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Neurological symptoms, evaluation and treatment in Danish patients with achondroplasia and hypochondroplasia

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ABSTRACT

Aim: To investigate the prevalence of neurological symptoms and the types of complications in a cohort of Danish patients with mutation verified achondroplasia and hypochondroplasia and compare the results with previously reported findings.

Methods: Retrospective descriptive study by chart review of patients followed in three outpatients clinics in the period 1997-2014. Forty-eight patients with achondroplasia and a median age of 9,5 years old and 20 patients with hypochondroplasia and a median age of 12 years old were enrolled. Neurological manifestations, epidemiological variables and clinical data were collected.

Results: Data on neurological symptoms and surgical interventions were extracted and compared with existing knowledge. Description of phenotypes revealed frequent headaches, pain in back, neck and lower limbs, sleep apnoea and conductive hearing loss. No sub-phenotype was predictive for referral to an MRI scan or neurosurgery.

Conclusion: Through investigation of phenotypes and genotypes in patients with achondroplasia and hypochondroplasia we report the frequencies of neurological symptoms, foramen magnum stenosis, spinal cord compression and neurosurgery in Danish patients. Variation in the evaluation of patients among the three clinics is found and discussed. To further standardise the management of patients, national guidelines for follow-up on children with ACH and HCH are recommended.

Keynotes

- Achondroplasia and hypochondroplasia patients can suffer from a small foramen magnum and a narrow spinal canal. Untreated this may lead to serious impediments.
- Foramen magnum stenosis was present in 54,2% and hydrocephalus was seen in 18,7% of the achondroplasia patients. A MRI scan of the cerebrum was performed in 62,5% of patients in this group.
- To standardise the management of these patients we recommend continuing collaboration and consensus of a national strategy for follow-up.

Introduction

Achondroplasia (ACH) (OMIM #100800) is the most common

form of skeletal dysplasia affecting over 250,000 people worldwide with a birth prevalence of 1 in 20,000-30,000 live-born infants¹. It is inherited as an autosomal dominant trait with complete penetrance, but 80-90% of the cases are caused by *de novo* mutations². Most cases are caused by one of two point mutations, G1138A or G1138C, and both mutations result in an amino acid substitution at position 380 of the fibroblast growth factor receptor 3 (FGFR3)³.

Hypochondroplasia (HCH) (OMIM #146000) and ACH have been proposed to be allelic disorders⁴. The C1620A mutation and the C1620G mutation in FGFR3 are recurrent in patients with HCH⁵. A number of patients do not have this mutation suggesting that HCH may also be caused by other mutations in FGFR3 or perhaps a mutation in another gene⁶. Patients with HCH may have the same clinical and radiological manifestations as ACH but the phenotype is usually less severe⁷.

Disproportionate growth between endochondral and membranous bone and the organs underneath causes different complications for individuals with ACH and HCH. The characteristic phenotype is abnormal short stature with rhizomelia, narrow trunk and macrocephaly^{8,9}. Because of defective endochondral ossification patients can suffer from a small, abnormally shaped foramen magnum. They have short pedicles, small neural foramina, and reduced interpedicular distance caudally and with age they are at risk of developing spinal canal stenosis. This may lead to serious impediments such as myelopathy, apnoea and sudden death¹⁰⁻¹². ACH patients also suffer from midfacial underdevelopment and that results in short Eustachian tubes and the tonsils and adenoids may be too large for the available space and this may cause respiratory symptoms¹³. The aim of this study is to investigate the prevalence of neurological symptoms and the general complications in a cohort of Danish patients with ACH and HCH as well as to describe the cohort regarding phenotype and genotype and compare the results with previously reported findings.

Patients and methods

All patients with ACH and HCH followed in the three outpatient clinics, Centre for Rare Diseases at Aarhus University Hospital (AUH) and Rigshospitalet (RH) in Copenhagen and H.C. Andersen Children's Hospital, Odense University Hospital (OUH) in the period 1997-2014 were included. Data was collected by chart reviews. The patients were registered with core date in RAREDIS[®], the Nordic database for rare and genetic diseases (www.raredis.eu). The study population comprised 68 patients, 48 patients with ACH and 20 patients with HCH. There was no significant sex difference with 46% males in the ACH population and 55% males in the HCH population.

