Mortality in Children With Early-Detected Congenital Central Hypothyroidism

Nitash Zwaveling-Soonawala,[1]* Jolanda C. Naafs,[1]* Paul H. Verkerk,[2] and A. S. Paul van Trotsenburg[1]

[1]Department of Pediatric Endocrinology, Emma Children's Hospital, Academic Medical Center, 1100 DD Amsterdam, Netherlands; and [2]Department of Child Health, Netherlands Organization for Scientific Research, 2301 CE Leiden, Netherlands

Context: Approximately 60% to 80% of patients with congenital central hypothyroidism (CH-C) have multiple pituitary hormone deficiencies (MPHDs), making CH-C a potentially life-threatening disease. Data on mortality in patients with CH-C are lacking.

Objective: To study the mortality rate in pediatric patients with early-detected and treated CH-C in the Netherlands and to investigate whether causes of death were related to pituitary hormone deficiencies.

Methods: Overall mortality rate, infant mortality rate (IMR), and under-5 mortality rate were calculated in all children with CH-C detected by neonatal screening between 1 January 1995 and 1 January 2013. Medical charts were reviewed to establish causes of death.

Results: A total of 139 children with CH-C were identified, of which 138 could be traced (82 with MPHD, 56 with isolated CH-C). Total observation time was 1414 years with a median follow-up duration of 10.2 years. The overall mortality rate was 10.9% (15/138). IMR and under-5 mortality rate were 65.2/1000 (9/138) and 101.4/1000 (14/138), respectively, compared with an IMR of 4.7/1000 and under-5 mortality of 5.4/1000 live-born children in the Netherlands during the same time period ($P < 0.0001$). Main causes of death were severe congenital malformations in six patients, asphyxia in two patients, and congenital or early neonatal infection in two patients. Pituitary hormone deficiency was noted as cause of death in only one infant.

Conclusion: We report an increased mortality rate in patients with early-detected CH-C that does not seem to be related to endocrine disease. This suggests that mortality due to pituitary insufficiency is low in patients with early-detected and early-treated CH-C. (***J Clin Endocrinol Metab*** **103: 3078–3082, 2018)**

Congenital hypothyroidism may be of thyroidal origin [congenital thyroidal hypothyroidism (CH-T)] or central (*i.e.* hypothalamic-pituitary) origin [congenital central hypothyroidism (CH-C)]. CH-C is less common than CH-T, with an estimated prevalence of 1 in 16,000 vs 1 in 3000 live births (1). From a public health perspective, CH-C is an important disease because of associated potentially life-threatening multiple pituitary hormone deficiencies (MPHDs). Undiagnosed central adrenal insufficiency and growth hormone deficiency may cause neonatal hypoglycemia and/or circulatory insufficiency (2). Approximately 60% to 80% of patients with CH-C have MPHD (2–5).

Worldwide, most neonatal CH screening programs are TSH based and effectively detect CH-T but not CH-C. Only a few countries use screening methods in which besides TSH also total or free T4 is measured, allowing CH-C detection.

ISSN Print 0021-972X ISSN Online 1945-7197
Printed in USA

Received 21 March 2018. Accepted 4 June 2018.
First Published Online 7 June 2018

*These authors contributed equally to this study.

Abbreviations: CDG, congenital disorder of glycosylation; CH-C, congenital central hypothyroidism; CH-T, congenital thyroidal hypothyroidism; IMR, infant mortality rate; MPHD, multiple pituitary hormone deficiency; TBG, T4-binding globulin; TNO, Netherlands Organization for Scientific Research.

The Dutch neonatal CH screening program began in 1995 and consists of a three-step approach: measuring T4 in all newborns with TSH determination in the lowest 20% of T4 concentrations and T4-binding globulin (TBG) measurement in the lowest 5% of T4 concentrations. This screening approach is very effective in detecting CH-C (1). As a result, the reported prevalence of CH-C in the Netherlands is one of the world's highest (2). Early detection and treatment of CH-C is assumed to reduce morbidity and mortality, especially in children with MPHD (2, 6). However, actual data on morbidity and mortality in early- and late-diagnosed CH-C, with or without MPHD, are lacking.

Currently, we are conducting a nationwide follow-up study on morbidity and developmental outcome in children with CH-C, detected by neonatal screening, since 1995. During the initial part of the study (*i.e.*, tracing all Dutch patients with CH-C), we observed a high pediatric mortality rate. This was in contrast with the assumption that early detection and treatment reduces mortality. To gain more insight into the cause(s) of death among the deceased children, we reviewed their medical charts.

