Natural course of pontocerebellar hypoplasia type 2

A booklet for parents

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Foreword

Pontocerebellar hypoplasia type 2 (PCH 2) is a rare, poorly understood disease that is associated with severe physical and mental impairment from birth on and a reduced life expectancy. In Germany, parents of affected children have come together in a self-help internet forum. Already for the second time, in October 2011 they organized a meeting, which brought together parents of affected children and leading German and international researchers in the field of pontocerebellar hypoplasia. During this meeting, the parents suggested to perform a study on their children's disease with a main focus on the natural course, in terms of growth, development and care. Thanks to this initiative and the support of these and many other parents, this study was finally born. The goals of the study are to gain new insights into the natural history of PCH 2, especially with regard to cognitive and motor development and growth. In addition, there will be a focus on the care and daily life with a child suffering from PCH 2. These findings will provide a more detailed insight into the disease and its progression, in order to provide more information for affected children, their families and medical staff working with these patients; with the aim to care in a more informed and efficient way for patients and families. We would like to express our sincere gratitude for the cooperation and support of the parents who participated and hope that our study and this booklet will provide guidance and support for relatives, parents, and medical staff, that it will be an orientation and support in dealing with their children/patients suffering from PCH 2.

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1 PCH 2

1.1 Historical background

In 1995, Barth et al described a group of 5 families with children suffering from PCH2. All families were from a small community north of Amsterdam (Netherlands), Volendam. Grounded in their history, in which the municipality of Volendam opposed the Reformation and remained faithful to the Roman Catholic faith, the inhabitants therefore lived isolated from neighbouring communities and marriage of closer relatives in Volendam apparently occurred more frequently which led to a reduction of the genetic pool. That explains the accumulation of cases in this small community. Because most European PCH 2 patients share the same mutation, it is assumed that they had a common ancestor who probably lived in the 17th century.

1.2 Causes

PCH 2 is an autosomal recessive inherited condition. The mutation that leads to the disease must be present on both chromosomes in both copies of the affected gene. So, one mutation must be inherited from the father and one from the mother. The parents each carry only one mutation, which means that they do not develop the disease. For unborn siblings, this means that there is a 25% risk of also developing PCH 2. In 2008, the causative mutation for PCH 2 was found. It is a mutation in the TSEN54 gene on chromosome 17q25. In most of the European patients the mutation 919 G>T, p.Ala307S is found.

1.3 Diagnosis

The diagnosis of PCH 2 can be based on the typical clinical symptoms and magnetic resonance imaging findings (see Figures 1 and 2) of the brain.

On the magnetic resonance images, a narrowing of the bridge and a significant reduction in size of the cerebellum is visible. The shape of the altered cerebellum is similar to the wings of a bat or dragonfly and is therefore also described as "bat-wing" or "dragon-fly-like".

Since the discovery of the mutation, a diagnosis can be confirmed by molecular genetic testing (blood test). Through this affected families can also be offered prenatal diagnostics.

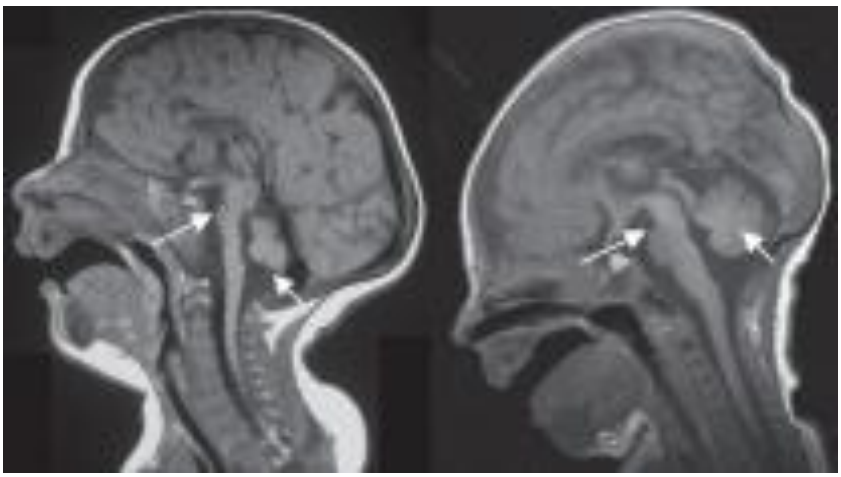


Figure 1 Magnetic resonance image of a PCH2 child (left) compared to a normal child (right). Arrows show the thinning of the bridge and the cerebellar vermis (short arrows).

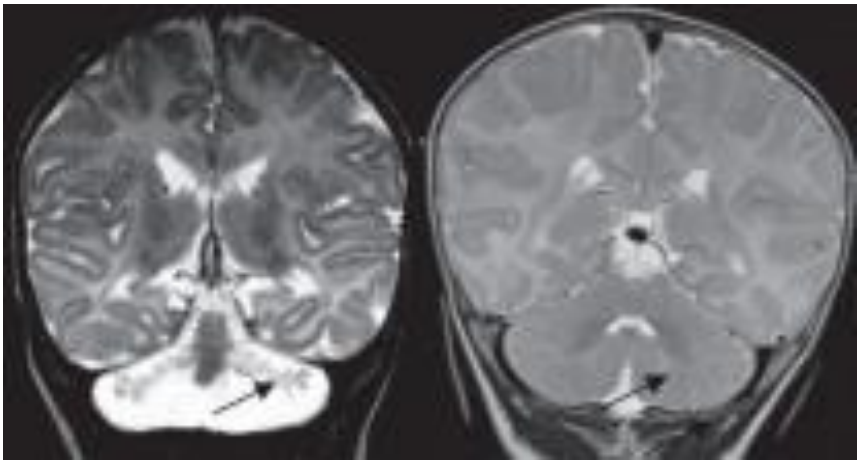


Figure 2 Magnetic resonance image of a PCH2 child (left) compared to a normal child (right). The arrows point to the cerebellar hemispheres, which are very narrow in PCH.

1.4 Symptoms

PCH 2 is characterized by

- an early-onset, so-called choreatic or dyskinetic movement disorder
- a strong impairment of the mental and motor development
- an increasing microcephaly (too small head circumference)

Obviously and presenting a big problem in the everyday care and life of the patients are the difficulties in swallowing and feeding. The children show a high susceptibility to infections and pronounced sleep problems. There are also indications of temperature

regulation disorders, with rapidly rising fevers causing crises accompanied by movement disorders, seizures, or even rhabdomyolysis.

Both the mental and the motor development of patients with PCH 2 are severely limited. In the literature, some developmental progress, such as head control or making contact in the form of social smiling have been described. A detailed description of motor and cognitive development, also regarding whether individual developmental steps, if once learned, may be unlearned in the course of time, is not yet available.

1.5 Therapy

A causal therapy is not known. An option is to try symptomatic treatment such as medication, physiotherapeutic and surgical treatments to reduce the symptoms and to simplify the care of the patients.

1.6 Other forms of PCH

Meanwhile, other forms of PCH have also been described. All forms are characterized by the typical imaging findings (cf. 1.3.) and clinically all affected individuals show microcephaly, as well as swallowing difficulties, seizures, and severe cognitive impairment.

The subdivision into 7 subtypes of PCH is based on additional criteria - such as abnormalities during pregnancy, damage to the optic nerve, etc. -some forms can only be described on the basis of a few affected individuals, sometimes even only a single one - as in the case of PCH type 7 -. The significance of these subtypes is not yet completely clear. Do they have different genetic findings? Does the assignment have significance for prognosis?

2 The study

Data collection was based on a comprehensive questionnaire, completed in a telephone interview together with the participating parents. This questionnaire was used to collect -among other- data on origin, pregnancy, birth, and neonatal period, as well as on growth and development, symptoms, and care.

The data collected this way were supplemented and verified on the basis of medical reports. The typical clinical symptoms (see 1.4) and the magnetic resonance images were decisive for inclusion in the study. The diagnosis was further confirmed by the available genetical findings.

3 Results

3.1 Study participants

33 children with the typical mutation (TSEN 54 919 G>T, p.Ala 307S).

Of these, 17 were boys and 16 girls.

3.2 Survival

Nine children (3 girls, 6 boys) had already died before data collection (mean age at death 7.5 years, the youngest death was at 7 months). The median age at the time of death was 91 months.

Causes of death were sudden unexplained death at night (5 cases), hypothermia (excessively low body temperature), multiorgan failure of unclear cause, and seizure with apnoea in one case each. One child died after severe pneumonia.

The average age of the 24 patients who did not die (11 boys, 13 girls) was 7 years and 9 months. The youngest child was 12 months old.