A positive family history was seen in four of the 48 ACH patients, two of them being siblings, and in seven of the 20

HCH patients, six consisting of three sets of siblings. The ACH patients were born in the period of 1960-2014 while the HCH patients were born in the period 1969-2012. The median age of the ACH patients was 9,5 years ranging from four months to 54 years old and it was 12 years ranging from two to 45 years old in the HCH patients.

Neurological manifestations considered relevant in this study were among others stenosis of foramen magnum, hypotonia, and hydrocephalus as described in the literature^{10,11,14}. Data on epidemiological variables and clinical data such as phenotypic features, respiratory problems and rate of development were collected as well as the genotype. It was noticed if the patients had been examined with a magnetic resonance imaging scan (MRI scan) or other forms of medical examinations or had been through neurosurgery such as decompression in the spinal canal or insertion of a shunt or both. Each patient's chart was read from either birth or from time of referral to one of the three outpatient clinics at AUH, RH or OUH and until autumn of 2014. Data were summarised, organized and analysed for correlations.

Data are reported as median values and range unless otherwise indicated. Pearson's chi-square was used to compare different groups. $p < 0,05$ was considered significant. An approval by an ethical committee was not applicable in this study. The study is registered according to the Danish Data Protection Agency and is not connected with any conflict of interests.

Results

Neurological manifestations and interventions

Review of the medical records of the ACH patients revealed 26 patients having foramen magnum stenosis (54,2%). Ten of the 26 patients had severe symptoms that had led to a foramen magnum decompression operation (20,8%). The median age of their first operation was one year old ranging from four months to 15 years old. In the HCH patient group one had a stenosis and was treated with an operation at the age of 10 months. The frequency of neurological symptoms in patients with ACH and HCH in this cohort is shown in table 1 and 2.

The reporting of clonus and hypo- and hyperreflexia was low. In the group of patients with ACH clonus was reported in four cases (8,3%), hyporeflexia in two cases (4,1%) and hyperreflexia in three cases (6,3%). Clonus was present in different periods of time in the four patients, approximately three years being the longest in a patient from the age of one year old to four years old. The pathological reflexes were reported to have lasted for a short period of time in the five patients. As expected the percentages of all the symptoms in the group that underwent surgery were higher compared to all the ACH patients except for hypotonia. But

Table 1: Neurological manifestations in patients with achondroplasia.

Sign/symptom	All patients with ACH nACH=48		Patients with ACH in need of neurosurgery nACH=16	
	No.	Percentage	No.	Percentage
Epilepsy	2	4,2	2	12,5
Headache	14	29,2	6	37,5
Nausea	6	12,5	4	25,0
Sleep apnoea	17	35,4	8	50,0
Pain back/neck	20	41,7	7	43,8
Pain lower limbs	24	50,0	9	56,3
Hypotonia	19	39,6	6	37,5
Paraesthesia	5	10,4	2	12,5
Bladder dysfunction	2	4,2	2	12,5
Bowel dysfunction	2	4,2	2	12,5

ACH, achondroplasia

Table 2: Neurological manifestations in 20 patients with hypochondroplasia.

Sign/symptom	No.	Percentage
Epilepsy	2	10
Headache	4	20
Nausea	1	5
Sleep apnoea	3	15
Pain back/neck	3	15
Pain lower limbs	7	35
Hypotonia	3	15
Paraesthesia	0	0
Bladder dysfunction	1	5
Bowel dysfunction	0	0

Only one patient with hypochondroplasia was in need of surgery (See table 3 and 4)

there was no significant difference in the frequencies of any of the symptoms between the two groups. The percentages of neurological symptoms were lower in the HCH group except for bladder dysfunction and epileptic seizures.

Nine ACH patients were reported having hydrocephalus (18,7%) and five of them were treated with a shunt (10,4%). The median age of the procedure was five years old ranging from 10 months to 15 years old. It is difficult to say which symptoms indicate hydrocephalus as none of the five patients who had a shunt inserted suffered from the exact same symptoms. The most frequent symptoms in the five patients were headache and nausea and the symptoms were seen in combination with pathological neuroimaging to be indicators for surgery (Table 3). Correspondingly two of the HCH patients had hydrocephalus (10%) and one of them (5%) needed treatment at the age of six months.