Methods

Since the start of the Dutch neonatal screening program in 1981, the Netherlands Organization for Scientific Research (TNO Leiden) has registered all abnormal neonatal screening results for CH plus final diagnoses by sending out questionnaires to treating pediatricians at several time points. The first questionnaire is sent out in the first month after a child is referred; the second questionnaire is sent out at the age of 4 years.

To verify the diagnosis of CH-C and to trace all patients with CH-C detected by screening since 1995 for a long-term follow-up study, we sent out a third questionnaire between 2013 and 2015. Subsequently, we received several notifications of deaths of patients with CH-C, prompting us to develop the current study to collect data on mortality. If a patient died, we asked to be sent all medical details to be able to assess the cause of death. Medical charts of deceased patients were reviewed by two clinicians (N.Z.-S. and J.C.N.).

The year 1995 was chosen as the start of the study period because at that time measurement of TBG in the lowest 5% of T4 concentrations was added to the T4-reflex TSH strategy in the Netherlands and because of anticipated difficulties in tracing data from patients born between 1981 and 1995. The use of the TNO database was in accordance with the Privacy Regulations of the Privacy Committee of the Dutch CH Screening Board. The study protocol was approved by the local medical ethics committee.

Statistical analysis

Our primary outcome was overall mortality rate, specified as infant mortality rate (IMR, probability of dying under 1 year of age) and under-5 mortality rate (probability of dying between birth and exactly age 5; both expressed per 1000 live births). Under-5 mortality was chosen because all children were followed until at least the age of 5 (follow-up until the age of 18 was not available for the entire cohort). Infant and under-5 mortality rates among children with CH-C with or without MPHD were compared with mortality rates in the Netherlands in the same period (*i.e.*, between 1 January 1995 and 1 February 2013), as registered by Statistics Netherlands. Children with CH-C were excluded from Dutch birth and mortality rates. Length of follow-up was defined as the time between the birth date and the date of sending out the third questionnaire or the date of the patient's hospital visit in the context of our current follow-up study.

Results

The TNO database contained 141 patients classified as having CH-C detected by neonatal screening between 1 January 1995 and 1 January 2013. Total observation time was 1414 years, with a median follow-up duration of 10.2 years.

Two patients did not have CH-C, and one patient with MPHD could not be traced. Of the remaining 138 patients, 82 patients had MPHD (69.5% male), and 56 patients had isolated CH-C (82.4% male). Three patients had isolated CH-C combined with a congenital disorder of glycosylation (CDG) syndrome.

In the studied cohort, 15 patients (10 with MPHD and 5 with isolated CH-C) died (overall mortality rate, 10.9%; 108.7 per 1000).

Nine patients died within the first year of life, resulting in an IMR of 65.2 per 1000. The Dutch IMR in the same period was 4.7 per 1000 live born children (OR, 14.5; 95% CI, 7.6 to 29.3; $P < 0.0001$). Fourteen patients died before the age of 5, corresponding with an under-5 mortality of 101.4 per 1000 live-born children, compared with 5.4 per 1000 live-born children in the Netherlands during the same time period (OR, 21.1; 95% CI, 12.1 to 36.6; $P < 0.0001$).

Patient characteristics and causes of death are summarized in Table 1, which shows several congenital malformations, birth asphyxia, and infections as the leading causes of death. Cause of death was attributed to pituitary hormone deficiency in one patient (case 9).

Additional diagnostic information was available for two patients with isolated CH-C. In case 7, CH-C was most likely caused by severe encephalopathy following birth asphyxia. In case 8, brain imaging via MRI was normal, but a TSH-releasing hormone test confirmed the diagnosis of isolated CH-C.

Discussion

The overall mortality rate in pediatric patients with CH-C detected by neonatal screening was 10.9% (15/138).