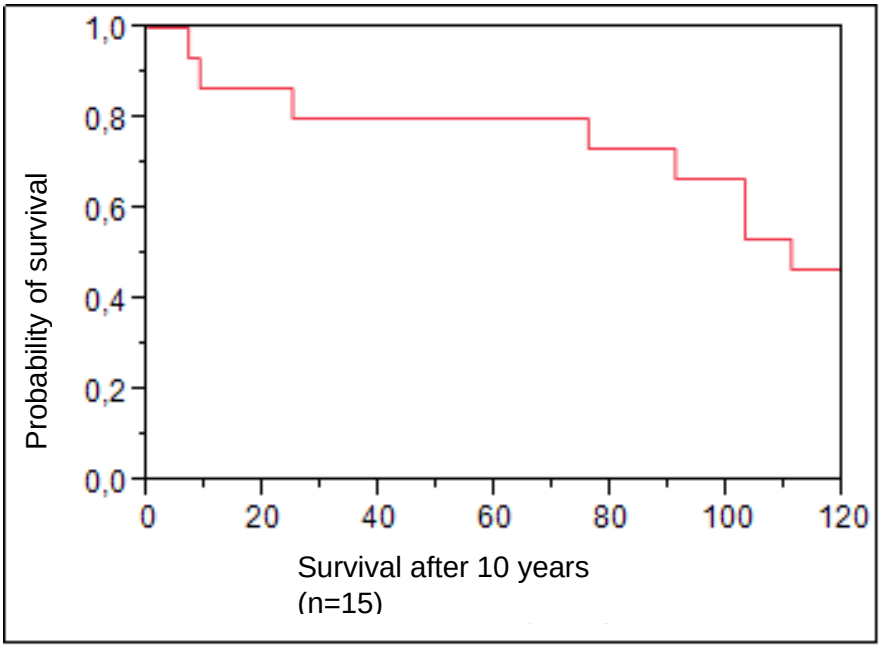


Figure 3 Kaplan-Meier curve for survival after 10 years (given in months). The 5-year survival probability was 88.5%, and the 10-year survival probability was 46.7%.

3.3 Course of pregnancy with a child suffering from PCH 2

One or more abnormalities occurred in 19 pregnancies.

The course of pregnancy was unremarkable in 14 cases. In 9 pregnancies unspecific abnormalities, such as cervical weakness or slower growth of the children occurred. In 10 pregnancies, abnormalities that are considered specific for PCH 2 were reported,

such as polyhydramnios (too much amniotic fluid; 4 of 33), myoclonia/tremor of the foetus (6 of 33), or a microcephaly (4 of 33).

None of the participating infants was diagnosed with PCH 2 before birth. Sonographic examinations of the brain were performed in 29 of 33 pregnancies in the second half of pregnancy. Apart from a fluid collection at the cerebellum in one case, and microcephaly (diagnosed between the 32nd and 35th week of gestation) in 4 cases, there were no other abnormal findings in any of the cases. In one pregnancy, a magnetic resonance imaging (MRI) examination was performed at 21 weeks of gestation. This was unremarkable.

3.4 Birth

Two children were born prematurely in the 36th week of pregnancy, the remaining 31 children were born between the 38th and 42nd week of gestation (mean: 39.8). In 9 cases (27.3%) a caesarean section was performed.

The mean birth weight was 3378.8 g, corresponding to an SD value of -0.25 (normal range).

Mean body length at birth was 51.4 cm, resulting in a mean SD value of -0.19 (normal range).

The mean head circumference immediately after birth was 33.5 cm, which corresponds to a mean SD value of -1.23 (lower than normal range). 6 children were already microcephalic at the time of birth with an SD value of less than -2. One additional child was exactly at the borderline of microcephaly (SD value of -2.0).

The values describing the well-being of a new born, viz. the umbilical artery pH and the APGAR values were within the normal range.

Nevertheless, 20 children had to be transferred to a paediatric hospital after birth. Two infants required short-term ventilation (less than 2 days).

Table 1 Reasons for continuing treatment in a paediatric clinic

Reason for continuing treatment in paediatric clinic	**Number** of children hospitalized for this reason after birth
Respiratory problems	14/20
Feeding difficulties	10/20
General adaption disorder	17/20
Others	2/20
	8/20

3.5 Neonatal period

In the neonatal period (birth to 28th day of life), 32 of 33 children were conspicuous by one or more of the symptoms listed in Table 2.

Table 2 Symptoms in the neonatal period. Children from whom no information was available were not included, resulting in the different case numbers.

Symptoms	**Total (n=33)**
Feeding difficulties (duration of one meal > 30min)	28/33 (84,8%)
Feeding difficulties that necessitated tube feeding	13/32 (40,6%)
Restlessness/ irritability	21/33 (63,6%)
Muscular hypertension in arms and legs	16/31 (51,6%)
Muscular hypotension in general	4/32 (12,5%)
Changing muscular tonus in arms and legs	6/30 (20%)
Definite seizures	2/33 (6,1%)
Long/ increased crying	14/33 (42,4%)
Increased sleep (child had to be awakened for feeding)	19/31 (61,3%)
others (esp. apnoea/bradypnea)	24/33 (72,7%)

The first signs of severe developmental disorder were described at a mean age of 1.4 months, with 16 children being clearly conspicuous from birth on.

3.6 Symptoms after the neonatal period

Table 3 shows in how many cases of the examined 33 children a symptom occurred or did not occur. Furthermore, it shows the number of cases in which a symptom appeared and disappeared again.

Table 3 Symptoms after the neonatal period by order of questioning in the questionnaire; n=33 (children from whom no information was available were not included, resulting in the different case numbers).

Symptom	occurred	Occurred and disappeared again
Feeding difficulties	33/33	2/33
Increased vomiting	31/33	11/31
Constipation	19/33	0/19
Dystonic attacks	11/33	5/11
Choreatic movements	29/32	0/29
Increased infections	17/33	7/17
Seizures	26/31	3/26
Status epilepticus	13/33	0/13
Temperature regulation disorder	22/33	1/22
Sleeping disturbance	32/33	9/32
Apnoea	22/31	5/22

3.6.1 Digestion

3.6.1.1 Feeding difficulties

Up to the age of 6 months, all children developed feeding difficulties, on average at the age of 0.5 months. They improved in 2 cases with increasing age of the children. The parents in these 2 cases stated that their children were able- from the age of 24 months on- to eat mushy food with small pieces inside up to more solid food such as rice, chocolate, or small fruits without choking. Since this is not possible in all other cases without exception, and all other children can only swallow finely pureed food, in some cases with considerable difficulty, this degree of swallowing ability was considered to be a cessation of the symptom *feeding difficulties* although it does not correspond to the food intake of a healthy person.

3.6.1.2 Increased vomiting and reflux

A total of 31 children exhibited increased vomiting, in 11 cases this improved during the course (frequency less than once per week). On average, the symptom "increased vomiting" occurred at the age of 9.5 months. In the 11 cases in which *increased vomiting* disappeared, it did so at an average age of 4 years (49.7 months). Twenty-one children vomited several times a day. In 23 cases gastroesophageal reflux disease was diagnosed by a physician.

3.6.1.3 Constipation

Constipation occurred in 19 children and did not disappear in any case. 15 children required regular medication (more than once a week) against it.

Possible causes: Switching from (breast) milk to other food (4 cases), change of medication (4 cases), too little fluid intake (2 cases).

Frequency of laxative medication: 1-2 times daily (7 of 15), more than 2 times daily (2 of 15), every 2 days or less often (4 of 15). Not stated (2 of 15).

Medications used for this purpose (multiple answers were possible) are CO2-laxatives (5 cases), Polyethylene glycol (5 case), lactulosis (1 case), clisterias (8 Cases), and chloral hydrate (1 case).

The mean age at which this symptom occurred was 2 years (23.9 months).

3.6.2 Dyskinetic movements and seizures

3.6.2.1 Excessive/choreatic movements

Overshooting, choreatic movements were present in almost all children (29/33). In the remaining 4 children a movement disorder in the sense of a predominant spasticity was present, in which the choreatic component was less prominent.

Thus, all 33 children showed a disorder of voluntary movements compatible with the diagnosis of PCH 2.

The parents stated, that their children's movements are always observable; increased, when the children are not feeling well, less pronounced when the children are happy.

Only during sleep the movements did stop in 26 of the 29 children with extending movements completely. Also, in the four children in whom the excessive muscle tone was more in the foreground, a relaxation could be observed in three cases during sleep.

Age at onset of symptom: mostly immediately after birth or within the first six months of life (average age 3.8 months).

A disappearance of the symptom could not be observed in any case.