An MRI scan of the cerebrum is the most important investigation to confirm a stenosis in the spinal canal. In the ACH group 30 patients were reported to have had an MRI scan of the cerebrum (62,5%). The median age of their first scan was one year ranging from a few months to 50 years. Only four of the patients scanned did not have stenosis at the foramen magnum level (13,3%). Of the 26 ACH patients with stenosis in the spinal canal diagnosed through an MRI scan 61,5% required operation because of neurological symptoms (Table 3 and 4). The decision criteria for surgery varied, however most operations were performed due to a combination of pathological neuroimaging and symptoms such as hypotonia and sleep apnoea. There was no clear

Table 3: Neurological symptoms of patients with ACH or HCH who have been operated (Decompression (D), shunt (S) or D+S) n=17.

Pt.	Diag.	Neurological symptoms								
		Headache	Nausea	Sleep apnoea	Pain back/neck	Pain lower limbs	Hypotonia	Paraesthesia	Bladder dysfunction	Bowel dysfunction
1	ACH (D)						+			
2	ACH (D)		+	+						
3	ACH (D)			+			+			
4	ACH (D)						+			
5	ACH (D+S)	+								
6	ACH (S)						+			
7	ACH (S)	+	+			+				
8	ACH (D)					+	+			
9	ACH (D)			+	+	+				
10	ACH (D*)				+	+		+	+	
11	ACH (D)			+	+	+	+			
12	ACH (D+S)	+	+	+	+	+				
13	ACH (D*+S)	+	+	+	+					
14	ACH (D*)	+		+	+	+				
15	ACH (D*)	+				+	+	+	+	
16	ACH (D*)			+	+	+				
17	HCH (D+S)		+				+			
Subset (%) of the 17 patients operated		35,3	29,4	47,0	41,2	53,0	41,2	11,8	11,8	11,8

*Decompression at the lumbar region Pt. ID, Patient ID; Diag., Diagnosis; ACH, achondroplasia; HCH, hypochondroplasia.

Table 4: Age at 1st MRI and 1st operation and outcome in the patients with ACH and HCH who have been operated (Decompression (D), shunt (S) or D+S) n=17

Pt. ID	Diag.	Operation					Outcome
		1. MRI (Age)	1.operation (Age)	Decompression (D)	Shunt (S)	D+S	
1	ACH	5 mo.	6 mo.	+			Doing well
2	ACH	3 mo.	4 mo.	+			On-going breathing troubles
3	ACH	1 y	1 y	+			Palsy in half of the body not reduced
4	ACH	3 mo.	10 mo.	+			Doing well
5	ACH	6 mo.	10 mo.	+	+	+	Doing well
6	ACH	1 y	< 2 y		+		Doing well
7	ACH	< 5 y	< 5 y		+		Doing well
8	ACH	1 y	1 y	+			Doing well
9	ACH	1 y	2 y	+			Doing well
10	ACH	4 y	12 y	+			Reduced pain in legs
11	ACH	11 mo.	11 mo.	+			Doing well
12	ACH	6 y	7 y	+	+	+	Doing well
13	ACH	Not known	15 y	+	+	+	Doing well
14	ACH	19 y	21 y	+			Doing well
15	ACH	Not known	19 y	+			Palsy from chest and down not reduced
16	ACH	42 y	49 y	+			Doing well
17	HCH	5 mo.	6 mo.	+	+	+	Doing well
Subset (%) of the 17 patients operated				88,2	35,3	23,5	

Pt. ID, Patient ID; Diag., Diagnosis; ACH, achondroplasia; HCH, hypochondroplasia, mo., months old; y, years old; patient 10, 14, 15 and 16 had a lumbar decompression surgery

chronology in appearance of the different symptoms in the patients with stenosis. Five HCH patients were scanned and the median age of the first scan was one year old ranging from a few months to 11 years old. Only one of them showed a foramen magnum stenosis and it required an operation. No specific neurological symptoms correlated to having an MRI scan as most of the patients scanned showed symptoms in various degrees. Most cases had sleep apnoea or hypotonia. But there was no significant difference between the frequency of these symptoms in the patients scanned and the patients not scanned.

A computed tomography scan (CT-scan) was performed on 14 patients with ACH (29,2%). Scans on two of the 14 patients confirmed stenosis (14,3%). Two HCH patients went through a CT scan because of potential hydrocephalus. Six ACH patients and three HCH patients had an ultrasound because of a possible hydrocephalus.

