that the study will comply with the General Data Protection Regulation and the Data Protection Act.

Patient inclusion flow

The patient inclusion flow is resumed in Figure 2:

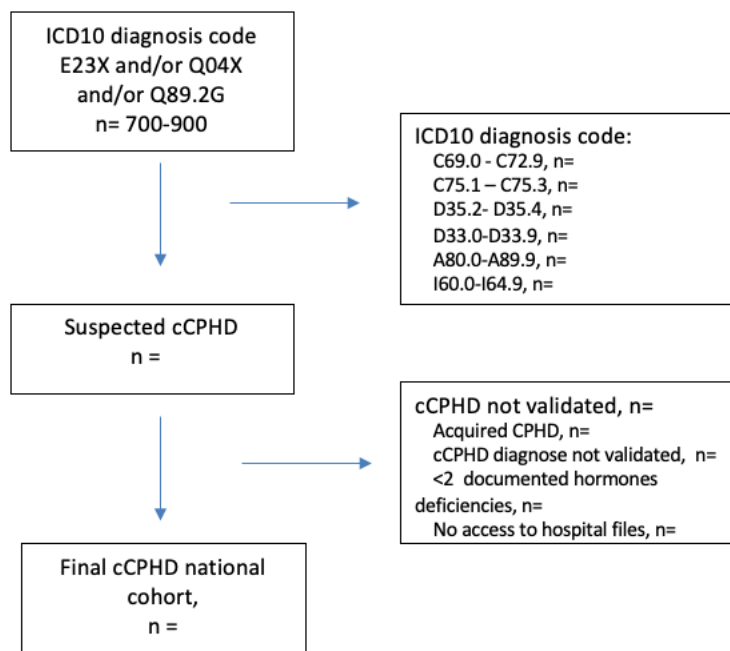


Figure 2. Patient inclusion flow chart.

Statistics

The incidence of cCPHD will be estimated by use of background population data retrieved from Statistics Denmark.

Ethics

The study will comply with the Helsinki declaration.

Permissions

This study was approved by The Region of Southern Denmark (j.no. 20/58158).

Participatory design

Our protocol is designed after preliminary contacts with 10 parents to children with cCPHD at Odense University Hospital. The parents expressed a need of dissemination of several aspects of cCPHD to improve future management of this rare disease. Some stressed the need of identification of early

signs of cCPHD to contribute to fastest possible diagnosis, as diagnosis delay has been a major, sometimes life-threatening problem for their children, e.g. severe hypernatremic dehydration with a sodium of 180 mmol/L in a neonate with cCPHD and diabetes insipidus. Others stressed the benefits of dissemination of good results of early and centralized expert treatment including androgen therapy in infant boys with hypogonadism. Others wanted to pass on a message that children with non-syndromic cCPHD can live a normal life with normal school performance. Others stressed that CPHD should be looked for in syndromes with potential CPHD or children with an unknown syndrome to optimize e.g. their growth and cerebral function. One parent has agreed to be a part of the project group.

Project group

Louise Kjersgaard Jakobsen, research year medical student

Rikke Beck Jensen, Consultant, ph.d, MD, Dept. Of Growth and Reproduction, Rigshospitalet. Study site collaborator

Niels Holtum Birkebæk, Consultant, ph.d, MD, Dept. of Pediatrics, Aarhus University Hospital Skejby, Denmark. Study site collaborator.

Dorte Hansen, Consultant, Associate Professor, ph.d, MD, Hans Christian Andersen Children's Hospital, Odense University Hospital, Denmark. Project co-supervisor.

Ann-Margrethe Rønholt Christensen, Associate professor, Dept. of Pediatrics, Aalborg University Hospital, Denmark. Study site collaborator.

Maja Carsting Bjerrum, MD, Hans Christian Andersen Children's Hospital, Odense University Hospital, Denmark.