Table 1. Cause of Death and Diagnosis in 15 Children With CH-C Detected by Neonatal Screening

Case	Sex	GA (wk)	BW (kg)	Age at Death (y)	Cause of Death	Diagnoses	Treatment		
							L-T4	HCT	GH
1	M	38 2/7	4.3	0.1	Renal and respiratory insufficiency	Joubert syndrome, intestinal malrotation, severe cerebral malformation, MPHD	Yes	Yes	No
2	M	36 6/7	2.3	0.1	Birth asphyxia, intracerebral bleeding	6p deletion syndrome, aortic coarctation, MPHD	Yes	No	No
3	M	38 1/7	3.0	0.1	Vena cava inferior thrombosis	Probable CDG syndrome, MPHD	Yes	Yes	No
4	M	37 1/7	2.8	0.1	Respiratory insufficiency	Congenital toxoplasmosis, MPHD	Yes	Yes	No
5	F	42 1/7	3.8	0.3	Cerebral malformation and insufficiency	Holoprosencephaly with hydrocephalus, MPHD		No[a]	
6	F	40 1/7	4.0	0.4	Circulatory insufficiency	Congenital heart disease, NEC, isolated CH-C	Yes	No	No
7	F	37 1/7	2.1	0.4	Respiratory insufficiency during aspiration pneumonia	Birth asphyxia after placental abruption, severe encephalopathy, isolated CH-C	Yes	No	No
8	M	34 4/7	2.7	0.6	Respiratory insufficiency	Severe lung hypoplasia, renal dysplasia, isolated CH-C	Yes	No	No
9	M	34 5/7	2.8	0.9	Cardiorespiratory arrest during adrenal crisis	Congenital pituitary malformation, MPHD	Yes	Yes	Not yet
10	M	37 5/7	2.9	1.0	Status epilepticus during meningitis	Epilepsy, MPHD	Yes	Yes	Not yet
11	F	39	1.5	1.6	Respiratory insufficiency	Partial trisomy 19p and deletion Xp22, truncus arteriosus, holoprosencephaly, MPHD (central hypothyroidism and diabetes insipidus)	Yes	No	No
12	M	42	3.9	2.1	Nephrotic syndrome and infection	Congenital heart disease, cystic kidneys, epilepsy, MPHD	Yes	Yes	No
13	F	37	3.2	6.7	Respiratory insufficiency during pneumonia with sepsis	Bacterial meningitis with hypothalamic infarcts, West syndrome, MPHD	Yes	Yes	No
14	M	40 1/7	2.9	1.1	Cardiorespiratory arrest during sepsis	CDG syndrome, isolated CH-C	Yes	No	No
15	F	37	2.1	1.7	Sepsis with multiorgan failure	CDG syndrome, isolated CH-C	Yes	No	No

Abbreviations: BW, birth weight; F, female; GA, gestational age; GH, growth hormone; HCT, hydrocortisone; L-T4, levothyroxine; M, male; NEC, necrotic enterocolitis.

[a]Parents declined endocrine treatment.

The infant mortality and under-5 mortality rates were 6.5% (9/138) and 10.1% (14/138), respectively. Severe congenital cerebral malformations, congenital heart defects, birth asphyxia, and infections were important causes of death, whereas hypopituitarism was not. Overall, CH-C was considered a comorbidity rather than the primary diagnosis in this group of deceased patients.

This is a report on mortality in an early-detected CH-C cohort originating from a screened population. Our results indicate that mortality due to pituitary deficiencies is low in early-treated patients. Despite early detection and treatment, one patient had died due to acute adrenal insufficiency during an infection, emphasizing the severity of MPHD. Unfortunately, mortality rates in unscreened populations are lacking. Early death in children with unrecognized CH-C might partly explain the lower observed CH-C prevalence in these countries (7).

An estimation of how many deaths or hypoglycemic events were prevented by early detection would be very valuable. Unfortunately, these data are not available. We are currently performing a long-term follow-up study of all children with CH-C detected by neonatal screening from 1995 onward. In this study, data on perinatal history, including occurrence of hypoglycemia, are being collected.

Although the Dutch neonatal screening effectively detects children with CH-C, missed cases might occur. Missed cases are not systematically registered, although pediatricians are encouraged to report these patients to TNO. In a recent study among Dutch children with nonacquired, presumed isolated growth hormone deficiency, 29 cases of probable CH-C that had been missed by neonatal screening were detected over 10 years (8). This suggests that the Dutch neonatal screening misses at least 2.9 children with CH-C per year. Extrapolating these data to our cohort indicates that ~52 children were missed by neonatal screening in this 18-year period; thus, 27% (52/191) of all CH-C cases were missed. From countries using different T4-based screening programs, higher percentages of missed cases have been reported. For example, in a cohort of 42 pediatric patients with CH-C, 81% had been missed with a neonatal screening

strategy that used a "fixed" T4 concentration cutoff of 5 μg/dL, which is ~65 nmol/L and corresponds to approximately −2 SDs (9). When imputing the estimated number of missed Dutch children in our calculations, the overall mortality rate declines (15/191; 7.9%) but is still considerably higher than in the general Dutch pediatric population.

