Natural History of Pontocerebellar Hypoplasia Type 2

A Guideline for Parents and Those Interested

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PCH2cure

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PCH2cure is a project of the German association PCH-Familie e.V.
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The treatment options and dosages listed here are based on data from the 2023 Natural History Study on PCH2. The list makes no claim to be exhaustive and represents neither a specific recommendation nor an endorsement of the drugs or treatment options mentioned. It is a compilation of measures that have been tried in the past and is intended for informative purposes only. PCH-Familie e.V. and the PCH2cure project assume no liability in this respect.

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Preface

Pontocerebellar hypoplasia type 2 (PCH2) is a rare, relatively unknown disease. As with most rare diseases, it is often difficult for those affected, but also for medical professionals, to find relevant information and support.

In Germany, parents of affected children have come together, initially via an online forum and at biannual family meetings, and more recently by founding a patient organization in 2018: PCH-Familie e.V.
This organization connects affected families and promotes the exchange of information between families through organized meetings, carries out public relations work and has set itself the task of decisively advancing research into the disease.

At the initiative of committed parents, an initial description and natural history study of the disorder was published back in 2014. The main focus of this study, which was carried out as part of a doctoral thesis, was to describe the natural history of the disorder in terms of growth, development and care, as well as everyday life with a child with PCH2. Another aim of this study was to compile a parent brochure on PCH2 (first edition 2014, revised 2019, second edition 2021).

In 2020, a second natural history study was planned in collaboration with PCH2 parents and carried out in the years that followed. The study aims to expand on and update the knowledge about the natural history of PCH2 using data from a larger group of patients, with a particular focus on the medical treatment of symptoms and the nutritional situation, as well as the growth and development of children with PCH2.

Hereafter, the term PCH2 is used in most contexts, even though the study results were obtained from a group of children with PCH2A, the most common variant of PCH2. Nevertheless, the clinical results can also be applied to PCH2 in general.

Please be advised that the study is centered around the German healthcare system and based on the two Natural History Studies conducted with families predominantly living in Germany. Legislation, trade names of medication and other aspects may differ from the situation in your country.

We would like to sincerely thank the participating parents for their cooperation and support – hoping that our study and this booklet will offer guidance to relatives, parents and healthcare professionals in dealing with their children and/or patients affected by PCH2.

1 Introduction and Fundamentals of PCH

1.1 Historical Background

Historically, pontocerebellar hypoplasia was usually included among the olivopontocerebellar atrophies. First reports of clinical symptoms such as swallowing difficulties, spasticity and a lack of cognitive and motor development can be found as early as 1928 [1]. The extrapyramidal component was first reported in 1977 [2].

This was followed by a 1990 study of five families with children affected by PCH2 [3]. All families came from a small Dutch municipality called Volendam, north of Amsterdam. Centuries ago, the municipality of Volendam had resisted the Reformation, remained faithful to the Roman Catholic Church and therefore lived in isolation from neighboring communities, resulting in a higher rate of marriage among close relatives and thus a depletion of the gene pool. This explains the high incidence of PCH2, an autosomal recessive hereditary disorder, among this small community. Given the fact that the exact same variant causing the disease was found homozygously (i.e. two identical copies) in almost all European PCH2 patients, it is assumed that they all share a common ancestor who probably lived in the 17th century [3-5].

1.2 Pontocerebellar Hypoplasia – a Group of Disorders

The term „pontocerebellar hypoplasia“ refers to a heterogeneous group of disorders that are associated with a developmental disorder of the brain and severe mental and physical disability [5, 6]. They follow an autosomal recessive inheritance pattern (see chapter on inheritance).

The term is a combination of the terms pons („bridge“), cerebellum („little brain“) and „hypoplasia“ (structure that is too small) and thus describes the structural abnormalities of the brain visible in MRI scans.
The cerebellum and the bridge in particular are significantly underdeveloped in those affected [7, 8]. The pons is an important junction between the spinal cord and the brain with major connections to the cerebellum. The cerebellum plays an essential role not only in the coordination of movements, but also through its abundance of projections towards the cerebrum. Early disorders of cerebellar development therefore also result in impaired cerebral development (microcephaly). However, it is likely that additional factors, depending on the respective genetic defect, also contribute to changes in the cerebrum [9].