In the ACH group 20 reported having back or neck pain at some point in their life (41,7%). The disclosure was made from when they were three to 49 years old. Likewise three HCH patients reported having pain in the back or neck (15%). In the group of ACH patients 24 reported to have pain in the lower extremities (50%) while seven HCH patients said the same (35%). The symptoms were reported from patients at age three to 48 years old. Most of these patients had both back and leg pain. Interestingly to

squat down relieved the back or leg pain in four of the ACH patients. Twenty-one of the 30 ACH patients and one of the eight HCH patients with pain in the back or neck or lower limbs had an MRI scan to clarify if there was a stenosis in the spinal canal corresponding with 70% and 12,5%. Seven of the 30 ACH patients with pain had a stenosis in the lower back (23,3%). Five ACH patients had a laminectomy (10,4%). The median age of the laminectomy in our study was 19 years old ranging from 12 to 51 years old. None of the HCH patients had a spinal stenosis. Five ACH patients reported symptoms of paraesthesia (10,4%) and three were clarified through an MRI scan of whom two went through a decompression procedure. Two ACH patients have permanent neurological injuries such as palsy and incontinence (4,2%). One of the two patients debuted with the symptoms at the age of 34 years old and the other has suffered from urinary- and faecal incontinence in all 15 years of his life.

Genotypes

Of the 48 ACH patients, 68,8% had the G1138A mutation in the FGFR3 gene. The rest had either not been tested or the data was not available. Of the 20 HCH patients, 80% had been diagnosed through genetic testing. Among this population there were 7 different mutations leading to HCH (Table 5). The high prevalence of *de novo* mutations previously described was confirmed².

Table 5: Mutations in 20 patients with hypochondroplasia.

Mutation	No.	Percentage
c. 1620 C>A	6	30
c. 1052 C>G	4	20
c. 1612 C>A	2	10
c. 1948 A>C	1	5
c. 970 C>G	1	5
c. 1619 A>G	1	5
c. 2005 C>G	1	5
Not known	4	20

Respiratory symptoms

Multiple otitis media is a well-recognised complication of ACH^{15,16}. In this study 27 of the ACH patients (56,3%) and 15 of the HCH patients (40%) reported it. Conductive hearing loss among these children is not uncommon and it was seen in 15 of the ACH patients (31,3%) and in three of the HCH patients (15%). Nine ACH patients (18,8%) went through a tonsillectomy or insertion of a ventilation tube. The percentage was 5% in the HCH group. Snoring was reported in 52% of the ACH patients. A sleep position in opisthotonus was stated in 25% of ACH patients' records and in 10% in the HCH patients. Sleep apnoea, which both can be caused by compression of the spinal canal and too large tonsils in an undersized throat, was reported in 35,4% of the ACH patients and in 15% of the HCH patients. Of the 48 ACH patients 21 were evaluated at a respiratory centre (43,8%) and 16 ended up getting respiratory therapy for sleep apnoea (33,3%). The median age of the test was six years old with a range of 3 months to 40 years old.

Phenotypic characteristics

Most ACH patients in our population had the phenotypic characteristics such as frontal bossing, bowed legs in particular regarding the tibia bone and rhizomelia. Clinical comparison showed that the patients with HCH in general had a milder phenotype, as they did not have as many of the characteristics as the ACH patients. The most dominating trait in their group was shortness of the limbs and lumbar lordosis. 62,5% of the patients with ACH was mentioned having a lordosis and the percentage was 45% for HCH patients. Almost every patient in the ACH group was hypermobile whereas it was less recurrent in the HCH group. The prevalence of elbow and hip extension defect was seen in 31,2% of the ACH group and it was primarily seen from the age of four years and became more frequent with increasing age. Extension defects was less recurrent in the HCH group.

Discussion

Medical and surgical interventions were within the range of intervention rates reported for previous cohorts. As mentioned 26 ACH patients had a foramen magnum stenosis (54,2%) and 10 had a foramen magnum

decompression operation (20,8%). The frequency of the operation in other studies was in the range from 6,8%-28%^{15,17-19}. The median age at first operation in our population was slightly lower than seen in previous studies. In one study the mean age was 23 months and in another it was 70 months^{12,17}. Fifteen of the 26 ACH patients in our study with foramen magnum stenosis were diagnosed before their first year of age (57,7%) and the median age of diagnosis for foramen magnum stenosis in our population was one year ranging from three months to 42 years. The percentage of a shunt insertion was slightly higher in our study compared to the newest reports but our result was almost identical with results from a study in 1998 (10,4% vs. 10,5%)^{15,17,18}. This may be because the two oldest patients with a shunt in our population were born in the early 1990's with less accurate modes of distinguishing between the benign ventriculomegaly and the pathological hydrocephalus in consideration of the former being very common in ACH²⁰.