This cohort study provides demographic data on children with CH-C. A strong male predominance was seen for both isolated CH-C and MPHD, as has previously been reported in smaller studies (3, 4). Recently, several X-linked genetic causes for isolated CH-C have been identified (*e.g.*, mutations in the *IGSF1* and *TBL1X* genes), which may explain the male predominance (10, 11).

In almost 60% of our cases, CH-C occurred within the framework of MPHD. In previous reports the proportion of children with MPHD ranged from 58% to 78% (3–5).

Our cohort included three patients with CDG. CDGs form a group of inborn errors in protein and lipid glycosylation. Because glycosylation is crucial in myriad processes, symptoms are highly variable, and diagnosis is often delayed (12). Abnormal results for neonatal CH screening, however, can be seen in children with CDG and might allow early diagnosis, especially when combined with other CDG symptoms or dysmorphic features (12, 13). Abnormal thyroid function tests in patients with CDG are caused by altered glycosylation of TSH and TBG. Abnormalities most often consist of low free T4 with elevated TSH or low total T4 caused by partial TBG deficiency (14). When measuring free T4 and TSH concentrations using equilibrium dialysis, values in the normal range have been reported (15). Although it has been concluded that most patients with CDG can be considered chemically euthyroid (14), patients with clinical symptoms of hypothyroidism requiring T4 supplementation have been reported as well (16). Whether these patients should be classified as having isolated CH-C is debatable.

This study has limitations. CH-C is not an easy diagnosis because it relies heavily on the serum or plasma free T4 concentration (given the hypothalamic-pituitary origin, measurement of TSH does not contribute to the diagnosis). Because patients were diagnosed by various pediatricians, misdiagnosis cannot be ruled out. In addition, in the deceased patients with presumed isolated CH-C and other "severe illnesses," the abnormal thyroid function tests might be explained by nonthyroidal illness (17). Because of these patients' early death, the permanence of isolated CH-C could not be verified after the first 2 to 3 years of life. We did, however, review medical charts of all deceased patients, including their neonatal screening results, laboratory values, and medication history.

Given the association between hypopituitarism and cerebral anomalies, an increased mortality rate in this subgroup of patients was to be expected, and therefore the results of this study are not surprising. However, at the same time, by tracing all patients with CH-C with or without MPHD detected by neonatal screening since 1995, we were able to show that the mortality in hypopituitarism without concurrent diagnoses is low: in our cohort only one patient died.

In summary, we report an increased mortality in patients with early-detected CH-C that does not seem to be related to endocrine disease. This suggests that mortality due to pituitary deficiencies is low in an early-detected and early-treated CH-C population, but the mortality rate for patients with CH-C in unscreened populations remains unknown.

Acknowledgments

Correspondence and Reprint Requests: Nitash Zwaveling-Soonawala, MD, Department of Pediatric Endocrinology, room H7-238, Emma Children's Hospital, Academic Medical Center, PO Box 22660, 1100 DD Amsterdam, Netherlands. E-mail: n.zwaveling@amc.uva.nl.

Disclosure Summary: The authors have nothing to disclose.

References

1. Lanting CI, van Tijn DA, Loeber JG, Vulsma T, de Vijlder JJM, Verkerk PH. Clinical effectiveness and cost-effectiveness of the use of the thyroxine/thyroxine-binding globulin ratio to detect congenital hypothyroidism of thyroidal and central origin in a neonatal screening program. *Pediatrics*. 2005;**116**(1):168–173.
2. van Tijn DA, de Vijlder JJM, Verbeeten B Jr, Verkerk PH, Vulsma T. Neonatal detection of congenital hypothyroidism of central origin. *J Clin Endocrinol Metab*. 2005;**90**(6):3350–3359.
3. van Tijn DA, de Vijlder JJM, Vulsma T. Role of the thyrotropin-releasing hormone stimulation test in diagnosis of congenital central hypothyroidism in infants. *J Clin Endocrinol Metab*. 2008;**93**(2):410–419.
4. Fujiwara F, Fujikura K, Okuhara K, Tsubaki J, Fukushi M, Fujita K, Fujieda K, Tajima T. Central congenital hypothyroidism detected by neonatal screening in Sapporo, Japan (2000-2004): it's prevalence and clinical characteristics. *Clin Pediatr Endocrinol*. 2008;**17**(3):65–69.
5. Adachi M, Soneda A, Asakura Y, Muroya K, Yamagami Y, Hirahara F. Mass screening of newborns for congenital hypothyroidism of central origin by free thyroxine measurement of blood samples on filter paper. *Eur J Endocrinol*. 2012;**166**(5):829–838.
6. Ford G, LaFranchi SH. Screening for congenital hypothyroidism: a worldwide view of strategies. *Best Pract Res Clin Endocrinol Metab*. 2014;**28**(2):175–187.
7. LaFranchi SH. Newborn screening strategies for congenital hypothyroidism: an update. *J Inherit Metab Dis*. 2010;**33**(Suppl 2):S225–S233.
8. van Iersel L, van Santen HM, Zandwijken GRJ, Zwaveling-Soonawala N, Hokken-Koelega ACS, van Trotsenburg ASP. Low FT4 concentrations around the start of recombinant human growth