Henrik Thybo Christesen, Consultant, Professor, ph.d, MD, Hans Christian Andersen Children's Hospital, Odense University Hospital, Denmark. Project supervisor.

Pernille Thomsen, parent of a 2-y-old child with cCPHD and SOD.

Perspectives

Given that cCPHD is a rare and complex, potentially life-threatening disease, the paucity of literature on the subject and the lack of estimates of incidence and prevalence, our study is expected to provide important information to be published. A good understanding of the illness is crucial and may lead to patients getting diagnosed earlier. Early diagnosis and fast treatment is very important for the clinical outcome and prognosis. This study is therefore expected to contribute with important new information.

Dissemination of results

The study will be published as one or two papers in peer-reviewed international journals. A Danish and English press release will be made at the time of publication. Oral presentation(s) or poster(s) will be presented at national meetings, e.g. The Danish Society of Paediatric Endocrinology (DSPE) and international meetings, e.g. the annual European Society of Paediatrics (ESPE) meeting. A popular talk is scheduled at a meeting in patient organization The Danish Pituitary Network.

Budget

Received grants will be transferred directly to an account belonging to Odense University Hospital, Region of Southern Denmark or HCA Forskning, Odense University Hospital.

This study has been initiated by Henrik Thybo Christesen and has been shaped and planned by the members of the product group. Funding organizations do not play a role in the study design; in the

collection, analysis and interpretation of data; in the writing of the article; or in the decision to submit the article for publication. There are no economic interests or connections between the researchers and the research funds applied.

| | | | DKK |
|----------------------|--|--|------------|
| Salaries | Scholar stipendium, 6 months | | 60.000 |
| Running costs | | | |
| | Hospital file search incl. travel expenses | | 12.000 |
| | Secretary assistance | | 10.000 |
| | The Danish National Patient Registry | | 15.000 |
| Miscellaneous | Publication fee (open access) | | 15.000 |
| Total budget | | | 112.000 |

Funds obtained

This work was supported by Odense University Hospital Fund (j.no. A4599), and Dagmar Marshalls Fund (29/04/2021).

References

1. Romero CJ, Nesi-França S, Radovick S. The molecular basis of hypopituitarism. *Trends Endocrinol Metab.* 2009;20(10):506–16.
2. Romero CJ, Pine-Twaddell E, Radovick S. Novel mutations associated with combined pituitary hormone deficiency. *J Mol Endocrinol.* 2011;46(3):93–102.
3. Choi JH, Jung CW, Kang E, Kim YM, Heo SH, Lee BH, et al. Rare Frequency of Mutations in Pituitary Transcription Factor Genes in Combined Pituitary Hormone or Isolated Growth Hormone Deficiencies in Korea. *Yonsei Med J.* 2017;58(3):527–32.
4. Haim-Pinhas H, Kauli R, Lilos P, Laron Z. Growth, development, puberty and adult height of patients with congenital multiple pituitary hormone deficiencies. *Growth Horm IGF Res.* 2016;27:46–52.
5. Cerbone M, Dattani MT. Progression from isolated growth hormone deficiency to combined pituitary hormone deficiency. *Growth Horm IGF Res.* 2017;37:19–25.
6. Child CJ, Blum WF, Deal C, Zimmermann AG, Quigley CA, Drop SL, et al. Development of additional pituitary hormone deficiencies in pediatric patients originally diagnosed with isolated growth hormone deficiency due to organic causes. *Eur J Endocrinol.* 2016;174(5):669–79.
7. De Rienzo F, Mellone S, Bellone S, Babu D, Fusco I, Prodam F, et al. Frequency of genetic defects in combined pituitary hormone deficiency: a systematic review and analysis of a multicentre Italian cohort. *Clin Endocrinol (Oxf).* 2015;83(6):849–60.
8. Brodsky MC, Conte FA, Taylor D, Hoyt CS, Mrak RE. Sudden death in septo-optic dysplasia. Report of 5 cases. *Arch Ophthalmol.* 1997;115(1):66–70.