3.6.2.2 Dystonic attacks

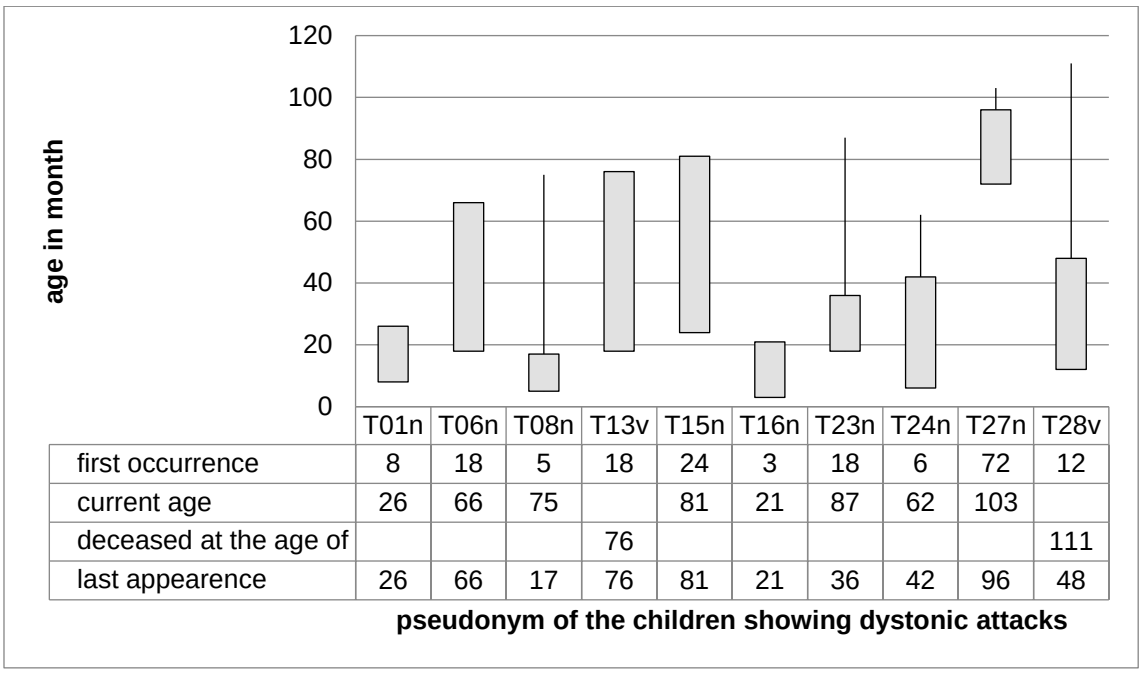
The symptom *dystonic attacks* refers to the description of a condition by parents and physicians, in which the children show partly due to a trigger such as physiotherapy, a left lateral position or a prone position, or even without a known trigger assume a c-shaped posture. This condition can last for several hours, the children usually feel poorly, are vomiting, and are crying a lot during this periods.

Occurrence: 11 children had dystonic attacks within the first 6 years of life. Children who had not shown any dystonic attacks until then did not develop dystonic attacks later in life, although in one case it was not possible to determine the age of onset of the symptom.

Description: The children adopted a c-shaped posture, which sometimes lasted for hours. According to our results, dystonic attacks occur with a general malaise, which is expressed by crying, screaming and in some cases vomiting. The children showed stereotyped movements, mostly in the form of a c-shaped bent posture, which can last for several hours. The crises were distinct from epileptic seizures and -if performed- were not associated with specific EEG changes. Triggers were not always known.

Disappearance: In nearly half of the cases (5/11), the dystonic attacks subsided again by the age of 8 years. A clear cause for the cessation could not be found in any case.

Therapy: In 8 of the 11 cases, the parents stated that the only way to break the c-shaped posture and the associated discomfort and vomiting was deep natural sleep. Sleep induced by medication did not show this effect. Only in two cases medication such as diazepam, chloral hydrate or metamizole, did help sometimes. In 2 cases, a reduction in the occurrence of seizures was related to an increase in the dose of a proton pump inhibitor (both cases omeprazole). In all the other cases, a clear connection to reflux and its treatment could not be established.



	T01n	T06n	T08n	T13v	T15n	T16n	T23n	T24n	T27n	T28v
first occurrence	8	18	5	18	24	3	18	6	72	12
current age	26	66	75		81	21	87	62	103	
deceased at the age of				76						111
last appearence	26	66	17	76	81	21	36	42	96	48

pseudonym of the children showing dystonic attacks

Figure 4 Representation of the occurrence of the symptom dystonic attacks in relation to age; n=10.

The 11th child does not appear in the figure due to the absence of the exact age data on the first occurrence of the symptom. In this case, the dystonic attacks did not stop until the current age of 19 years. The column "last occurrence" indicates only in 5 cases that the symptom has disappeared, this is the case for T08n, T23n, T24n, T27n, and T28v. In the remaining 5 cases, the current age, or the age at which an affected child died coincides with the age of last onset, so the symptom was still present at the time of data collection or at the time of death.

3.6.2.3 Epileptic seizures

Occurrence and cessation: Epileptic seizures occurred according to the data provided by the parents, in 26 of the 33 children. In 3 cases they stopped with increasing age. On average, the first epileptic seizures occurred at the age of 2 years and 5 months. A graphical overview of the time course of seizures in all children who suffered from epileptic seizures is given in figure 5. All children, who did not show seizures in our study were 28 months of age or younger.

Type of seizures: The description of epileptic seizures was very varied. In addition to generalized tonic-clonic seizures, absences and atonic seizures also occurred.

Therapy: A cessation of the epileptic seizures was observed in 3 children. In 2 cases this was related to a permanent antiepileptic medication (phenobarbital/ tizanidine and

lorazepam), in one case the parents directly related the cessation to the insertion of a PEG tube and the associated increase in fluid intake.

There is no known clearly successful therapy for epileptic seizures occurring in PCH 2 patients.

Table 4 Effective (reduction of seizure frequency) and ineffective medications for treatment of epileptic seizures in PCH2 (multiple responses were possible) (**bold print**= frequent successful treatments described; *cursive print*= frequent unsuccessful treatments or too many side effects described).

Drug (active ingredient)	**Unsuccessful treatment attempt**	**Treatment success in the context of permanent medication**	**Treatment success in emergency**
Clobazam	5	1	0
Clonazepam	0	3	0
Diazepam	3	2	5
Lamotrigine	2	1	0
Levetiracetam	6	2	0
Lorazepam	1	1	1
Oxcarbazepine	3	1	0
Phenobarbital	4	11	0
Sulthiame	2	2	0
Topiramate	1	6	0
Valproate	3	3	0
Vigabatrin	2	1	0

3.6.2.4 Occurrence of status epilepticus

Status epilepticus occurred in 13 of the 33 children. The age distribution of the first occurrence of status epilepticus was very different. On average, the children had their first or, in 9 cases, only status epilepticus at just under 4 years of age.

Drug interruption of status epilepticus: not possible (5/13), diazepam alone (2/13), diazepam and phenobarbital (2/13), diazepam and clonazepam (1/13), diazepam and chloral hydrate (1/13), diazepam and lorazepam (1/13), midazolam (1/13).

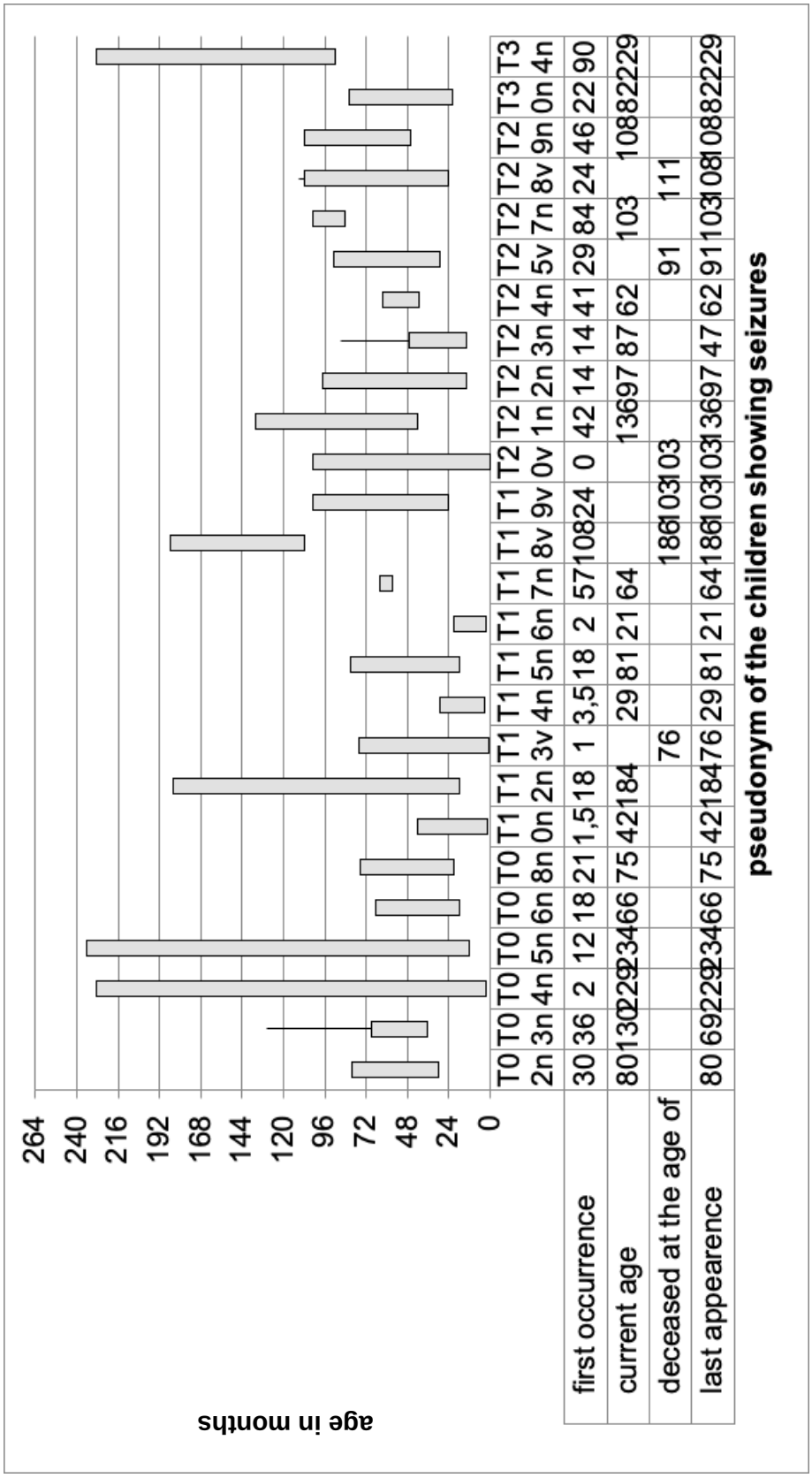


Figure 5 Representation of the occurrence of the symptom epileptic seizures in relation to age in months; n=26.