hormone treatment: predictor of congenital structural hypothalamic-pituitary abnormalities? *Horm Res Paediatr*. 2018;**89**(2):98–107.
9. Nebesio TD, McKenna MP, Nabhan ZM, Eugster EA. Newborn screening results in children with central hypothyroidism. *J Pediatr*. 2010;**156**(6):990–993.
10. Joustra SD, Schoenmakers N, Persani L, Campi I, Bonomi M, Radetti G, Beck-Peccoz P, Zhu H, Davis TM, Sun Y, Corssmit EP, Appelman-Dijkstra NM, Heinen CA, Pereira AM, Varewijck AJ, Janssen JA, Endert E, Hennekam RC, Lombardi MP, Mannens MM, Bak B, Bernard DJ, Breuning MH, Chatterjee K, Dattani MT, Oostdijk W, Biermasz NR, Wit JM, van Trotsenburg AS. The IGSF1 deficiency syndrome: characteristics of male and female patients. *J Clin Endocrinol Metab*. 2013;**98**(12):4942–4952.
11. Heinen CA, Losekoot M, Sun Y, Watson PJ, Fairall L, Joustra SD, Zwaveling-Soonawala N, Oostdijk W, van den Akker EL, Alders M, Santen GW, van Rijn RR, Dreschler WA, Surovtseva OV, Biermasz NR, Hennekam RC, Wit JM, Schwabe JW, Boelen A, Fliers E, van Trotsenburg AS. Mutations in TBL1X are associated with central hypothyroidism. *J Clin Endocrinol Metab*. 2016; **101**(12):4564–4573.
12. Funke S, Gardeitchik T, Kouwenberg D, Mohamed M, Wortmann SB, Korsch E, Adamowicz M, Al-Gazali L, Wevers RA, Horvath A, Lefeber DJ, Morava E. Perinatal and early infantile symptoms in congenital disorders of glycosylation. *Am J Med Genet A*. 2013; **161A**(3):578–584.
13. Shanti B, Silink M, Bhattacharya K, Howard NJ, Carpenter K, Fietz M, Clayton P, Christodoulou J. Congenital disorder of glycosylation type Ia: heterogeneity in the clinical presentation from multivisceral failure to hyperinsulinaemic hypoglycaemia as leading symptoms in three infants with phosphomannomutase deficiency. *J Inherit Metab Dis*. 2009;**32**(Suppl 1):S241–S251.
14. Miller BS, Freeze HH. New disorders in carbohydrate metabolism: congenital disorders of glycosylation and their impact on the endocrine system. *Rev Endocr Metab Disord*. 2003;**4**(1):103–113.
15. Macchia PE, Harrison HH, Scherberg NH, Sunthornthepfvarakul T, Jaeken J, Refetoff S. Thyroid function tests and characterization of thyroxine-binding globulin in the carbohydrate-deficient glycoprotein syndrome type I. *J Clin Endocrinol Metab*. 1995;**80**(12):3744–3749.
16. Mohamed M, Theodore M, Claahsen-van der Grinten H, van Herwaarden AE, Huijben K, van Dongen L, Kouwenberg D, Lefeber DJ, Wevers RA, Morava E. Thyroid function in PMM2-CDG: diagnostic approach and proposed management. *Mol Genet Metab*. 2012;**105**(4):681–683.
17. Persani L. Clinical review: Central hypothyroidism: pathogenic, diagnostic, and therapeutic challenges. *J Clin Endocrinol Metab*. 2012;**97**(9):3068–3078.