In addition to the similarities mentioned above, the various types of pontocerebellar hypoplasia differ in the genes responsible for the condition and in their clinical symptoms. Initially, the disorders were primarily defined based on imaging, i.e. the presence of pontocerebellar hypoplasia, and were classified into different types based on their severity, clinical symptoms and, if applicable, lab parameters. It was not until the underlying genetic defects were discovered that a more specific classification became possible. However, many subtypes have only been described in a few affected individuals to date, as the disorder remains very rare overall. Over 17 types of PCH have now been described, some of which are further categorized into subtypes [6, 10, 11]. Within and between the subtypes, however, a wide range of clinical symptoms and imaging results exist. In addition, there are patients who meet all the

criteria for PCH but do not have any of the known genetic variants. The clinical picture of the PCH group of disorders is therefore very broad and heterogeneous.

Below, the best described and more frequent subtypes are explained in more detail, concentrating on the clinical symptoms. Details of the underlying specific causative genes can be found in literature, in particular in the article „What's new in pontocerebellar hypoplasia? An update on genes and subtypes" [6].
Further resources for professionals and those interested include the overview „Pontocerebellar Hypoplasia: a Pattern Recognition Approach" [10], which presents the various clinical pictures associated with a reduced volume of the pons and cerebellum, as well as the online OMIM database [Online Mendelian Inheritance in Man] [11].

- PCH1: In addition to the neuropathological changes described above, this type also causes a disorder of the anterior horn cells of the spinal cord. Patients therefore show severe muscle weakness and have trouble breathing. As the children cannot swallow properly, polyhydramnios (excessive amniotic fluid) often occurs before birth.
- PCH2: PCH2 is probably the most common subtype and is further subdivided into the types PCH2 A-F. Apart from severe mental and physical disability, it is characterized by a dyskinetic motor disorder.
- PCH3: PCH3 is characterized by hypotonia (insufficient muscle tone) with, however, increased reflexes, as well as facial malformations. As the disease progresses, optic nerve atrophy (death of nerve fibers in the eye) occurs, leading to severe visual impairment. Affected children also have small statures. The motor disorders typical of PCH2 do not occur in PCH3.
- PCH4 and 5: Affected children share many similarities with PCH2 patients, but have a more severe progression which, with few exceptions, leads to death in the neonatal period. Prior to birth, an excess of amniotic fluid and contractures in the unborn child are usually noticeable. Differences previously observed between these two types could no longer be verified in recent studies, making the distinction between PCH4 and 5 obsolete.

- PCH6: Children with PCH6 show generalized hypotonia (low muscle tone) after birth. Spastic motor disorders, apnea and epileptic seizures as well as severe developmental delay occur in the course of the disease. There are also specific changes of the blood parameters (increase in plasma lactate).
- PCH 7: A few case reports have indicated that this type can also be associated with hypoplastic (too small) male genitalia, muscular hypotonia and apnea.
- PCH 8: Unlike the other types, PCH8 appears to be a stable neurological state. No evidence of progression of the disease has been found to date.
- PCH9: This type is characterized by progressive microcephaly, severe developmental retardation, cortical visual impairment, swallowing difficulties and spasticity. There have been isolated reports of physical abnormalities, mainly affecting the face and teeth.
- PCH10: Affected children have severe developmental retardation, seizures, progressive spasticity, facial abnormalities and microcephaly.
- PCH11: This is another non-progressive type of PCH. Affected children have severe developmental delay, microcephaly and muscular hypotonia.

Some patients were able to walk independently and convulsions only occurred in a minority of those affected.