3.6.3 Infections and temperature regulation disorder

3.6.3.1. Increased infections

Occurrence and cessation: 17 of the 33 children showed increased infections in the sense of the question (> 5 infections /half year). The increased infections of their children were noticed by the parents at a mean age of 14.4 months. In 7 cases, these became less frequent from a mean age of 5 years and 3 months (63.3 months) on.

When asked about the type of infections, respiratory infections or pneumonias of infectious genesis were mentioned in 11/17 cases. In 6 cases aspiration was the main cause of pneumonia. Only in one case, in addition to pneumonia, a disease independent of the respiratory tract (accumulation of urinary tract infections) was reported.

Possible reasons for cessation: Placement of a PEG tube (2 cases), improvement of the swallowing process by the aid of a palatal plate (1 case) and thus reduction of the risk of aspiration.

3.6.3.2 Temperature regulation disorder

Temperature regulation disorders without an identifiable, for example infectious, cause or very rapid fever rises during infections were shown by 22 of 33 children. Rhabdomyolysis was observed in one child. One child showed hyperthermic derangements in early childhood, but then died from hypothermia that progressively worsened over several weeks at the age of 15.5 years. Another child developed hypothermia immediately after birth. The remaining 20 cases showed hyperthermia with no apparent cause.

In addition, the parents frequently reported a rapid rise in fever, which was usually accompanied (in 15 of the 20 cases) by extreme restlessness or crying of the children. This restlessness sometimes started even before the temperature was measurably elevated, but then persisted during the fever episode.

Antipyretic drugs did not help to lower the body temperature in all cases, but - if necessary combined with antiepileptic drugs – could help to calm the children. Physical cooling in the form of cool baths, etc., on the other hand, helped to lower the body temperature in many children.

3.6.4 Sleep disturbance

3.6.4.1 Difficulty falling asleep

In total, difficulties in falling asleep as defined in the question occurred in 31 children. In 12 cases, they subsided again with increasing age. The mean age of onset was 7.3 months. In the 12 cases in which the symptom subsided, the children were on average 5 years old at the time of the disappearance of the sleep disturbance. The 2 children who did not experience difficulties in falling asleep were 2 years and 4 months and 6 years and 10 months of age.

The children who exhibited sleep disturbances took a mean of just over an hour to fall asleep (mean: 70 min).

3.6.4.2 Sleep through disturbance

A sleep-through disturbance occurred in 29 of the 33 children, but in 6 cases it subsided again with increasing age. Only 4 children showed no problems with sleeping through during the night in the sense of the question. The parents indicated an average age of 3.8 months, from which they as parents first noticed the problems with sleeping through the night in their children. In the 6 cases in which the sleep disturbance improved again, this occurred at a mean age of 5 years and 6 months (66.4 months).

The mean frequency of nocturnal awakening was 3 times. In isolated cases nocturnal awakenings up to 10 times were reported.

In only one case a significant improvement in sleep through the night was described under continuous medication with phenobarbital.

In 10 other cases, medication was administered to help the children to fall asleep again after an awakening, in particular chloral hydrate and diazepam, but they failed to achieve a lasting improvement of the sleep-through disturbance.

3.6.5 Apnoeas

A total of 22 children showed apnoeas. These occurred mainly at night which, among other things, led to 13 of the participating 33 children being or having been monitored at night by a pulse oximeter. In 5 of the 22 children who suffered from apnoea, the apnoea stopped at a certain age (median: 42 months; youngest child in whom apnoea stopped again: 8 months; oldest child: 192 months). In 9 children, no apnoeas were described and in 2 cases no information could be provided. When asked about the occurrence of apnoeas during sleep, the frequency ranged from 1 apnoea every other

night to 20 apneas per night. Most of the children with data on the frequency of nocturnal apnoeas (10 data) showed between 2 and 4 apnoeas per night. Treatment attempts with caffeine citrate or formoterol were effective in 2 cases in the acute setting. Three other children received oxygen when needed, and 5 of the children who had apnoeas were fitted with a tracheostoma.

3.6.6 Puberty and sexual development

Due to the scarcity of data, little information can be given on the course of puberty. However, it is interesting to note that pubertal development was described as significantly too early in two girls (6 years and 2 years, respectively). Also, worth mentioning was, that in 8 out of 10 cases of the male participants a maldescensus testis (undescended testis) was observed, and one child showed one hypoplastic male genitalia.

3.7 Development

The motor and cognitive development of children with PCH 2 is severely limited. Thus, only very few children reach milestones of child development such as sitting without support. The control of voluntary movements is severely impaired. However, there are also sometimes huge differences in the degree of cognitive and motor development within the group of children with the same (PCH 2-) mutation.

Table 5 Overview of the skills surveyed. Children whose parents could not provide any information were not included, resulting in the different numbers of cases.

Ability	Number of children who achieved certain ability	Median age at which a certain ability was achieved (in month)	25% quantile (in month)	75% quantile (in month)
Head control	23/33	12	4	30
Moving in prone position	3/33	24	18	36
Rolling from prone to supine	18/33	12	7,5	24
Standing in quadrupedal position	2/32	78	60	96
Sitting without support	3/33	48	36	60
Attempt to grasp	25/33	12	8	24
Targeted grasping	8/33	42	27	57

Using sounds purposefully and repeatedly	19/33	24	12	45
Specific words	4/33	49,5	43,5	57,75
Reaction to praise/ reprimand	26/33	22	10,5	42
Social smile	24/33	11	6	36
Recognizing familiar persons	32/33	8	4	23
Reactions to familiar objects	29/33	22	6	30
Fixing and following with the eyes	26/33	14,5	6	36,25
Reaction to sounds	28/32	18	6	24

3.7.1 Motor development

After reviewing the medical reports, the picture that emerged was that head control in the sense of the head control of healthy children, which remains constant through changes in position, is not or only rarely observed in children with PCH 2. Nevertheless, a moderate control of the head and a turning of the head in a certain direction is definitely present. It was precisely on this point that the parents' statements regarding to the constancy and duration of head control differed considerably from the opinion of the examining physicians. However, if it was noted in a medical report, that head control was present, even if only for a short period of time, the information given by the parents was considered to be correct. From this combination of the physicians' data and those of the parents revealed that 23 of the 33 children examined had developed head control up to a median age of 12 months. In no case it was indicated that head control, once learned, had been unlearned again.

As a second gross motor ability, the ability to move in prone position was asked, regardless of whether this locomotion was achieved by some kind of robbing or rolling. From the information provided by the parents and the results of the review of the medical information, it was found that a total of only 3 children learned this kind of locomotion at the age of 1.5-3 years and they did not unlearn it in the further course.

Turning from the prone to the supine position or vice versa was learned by a total of 18 of the 33 children. The median age at the time of the first turning was 12 months. Between the ages of 2 and 8 years, however, 5 children stopped turning again.

A total of 2 children were able to stand in a quadrupedal position, one at the age of 5 years, another one at the age of 8 years, but the second one lost the ability again at the age of 8.5 years.

2 children learned to sit without support in the intermediate heel seat. One child was able to do this from the age of 5 years on (at the same age the same child also went into quadrupedal position), in the other case no age information was available. A third child was able to sit cross-legged from the age of 3 years on, but lost this ability at the age of 8.5 years again. In all 3 cases, this could be confirmed on the basis of the medical data.

For the fine motor development, a distinction was made between the attempt to repeatedly reach for offered things and targeted grasping. It was found that 25 children did try to focus their movements on an object offered to them. However, targeted grasping was not always possible for them due to the movement disorder associated with their underlying disease. Thus, the parents of the above-mentioned 25 children described that if, for example, an interesting toy is held within reach and sight, the movements of the limbs increasingly narrowed down in the direction of this toy. However, a safe reaching in the sense of a grasping and holding on to the offered objects succeeded in only 8 of the children. The attempt to reach for offered objects was observed from a median age of 12 months. In the 8 cases in which targeted grasping was possible, it was from a median age of 3.5 years (75% quantile: 57 months; 25% quantile: 27 months). In 2 cases, parents indicated that their children, who in each case had shown only an attempt to reach for offered things, did not do so anymore from the age of 6.5 and 8 years on.

3.7.2 Language and comprehension

19 Children used sounds purposefully and repeatedly to express liking or disliking. In one case, no information could be given about the temporal course. In the other 18 cases, the median age was 24 months (75% quantile: 45; 25% quantile: 12), from which on a targeted vocalization was possible. In these cases it was described that pleasure or well-being could be distinguished from discomfort. In 3 cases, according to the parents, differentiated vocalizations were present, one child had different sounds

for reacting to different caregivers or for expressing hunger and thirst. In addition, another child repeatedly showed agreement or disagreement via gestures accompanied by sounds. One child stopped vocalizing with the onset of seizures at the age of 9 years completely.