In all, 75% of the 16 ACH patients who underwent operation were confirmed having the most common mutation in FGFR3³. The high frequency of this mutation has also been shown in Sweden²¹.

The rest had either not been tested or the data was not available. All who went through a foramen magnum decompression had this mutation, one of the two who had a shunt inserted were confirmed, three of the four who had a foramen magnum decompression and a shunt inserted were confirmed and two of the four, who went through a lumbar laminectomy, were confirmed with the mutation. The one HCH patient who went through foramen magnum decompression and a shunt insertion had the most common HCH mutation in the FGFR3 gene⁵. These observations show that the genotype cannot predict the later need for neurosurgery.

Anticipatory care should be directed at children who are at high risk of severe complications to be able to intervene in time of emergent problems. A multidisciplinary team of doctors is needed to ensure the best care. Health Supervision Guidelines for Children with ACH have been developed to aid primary care physicians in the management of these children²².

Slightly above 60% had an MRI scan in our population. Thus the Danish clinical tradition in total do not follow the American guidelines with respect to use of neuroimaging since they suggest MRI scans in every infant with ACH²². In an Australasian study 22 of 53 children (41,5%) were reported as having had MRI or CT studies by age three¹⁸.

Even though the rate of using neuroimaging was lower in our study the rate of surgical interventions was within or above rates in other studies. Overall we found that patients with severe complications were diagnosed and

treated according to international standard. There was a slight dissimilarity in the management among the three clinics in this study. In one clinic almost every ACH patient had their first MRI scan in their first year of life and the scans were often repeated several times in their childhood. This suggests a wish to follow the American guidelines²². Systematic scanning of the patients was not seen in the other two centres as the MRI scans were mostly indicated by clinical manifestations. The variation of practice in our study may be due to the fact that there is some controversy about when children with ACH should be fully evaluated including an MRI scan to identify possible stenosis in the spinal canal. Multiple authors recommend full investigation in the first six months of life or when first referred and neuroimaging should be repeated at a predetermined interval afterwards^{17,19,22-24}. Another author argues against these criteria as it was found that the MRI scans showed that most of the affected children have some degree of cord compression and most of them gain normal motor development and neurological function suddenly within the first two to three years of age as the cord compression disappears²⁵. In a recent study 11 multidisciplinary international experts on skeletal dysplasia discussed various statements regarding neurological symptoms in children with ACH and concludes that they do not recommend universal screening of infants with ACH due to risks of over treatment and sedation²⁶.

Full anaesthesia is required during the MRI scans when the patients are at a young age and the anaesthetic management of these patients is a significant challenge mainly because of associated airway difficulties with the diagnosis. This fact argues against multiple MRI scans without substantial suspicion. Most of the patients in our study who went through an MRI scan had a foramen magnum stenosis and slightly more than half of them needed an operation because of severe symptoms. It suggests that the clinical manifestations are just as important as are the MRI scan results to determine if a procedure is relevant and it would be reasonable to wait with the neuroimaging until symptoms are present. None of the patients experienced sudden death, which is a risk from cord compression. But two patients had permanent neurological sequelae and this, along with a statistical increased risk of sudden death, may advocate for frequent scans even when no symptoms are present.

Epilepsy was reported in two of the patients with HCH. Both of the patients had the 1620 C>A mutation resulting in Asn540Lys. This correlates to previous studies showing the association between patients with this mutation and temporal lobe dysgenesis and epilepsy^{27,28}. The association was also just presented in a recent study²⁹. No data on possible temporal lobe dysgenesis is present in our study and the rate of development of both the ACH and HCH

patients was described insufficiently in the charts to present any data from. Mental deficiency has previously been reported in HCH patients as well as learning disorder and mild intellectual delay^{30,31}.