1.3 Pontocerebellar Hypoplasia Type 2

PCH2 is the most common type of pontocerebellar hypoplasia [6,10]. It is characterized by the presence of a dyskinetic motor disorder, i.e. involuntary, typically rapid (choreoathetoid) movements of the limbs, or abnormal postures and distorted voluntary movements with increased muscle tone (dystonia). In the course of the disease, a spastic motor disorder is typically observed. Other typical symptoms of PCH2, which occur in the majority of subtypes, include a small head circumference, a severe general developmental disorder and the development of epilepsy [5, 6, 12]. PCH2 is further subdivided into the subtypes PCH2A-F. The genetic cause of PCH2A, B, C and F lies in different regions of the TSEN complex (tRNA splicing endonuclease), while the other subtypes involve different genes. PCH2A is the most common subtype of PCH2 [6, 10].

1.4 Incidence and Inheritance of PCH2

PCH2A is a very rare disease. The estimated incidence (number of new cases per year) is less than 1:200,000, i.e. in Germany one PCH2 child is born for every 200,000+ newborns.

In 2008, the pathogenic (disease-causing) genetic alteration for PCH2A was found [4]. It is a mutation in the TSEN54 gene on chromosome 17q25. Almost all European patients with PCH2A have the identical pathogenic variant c.919 G>T, p.Ala307S.

Human genetic information (DNA) is found „tidied up“ in so-called chromosomes within a cell. There are two copies of each chromosome in every human cell (with the exception of the X chromosome in men). These chromosomes store our genetic material. Specific sections that can be translated into certain proteins are called genes.
Parents pass on one copy (allele) of a gene to their biological children. PCH2 has an autosomal recessive inheritance pattern, which means that the disease only develops if the mutation is present in both the maternal and paternal copies of the affected gene. Parents who are carriers of the PCH2 mutation therefore each pass on a genetically modified copy of the gene to their child. As a result, the

child carries two mutated copies of a gene (this is called homozygous), which leads to the development of PCH2. If only one parent passes on the altered gene to the child, but the other parent passes on a healthy allele (this is called heterozygous), the child will not develop PCH2. This makes the child a carrier, however, and it can pass the mutation on to its own children. If both parents pass on the healthy allele (i.e. the unaltered copy of the gene) to their child, the child will be healthy and not a carrier. (Fig. 1)

In purely mathematical terms, parents who are both carriers of the altered gene copy therefore have a 25 % risk of conceiving a child with PCH2 for each pregnancy. There is a 50 % probability that each child will be a carrier without developing PCH2, and a 25 % probability that the child will not inherit any mutation at all.

1.5 Neuroradiological Diagnostics of PCH2

Before the genetics of the disease were known, diagnosis was based on its typical clinical symptoms and magnetic resonance imaging (see Figs. 2 and 3) of the brain. The MRI scans show a thinning of the pons and a significant reduction in the size of the cerebellum. Hence the name “pontocerebellar hypoplasia“. The shape of the abnormal cerebellum is reminiscent of the wings of a bat or dragonfly and is therefore also described as “bat-wing“ or “dragonfly-like” [5, 8, 9].