When asked for the use of specific words such as "yes" or "no" to express agreement or disagreement, the parents of 4 children indicated that their children learned to do so between the ages of 3.5 and 5 years. Here, words were mostly used for caregivers such as "mom" or words of agreement/disagreement such as "yes/no." However, confirmation of this could not be found in medical reports.

The last question in the area of language and comprehension was, whether parents feel that their children respond to prompts, praise, or reprimand from caregivers adequately. This was true in 26 cases and from a median age of 22 months on (75% quantile: 42; 25% quantile: 10.5). Here, most children tended to respond to praise with expressions of pleasure such as a smile. In one case, a corresponding reaction to simple prompts such as "open your mouth" was also described.

3.7.3 Cognitive abilities

A social smile in the sense of smiling back in response to being smiled at was shown by 24 children (median age: 11 months). In one case, this no longer occurred from the age of 13.5 years.

A total of 32 children recognized persons who were familiar, such as parents, and responded differently to them than to persons unfamiliar to them. For the onset of distinguishing between familiar and unfamiliar persons, the median age was 8 months. Here in 11 cases the parents stated that the children recognized familiar persons especially by the way they handled them or by their voice. In the remaining cases, visual recognition was described. A reaction to familiar things was shown by 29 children (median age: 22 months).

Fixation on (interesting, high-contrast) things and following these objects -when moving-with the eyes was evident in 26 children (from a median age of 14.5 months). Whereby here -after checking the medical reports- it must be added that the objects were not allowed to move too fast and that both fixation and tracking were mostly reproducible over short time intervals only. In one case, a child no longer showed any gaze-following movements from the age of 6 years on.

A turning of the head in the direction of a sound source was shown by 28 children from a median age of 18 months.

Although the data in the present study were provided by the parents of the affected children and therefore have a subjective influence, they could be verified to a large extent by medical reports. Thus, there is an observation from 2 sides which clearly shows that children with PCH 2 can, under certain conditions, achieve certain motor and cognitive developmental steps, albeit with a significant delay. Prerequisites for this are a comprehensive support (professional and private), as well as the best possible adjustment of accompanying symptoms, such as epilepsy, dystonic attacks, possible existing pain due to reflux, contractures, etc.

3.8 Growth

The body length, body weight and head circumference were asked at the 10 screening examinations in childhood (U1-U9, for an explanation of the German screening system see *6 Abbreviations and explanation of technical terms 'Screening system in childhood in Germany'*).

In all cases, the SD values were used. SD values, are values that describe the relationship of values found in a group to the norm, i.e., whether they correspond on average to the norm or are below/above it (see Figures 7-10). See list of abbreviations for explanation of SD value.

Overall, the SD values for all collected data (body length, body weight, head circumference) were within the normal range at the beginning, but deviated downward during the course, i.e., length, weight and head circumference developed significantly below average in the children. Especially the head circumference showed a particularly

restricted growth and dropped to - 5.5 SD by the age of 2 years, but then stabilized in this range. Also, for body weight and body length, the mean SD values dropped from the normal range into a pathological range, which, however, did not deviate as far from normal as the head circumference. The BMI (body mass index, i.e. a measure of the ratio of length to weight) is an exception. It first dropped to -2 SD, then recovered to -1.5 SD at U9. This means that the children are not increasingly dystrophic or malnourished, but that their weight was more in line with their body length. This sheds a positive light on the nutritional situation during the course of the childrens life.