The neurological symptoms registered in ACH patients in this study correspond to the symptoms recently described¹⁰. The percentage of sleep apnoea in our study was high but within the range seen in other studies^{15,24,32,33}. The high rate of sleep apnoea could be due to frequent upper airway infections combined with the midfacial hypoplasia in patients with ACH and HCH. To reduce the symptom it may be helpful to lower the threshold for tonsillectomies. The number of tonsillectomies or insertion of a ventilation tube in our study was low compared to other studies^{15,18}. Snoring was less frequent in our study compared to another³². The rate of pain in the lower limbs were similar to another study's cumulative rate (50% vs. 47,2%)¹⁵. The number of patients with pain in back or neck resemble results in another study although their cumulative rate exceeds ours for patients above age 30 years but the prevalence of bladder dysfunction in our studies is very similar even though our data is limited and therefore not conclusive (4,2% vs. 3,1%)¹⁵. The occurrence of hypotonia was lower in our study compared to another (39,6% vs. 58,9%) and the rate of paraesthesia was higher in our study (10,4% vs. 2,6%)²⁴. The rate of conductive hearing loss in our study was comparable with other results (31,3% vs. 38%) but the rate of tonsillectomy was low in our study (18,8% vs. 40%)¹⁵. This may be due to underreporting. Of the 48 ACH patients 21 were evaluated at a respiratory centre (43,8%) and 16 ended up getting respiratory therapy for sleep apnoea (33,3%). The median age of the test was six years old with a range of 3 months to 40 years old. One study reported 64% of 53 children ranging from zero to five years old to have had formal polysomnography studies by age three¹⁸.

Our study was conducted as a retrospective study with the limitations of a relatively small cohort and the risk of lack of registration. Strength in our study is that it is experts handling the treatment and control of the patients because the treatment is centralised in Denmark. Another strength is that there is free access for the patients to a public financed health care in Denmark.

A recent published study has shown that using diffusion tensor imaging it may be possible to quantify changes in the brainstem white matter that correlate with the severity of craniocervical junction narrowing in patients with ACH³⁴. This might be a new improved method to identify suitable patients for therapeutic decompression and monitor response to the treatment. In the future medical treatment may be able to both benefit growth and minimise neurological symptoms in patients with ACH and HCH³⁵.

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Conclusion

This study provides an original overview of the clinical manifestations and management of a cohort of Danish patients with ACH and HCH and reports new data on the frequency of apnoea, hypotonia and neurosurgery in patients with foramen magnum stenosis. Furthermore we find and discuss variation in the evaluation of the ACH and HCH patients between the three clinics included in our study. To standardise the management of these patients we recommend continuing collaboration, national guidelines and a future national or international multicentre prospective study. In such use of the Raredis database would be possible. Thus it will be possible to gain more information about the phenotypic characteristics, neurological symptoms and need for neuroimaging and neurosurgical treatment in ACH and HCH patients. The authors' contribution to standardisation of care and management for patients with ACH regards regular clinical controls and MRI scans of the patients. The authors recommend to enrol patients to clinical controls at skeletal dysplasia clinics with expertise in paediatric neurology twice a year from birth until the age of five and thereafter once a year until the age of 15 years and once at age 30 years. Extra clinical control should take place if indicated by symptoms. Furthermore MRI scans of the brain including the foramen magnum level should be performed at the age of one, three, seven, 15 and 30 years with the latter including MRI scan of columna totalis. With any sign of neurological symptoms additional controls and scans should be performed. The author's recommendation regarding diagnostics and clinical control of HCH patients also is examination of the patients at skeletal dysplasia clinics with expertise in paediatric neurology. Due to a less severe phenotype the interval of clinical controls and MRI scans should be determined individually.

Abbreviations

ACH, achondroplasia; HCH, hypochondroplasia; FGFR3, fibroblast growth factor receptor 3; MRI scan, Magnetic Resonance Imaging Scan; CT-scan, Computed Tomography Scan; AUH, Aarhus University Hospital; OUH, Odense University Hospital; RH, Rigshospitalet.

Authors' contributions

Mia Aagaard Doherty MS had primary responsibility for protocol development, collecting of data and preliminary data analysis and writing the manuscript.

Drs Hanne Hove and Thomas Hertel contributed with additional patients, analysing data and to the writing of the manuscript.

Dr Annette Haagerup initiated the project and supervised the design and execution of the study, performed the final data analyses and supervised and contributed to the writing of the manuscript.

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