9. Cameron FJ, Khadilkar VV, Stanhope R. Pituitary dysfunction, morbidity and mortality with congenital midline malformation of the cerebrum. *Eur J Pediatr*. 1999;158(2):97–102.
10. Ascoli P, Cavagnini F. Hypopituitarism. *Pituitary*. 2006;9(4):335–42.
11. Braslavsky D, Keselman A, Chiesa A, Bergadá I. [Diagnosis of congenital endocrinological disease in newborns with prolonged jaundice and hypoglycaemia]. *An Pediatr (Barc)*. 2012;76(3):120–6.
12. Toogood AA, Stewart PM. Hypopituitarism: clinical features, diagnosis, and management. *Endocrinol Metab Clin North Am*. 2008;37(1):235–61.
13. Birkebaek NH, Patel L, Wright NB, Grigg JR, Sinha S, Hall CM, et al. Endocrine status in patients with optic nerve hypoplasia: relationship to midline central nervous system abnormalities and appearance of the hypothalamic-pituitary axis on magnetic resonance imaging. *J Clin Endocrinol Metab*. 2003;88(11):5281–6.
14. Blum WF, Klammt J, Amselem S, Pfaffle HM, Legendre M, Sobrier ML, et al. Screening a large pediatric cohort with GH deficiency for mutations in genes regulating pituitary development and GH secretion: Frequencies, phenotypes and growth outcomes. *EBioMedicine*. 2018;36:390-400.
15. Larson A, Nokoff NJ, Meeks NJ. Genetic causes of pituitary hormone deficiencies. *Discov Med*. 2015;19(104):175-83.
16. Omer A, Haddad D, Pisinski L, Krauthamer AV. The Missing Link: A Case of Absent Pituitary Infundibulum and Ectopic Neurohypophysis in a Pediatric Patient with Heterotaxy Syndrome. *Journal of radiology case reports*. 2017;11(9):28-34.
17. Bas F, Darendeliler F, Yapici Z, Gokalp S, Bundak R, Saka N, et al. Worster-Drought syndrome (congenital bilateral perisylvian syndrome) with posterior pituitary ectopia, pituitary

hypoplasia, empty sella and panhypopituitarism: a patient report. *J Pediatr Endocrinol Metab.* 2006;19(4):535-40.

18. Pepin L, Colin E, Tessarech M, Rouleau S, Bouhours-Nouet N, Bonneau D, et al. A NEW CASE OF PCSK1 PATHOGENIC VARIANT WITH CONGENITAL PROPROTEIN CONVERTASE 1/3 DEFICIENCY AND LITERATURE REVIEW. *J Clin Endocrinol Metab.* 2018.

19. Vajravelu ME, Chai J, Krock B, Baker S, Langdon D, Alter C, et al. Congenital Hyperinsulinism and Hypopituitarism Attributable to a Mutation in FOXA2. *J Clin Endocrinol Metab.* 2018;103(3):1042-7.

20. Romero CJ, Nesi-Franca S, Radovick S. The molecular basis of hypopituitarism. *Trends Endocrinol Metab.* 2009;20(10):506-16.

21. Chung TT, Koch CA, Monson JP. Hypopituitarism. In: De Groot LJ, Chrousos G, Dungan K, Feingold KR, Grossman A, Hershman JM, et al., editors. *Endotext*. South Dartmouth (MA): MDText.com, Inc.; 2000.

22. Romero CJ, Pine-Twaddell E, Radovick S. Novel mutations associated with combined pituitary hormone deficiency. *J Mol Endocrinol.* 2011;46(3):R93-r102.

23. Kelberman D, Rizzoti K, Lovell-Badge R, Robinson IC, Dattani MT. Genetic regulation of pituitary gland development in human and mouse. *Endocr Rev.* 2009;30(7):790-829.