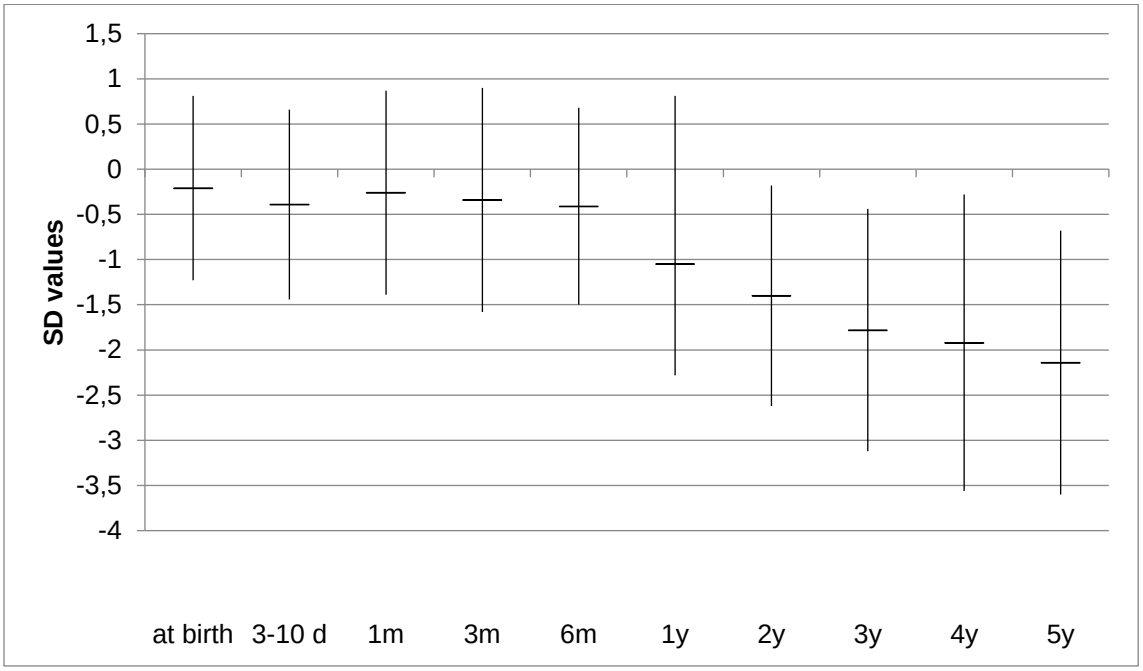


Figure 7 SD values +/- standard deviation for body length

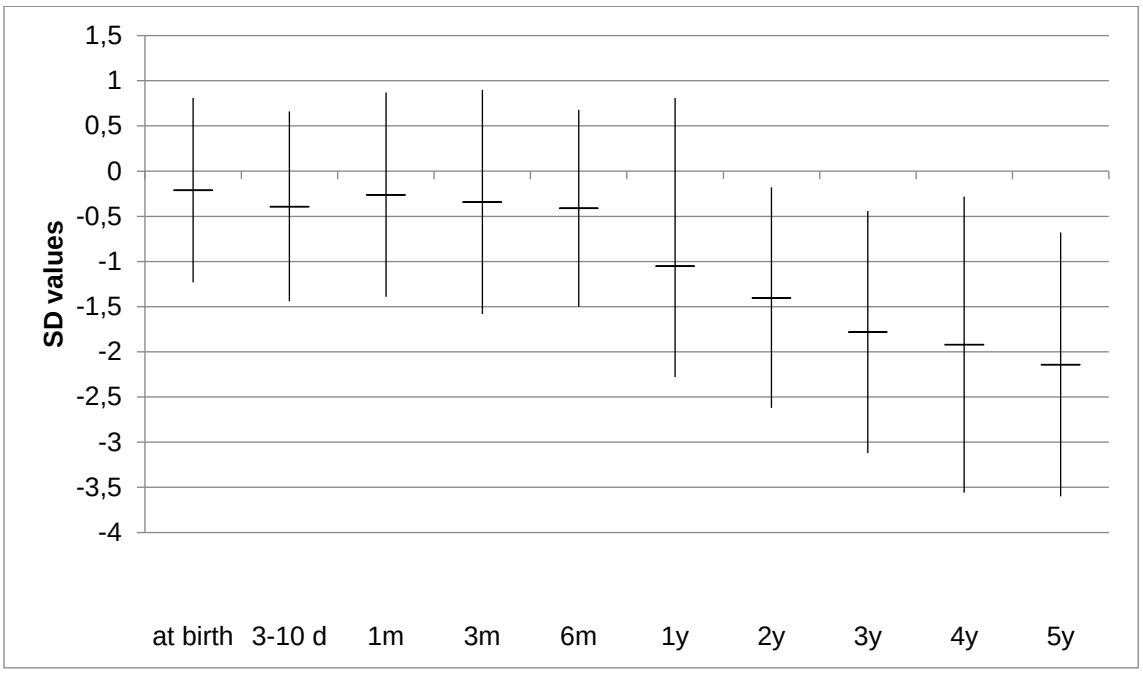


Figure 8 SD values +/- standard deviation for body weight

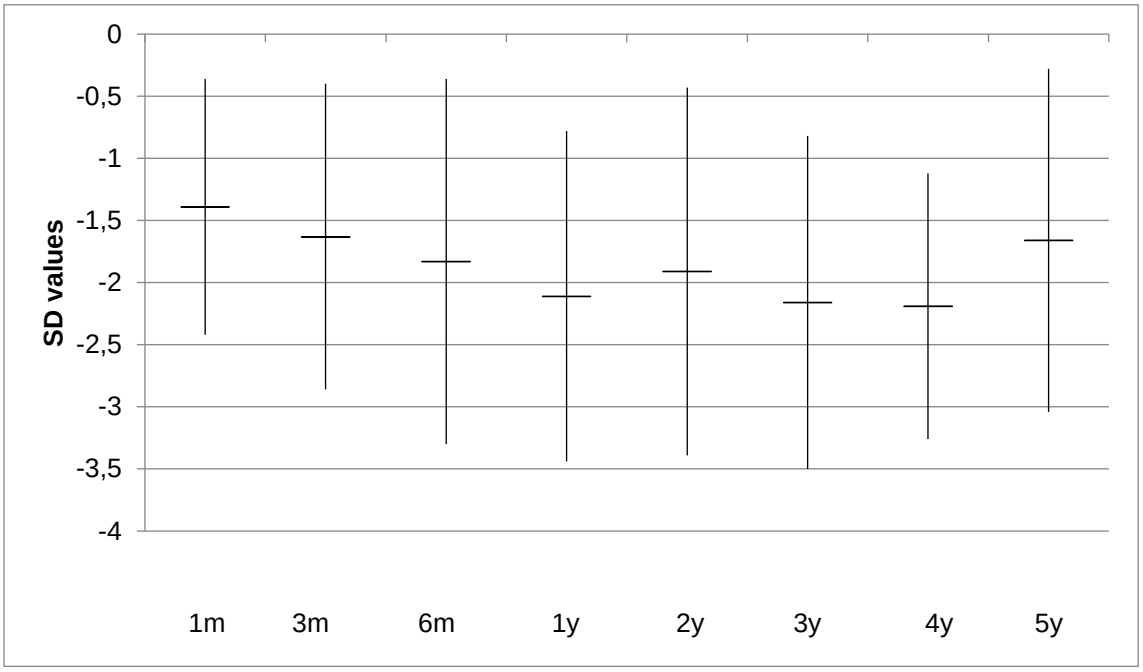


Figure 9 SD values +/- standard deviation for BMI

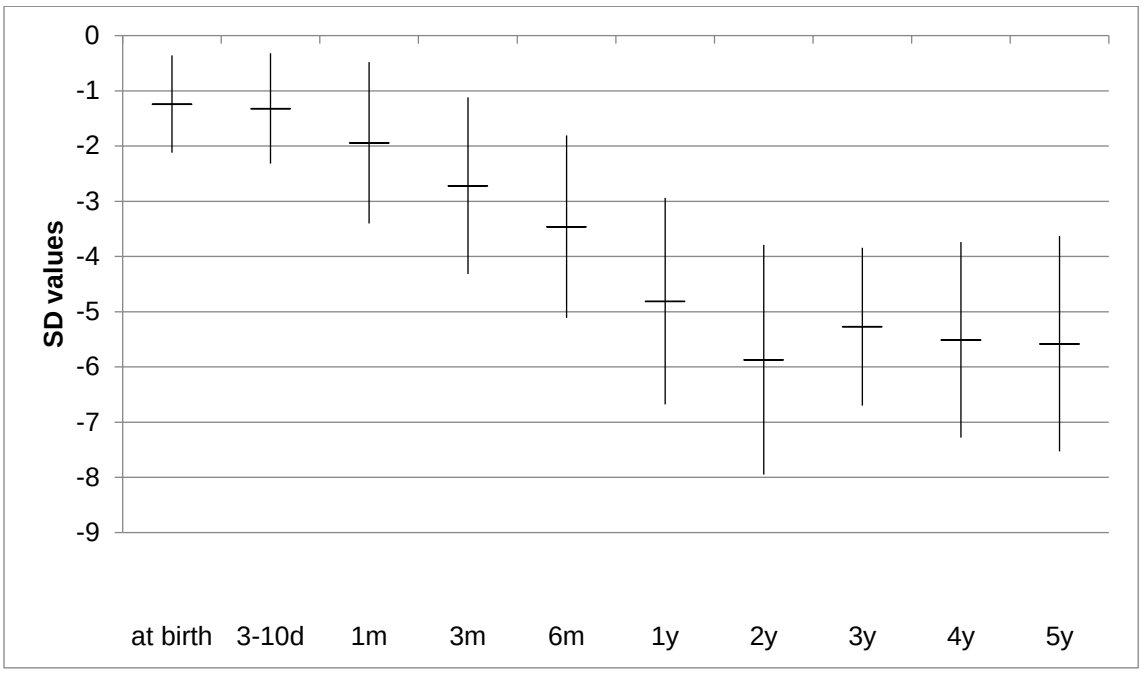


Figure 10 SD values +/- standard deviation for head circumference

3.9 (Continuous) medication and operations

Continuous medication was present in 29 children with at least one medication (average 4 medications) per day.

Type of continuous medication:

- Antiepileptic drug (25 of 29) or combination of different antiepileptic drugs (14 of 25).

- Proton pump inhibitor (17 of 29)

- laxative medication (12 of 29)

- sedatives (9 of 29)

- Muscle relaxants (2 of 29)

- Melatonin (4 of 29)

Table 6 Performed Operations

Type of surgery	Number of children who underwent surgery	Average age at the time of surgery (indicate the mean value, as well as the minimum and maximum ages)
Fundoplication	12	5,8 years (min. 9 months; max. 19,1 years)
Tracheostoma	5	7 years (min. 15 months; max. 14,5 years)
PEG tube	21	3,8 years (min. 6 months; max. 14 years)
Tonsillectomy	3	3,5 years (min. 2,8 years; max. 4,7 years)
Orthopaedic surgery	2	min. 7,6 years; max. 14 years
Other operations	30	

3.10 Social paediatric aspects and care

3.10.1 Disability certificate/level of care

29 of the 33 children had a disability certificate, issued at an age between 0 and 5 years (mean: 13.7 months). In 28 cases this confirmed a 100% disability, in one case only a 90% disability. 31 children had a level of care.

Table 7 Classification into care levels (see *6 Abbreviations* for explanation of German care levels); n=31

Care level	Number of children with this level of care as highest level of care	Age at which classification into this care level took place (mean value)	Youngest child who has received this care level (age in months)	Oldest child who has received this care level (age in months)
1	2	11 months	9	12
2	5	28 months	12	60
3	23	29 months	2	84

3.10.2 Kindergarten and school

Admission to kindergarten occurred at an average of 3 years and 4 months. The youngest child entered kindergarten at 2 years, and the oldest at 5 years and one month. Of the 14 children, who were not in kindergarten, 9 were younger than 3 years (or died before they were 3 years old).

The mean age of school enrolment was 6 years and 3 months. The youngest child was 5 years old at enrolment, and the oldest was 7.5 years. Of the 17 children who were not (yet) attending school, the oldest was 7 years and 3 months old at the time of data collection, all others were younger or had passed away at a younger age.

Table 8 Type of kindergartens/schools attended and respective number of children

	Type of institution	**Number of children**
Kindergarten		19/33
	regular kindergarten with accompaniment*	1/19
	integrative kindergarten (healthy and disabled children together)	10/19
	special kindergarten without accompaniment* (e.g., kindergarten for physically and mentally disabled children)	6/19
	special kindergarten with accompaniment*	2/19
School		16/33
	Regular school with accompaniment*	1/16
	Special school without accompaniment*	11/16
	Special school with accompaniment*	4/16

* Accompaniment means a professional who exclusively takes care of the child in question

3.10.3 Provision of aids and supportive therapies

The children had a mean of six assistive devices (min.0; max.14). These are listed in more detail in table 9. Only one child had no assistive devices.

Table 9 Assistive devices; n=33

Assistive device	**Number of children with this device**
Foot orthoses	17
Abduction splint	4
Full body support splint	3
Adapted seat shell	26

Stand to support standing	20
Wheelchair	30
Lifter	6

In 22 cases, families had additional assistive devices apart from those listed above, including custom-made car seats, communication systems, special devices on bathtub or shower, pulse oximeters, suction and inhalation devices and corsets.

Eight children showed problems accepting the assistive devices. Sitting in the wheelchair or the specially made seat shells with strap-on system was particularly difficult for the younger children (5 of the 8 children were 5 years old or younger).

Therapies: All 33 children received at the time of data collection or, in the case of the deceased children, until their death, physiotherapy, 15 children received ergotherapy and 14 children were treated by a speech therapist. In addition to these therapies, a total of 18 children received further therapies, including early vision support, respiratory and riding therapy.

3.10.4 Family environment and utilization of support

On average, 2 children - including the sick children - lived in one household.

Help was sought for the first time at an average age of 2.5 years. The parents who used assistance in the care of their children, did so for 53 hours (minimum: 2 hours; maximum: 168 hours) weekly. The time a child spends in school or kindergarten did not count toward this total unless, the child is accompanied by a caregiver or specialist from home. Table 10 shows which types of assistance were used.

Table 10 Support with the care of the children

Single parent		4/33
Parents seeking (professional) help		27/33
	Nursing home	5
	relatives	9
	Nursing service	13
	Paediatric hospice service/ private paid help	13

	Paediatric hospice/ private paid nursing home during holidays	14

3.10.5 Feeding

Twenty-one children were reported to be fed by PEG tube. However, seven received predominantly oral nutrition in this process, six were mainly, and eight were completely fed via PEG tube. Eating from a spoon: 28 children were able to do so from 7 months of age (min 3 months; max 42 months). The 5 children who were not fed with a spoon, were fed by a PEG tube in 4 cases, and in one case the child was fed until death at the age of 9 months with the bottle. 10 of the children who were able to be fed with a spoon were fed exclusively or predominantly by a PEG tube.

Number of meals: The children were fed on average every 3 hours, equivalent to 8 meals in 24 hours. 10 children received nocturnal meals, of which 5 children received their nocturnal meal via PEG tube, the other 5 were children of whom the eldest was 2 years old.

Intolerances to certain foods such as strawberries, lactose-containing products, or foods that contain a lot of acid, particularly in the context of increased reflux, were reported for 10 children.

Liquids could be consumed by 15 children from a (special) cup, such as F.O.T.T. cup® or a soft cup with a wide upper rim. This was learned at a mean age of 28 months. 5 of these children nevertheless received most of their daily fluid intake via PEG tube. Of the 18 children who could not drink from a cup/glass, 13 also received their fluids via a PEG tube. In the remaining 5 cases, the children were either able to take in the required amount of fluid themselves via a sucker or the fluids were injected with a syringe into the cheek pouch. In total, 7 parents whose children did not receive their fluids via a PEG tube reported that the ingestion of the fluid and the process of swallowing was easier for their children when using thickened drinks.

3.10.6 Nocturnal monitoring

Nocturnal monitoring of vital signs using a pulse oximeter was performed in 13 children. Of these 13 children, 6 showed regular bradypneas with a respiratory rate of a minimum of 5 breaths per minute during sleep. The respiratory rate ranged from 10 to 22 breaths per minute (mean: 16.3 breaths per minute; standard deviation: 5.3). In 9 cases, the devices regularly indicated apnoeas, which occurred between 1 and 11

times per night. Heart rate ranged from 60 to 100 beats per minute (mean: 69.4 beats per minute; standard deviation: 13.5).

3.10.7 Breathing and tracheostoma

As mentioned above, 5 children had a tracheostoma, through which they were ventilated only as needed. Oxygen was necessary regularly in 6 children, and in 4 children occasionally (for example, in case of saturation drops or respiratory infections). 17 children have been inhaled regularly, i.e., at least once a day, mean: 3.6 times a day.

3.10.8 Individual course after PEG tube insertion

Of 4 children, at least 4 data on height, weight and head circumference were still available after insertion of the PEG tube at the age between 6 and 24 months. So, the course of these values after PEG tube can be shown in more detail (see table 11 and figure 11- 14).

Table 11 Patients for whom a progression of growth parameters can be shown after insertion of a PEG tube

Pseudonym of the child	Gender	PEG tube placement at the age of (in months)	Age in months at the time of the last measurement (corresponds to age at the time of data collection)
T02n	female	16	80
T06n	female	24	66
T22n	female	6	97
T30n	female	13	82

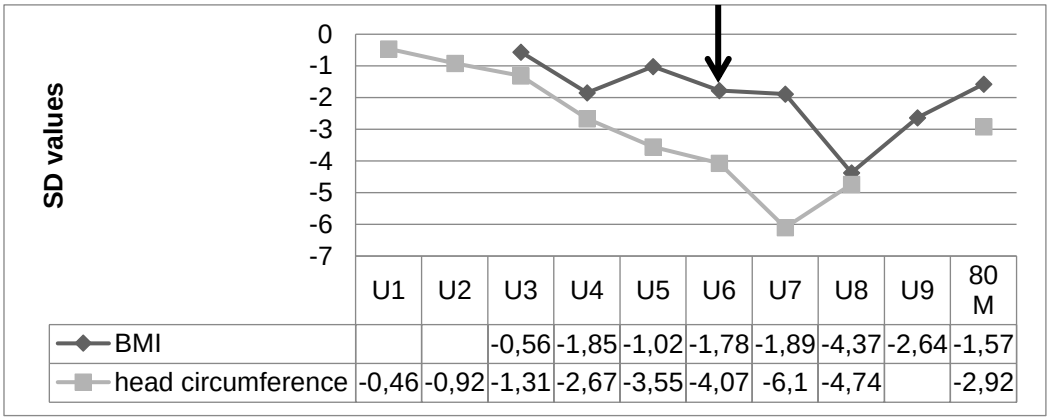
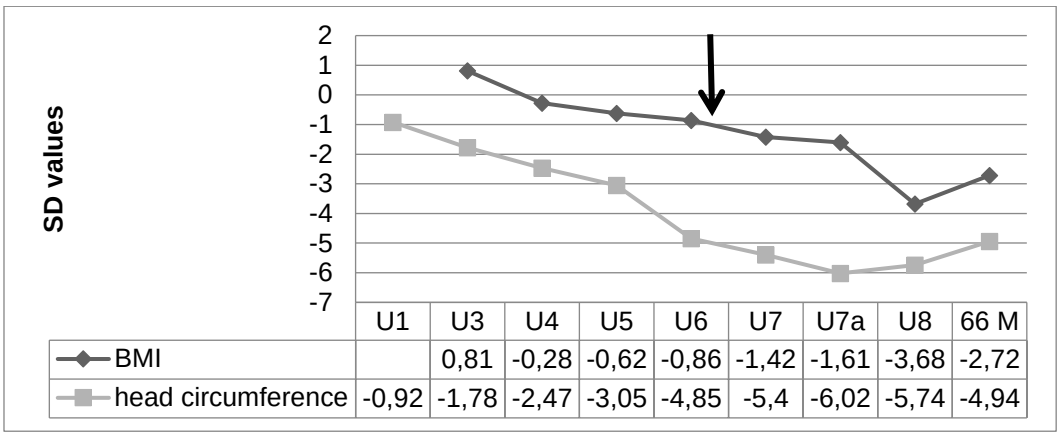
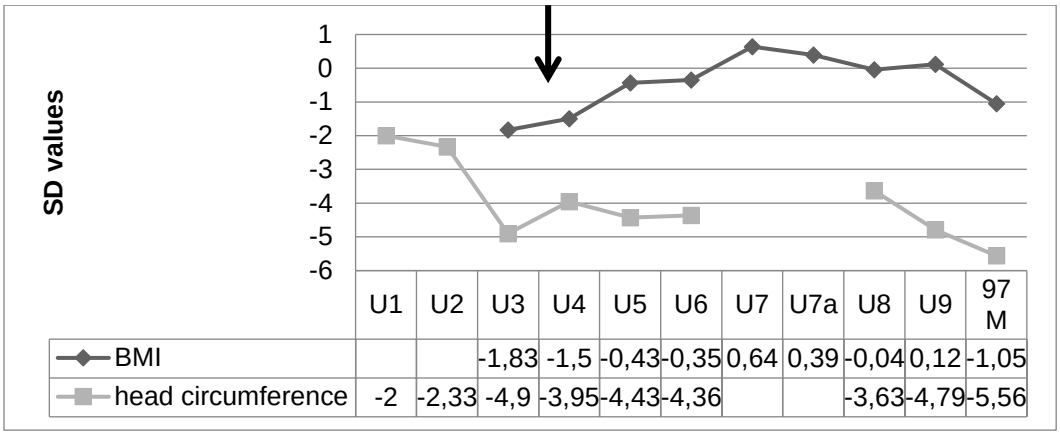


Figure 11 Individual course of BMI and head circumference after insertion of a PEG tube for T02n; PEG tube present from U7 (see arrow).*



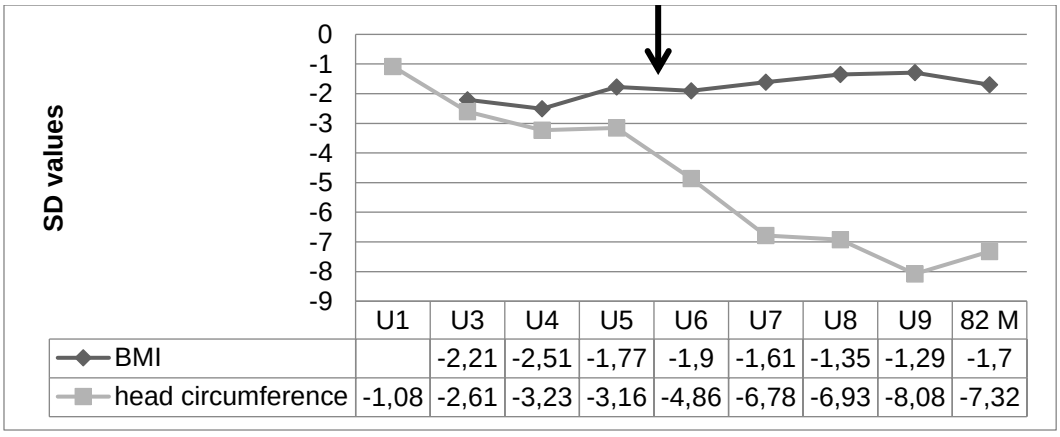
	U1	U3	U4	U5	U6	U7	U7a	U8	66 M
BMI		0,81	-0,28	-0,62	-0,86	-1,42	-1,61	-3,68	-2,72
head circumference	-0,92	-1,78	-2,47	-3,05	-4,85	-5,4	-6,02	-5,74	-4,94

Figure 12 Individual course of BMI and head circumference after insertion of a PEG tube for T06n; PEG tube present from U7 (see arrow).*



	U1	U2	U3	U4	U5	U6	U7	U7a	U8	U9	97 M
BMI			-1,83	-1,5	-0,43	-0,35	0,64	0,39	-0,04	0,12	-1,05
head circumference	-2	-2,33	-4,9	-3,95	-4,43	-4,36			-3,63	-4,79	-5,56

Figure 13 Individual course of BMI and head circumference after insertion of a PEG tube for T22n; PEG tube present from U5 (see arrow).*



	U1	U3	U4	U5	U6	U7	U8	U9	82 M
BMI		-2,21	-2,51	-1,77	-1,9	-1,61	-1,35	-1,29	-1,7
head circumference	-1,08	-2,61	-3,23	-3,16	-4,86	-6,78	-6,93	-8,08	-7,32

Figure 14 Individual course of BMI and head circumference after insertion of a PEG tube for T30n; PEG tube present from U7 (see arrow).*

*For explanation of the German screening system (U1-U9) see *6 Abbreviations*

In patients T22 and T30, who received a PEG relatively early, the BMI was stable during the course of the study, but the head circumference was clearly below average. In T02 and T06, the BMI first decreased, then recovered, very significantly in the case of the first child. Interestingly, the head circumference trend showed a slight increase in three of the four children at the end of the observation period. These 4 children did not differ in their symptom profile from the other children. A direct correlation between the age at which a symptom disappeared and the age at the time of PEG tube placement was not evident in any case.

Table 12 Symptoms of the selected children with existing PEG tube

	T02n	**T06n**	**T22n**	**T30n**
Increased vomiting	+	+	- (since the age of 30 months)	+
Obstipation	-	-	+	+
Dystonic attacks	-	+	-	-
Increased infections	+	+	-	- (since the age of 60 months)
Seizures	+	+	+	+
Temperature regulation disorder	-	+	- (since the age of 72 months)	-
Sleep disturbance	- (since the age of 6 months)	+	+	- (since the age of 60 months)
Apnoeas	- (since the age of 42 months)	+	+	-

4 Discussion

Thanks to the encouragement and active support of the PCH Parents' Initiative 33 children with pontocerebellar hypoplasia type 2 could be systematically recorded with regard to their clinical picture and in particular its course. Molecularly, they all showed the homozygous phenotype, most frequently described for PCH2 *homozygous missense mutation 919 G>T, p.Ala307S in the TSEN 54 gene*. This group is also called PCH2A. With these systematic data on the course of the disease it is possible to describe how variably a certain mutation is expressed in the clinical picture. This is also called genotype-phenotype correlation.

The following areas could be characterized in more detail:

- Life expectancy and the role of a prenatal onset

- Development of physical measures

- Neurological symptoms including seizure phenomena

- Developmental course

- Additional disease symptoms such as nutritional and sleep problems.

Life expectancy proved to be significantly shortened; most patients did not reach puberty, as has also been reported in the literature [1]. As in the literature an occurrence of certain symptoms such as an excess of amniotic fluid, a too small head circumference and conspicuous movement patterns even before birth are associated with a more severe course of the disease [2;3;4;5;6], we compared the course of the disease of the 10 children who showed these prenatal symptoms with that of the others. In our study no difference was found neither in life expectancy nor in body measurements and disease symptoms. The developmental course was also similar. One can therefore conclude that in children with the typical mutation in the TSEN54 gene, a prenatal onset does not herald a more severe course. This is very important for the counselling of the affected families.

The body measurements of the children were mostly in the normal range at birth. Then the very below-average development of the head circumference or progressive microcephaly, already described in literature [4; 7], showed. Weight and length also develop below average at PCH2. They drop to below -2 SD value on average; in comparison, microcephaly is even more pronounced, with values around -5 SD.

Neurological symptoms including seizures and seizure like phenomena: almost 90% of the children showed the choreoathetotic movements described as typical, which was already apparent in the first month of life. Only a few children showed predominant spasticity. This is similarly described in the literature [8].

Epileptic seizures were frequent and of variable form and severity. Quite a few children showed one or more prolonged seizures or series of seizures in terms of epileptic status. In most cases, the epilepsy was refractory, i.e., it did not respond sufficiently to medication. In an analysis of the used medications, phenobarbital and topiramate most frequently showed some effect on seizures.

The fact that all children who did not show seizure activity in our study were 28 months of age or younger confirms the statements in the literature that the likelihood of developing seizures increases as children get older [4].

Dystonic attacks have not yet been systematically described. There is only one case report [3] with 'dystonic crises', which were similar to the dystonic attacks shown by the children in our study. One third of our children had such sudden onset states, which proceeded very similarly: a stiff, c-shaped posture of the trunk (parents also called it 'lop-sidedness') for several hours. The children feel bad during this, some of them vomit; the attack is ended by a spontaneous sleep. In half of them the conditions stopped again during the course. They did not really respond to medication. A relation to reflux could not be clearly proven.

Developmental course: PCH2 is characterized by severe global disability [1;2;4; 8]. Also, in this study none of the children learned milestones such as crawling, standing or walking. But at least about two-thirds of the children made developmental progress, albeit slowly and only to a certain extent: they achieved some head control, could turn, tried to grasp, expressed liking and disliking through sounds, showed a smile on contact, recognized familiar persons, and followed nearby objects with their eyes. A few were even able to sit without assistance. It was also important to determine, that if the child could not grasp, it was not so much due to its mental ability than due to the dyskinetic movements.

Only a few children lost functions again that they once had learned.

Such differentiated developmental data did not previously exist on PCH2. They are not only important for the counselling of parents, who are often told that their children will

not make any developmental progress. They are also important for a better understanding of the disease mechanisms in PCH2. They give an indication that after early degeneration of the cerebellum (in late pregnancy), the brain shows some recovery and stabilization that may allow developmental progress.

Additional disease symptoms:

Feeding or swallowing difficulties are described in all publications as a typical symptom of PCH 2 [2;4;7]. However, an improvement of feeding difficulties with increasing age of the children, as we saw it, has not been reported in the literature so far.

Almost all children had a diagnosis of gastroesophageal reflux disease or showed clear clinical signs of it. This observation also seems to be important for consultation, i.e., one must think about it early on and initiate diagnostics and therapy.

21 children had to be treated with a PEG tube. The effect of PEG tube feeding on somatic parameters could only be examined more closely in four selected examples, where BMI stabilized. Whether this situation also has a positive effect on head growth and development cannot be deduced from these data. Further studies are necessary for this. Subjectively, however, 18 parents mentioned the PEG tube as a necessary and important step that improves the nutritional situation, relaxed the living situation with the children and had a positive effect on the development of the children.

The literature does not report anything about sleep problems, although we found them in almost all children. Apnoeas (pauses in breathing during sleep) were described in about two-thirds of the children.

5 Summary

In summary, the children with PCH2 showed a very severe clinical picture with significantly reduced life expectancy. The growth, normal at birth, was clearly below average during the course, especially that of the head. Neurologically, the focus was on the severe dyskinetic movements. Epilepsy always occurred after the age of 2 and the seizures were difficult to treat. This was also true for the dystonic attacks occurring in one third of the children. Feeding problems, which often required a PEG tube, and gastroesophageal reflux disease, as well as severe sleep problems and frequent infections contributed to the severity of the condition and the burden of care. Despite this, two-thirds of the children made developmental progress, in both motor and mental development.

This study was published:

Sánchez-Albisua I, Frölich S, Barth PG, Steinlin M, Krägeloh-Mann I. Natural course of pontocerebellar hypoplasia type 2. Orphanet Journal of Rare Diseases, 2014, 9:70, 1-11.

6 Abbreviations and explanation of technical terms

apnoea = suspension of breathing

aspiration pneumonia = pneumonia caused by inhalation of food or vomit

bradypnea = breathing rate that is too slow

care levels in Germany= 1 (significant need for care); 2 (severe need for care); 3 (more severe need for care than in level 2)

diabetes = sugar disease

gastroesophageal reflux = reflux of stomach contents into the oesophagus

hyperexcitability = over-excitability

hyperthermia = body temperature is too high

hypothermia = body temperature is too low

microcephaly = too small head circumference

muscle tone = state of tension of the muscles

muscular hypertonia = too high muscle tone

muscular hypotonia = too low muscle tone

myoclonia = rapid involuntary muscle twitching

neonatal period = 1st-28th day of life.

constipation = defined here as spontaneous bowel movements less than once per day

pneumonia = lung disease caused for example by pathogens or aspiration

polyhydramnios = excessive amount of amniotic fluid

rhabdomyolysis = dissolution of muscle fibres, muscle atrophy

Screening System in childhood in Germany = there are 10 screening examinations recommended and free of charge in Germany till the age of 5 years
U1: directly after birth; U2: 3-10 days; U3: 1 month; U4: 3 months; U5: 6 months; U6: 1 year; U7: 2 years; U7a: 3 years; U8: 4 years; U9: 5 years

SDS score = standard deviation score. It indicates by how many times a standard deviation an individual value is above or below the median value of the reference group

for a corresponding age. Values that exceed 2 times the standard deviation are therefore to be classified as pathologically too large (greater than +2) or too small (less than -2).

status epilepticus = prolonged epileptic seizure lasting for more than 20 min or series of seizures between which consciousness is not regained.

growth retardation = growth is delayed

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