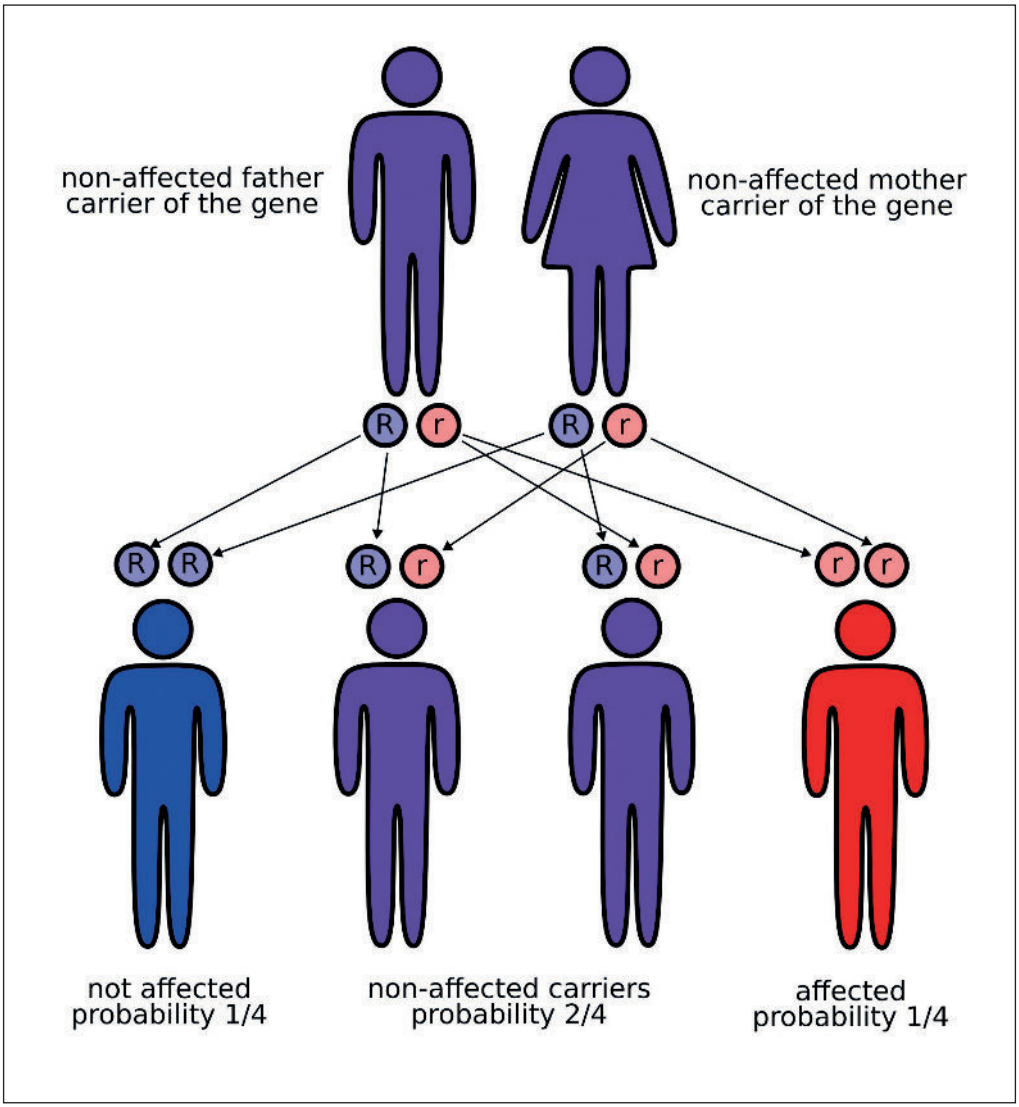


Fig. 1: Depiction of autosomal recessive inheritance.

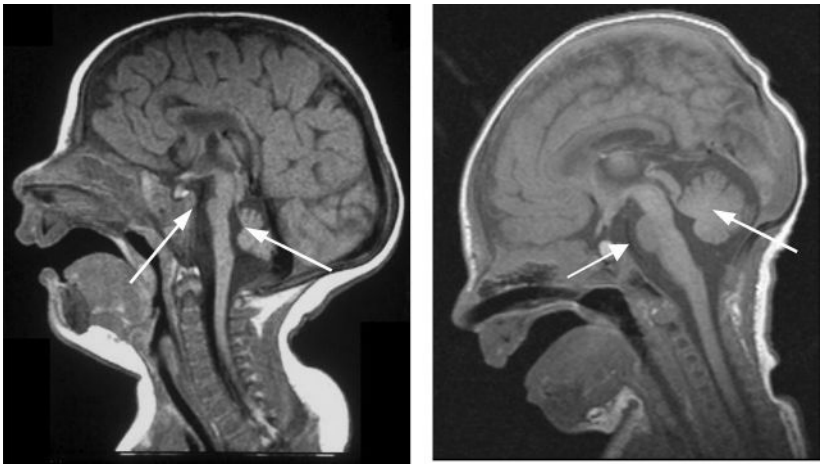


Fig. 2: Magnetic resonance image of a child with PCH2 (left) compared to a normally developed child (right); the arrows show the underdeveloped pons and cerebellar vermis (short arrows) (Sanchez et al.)

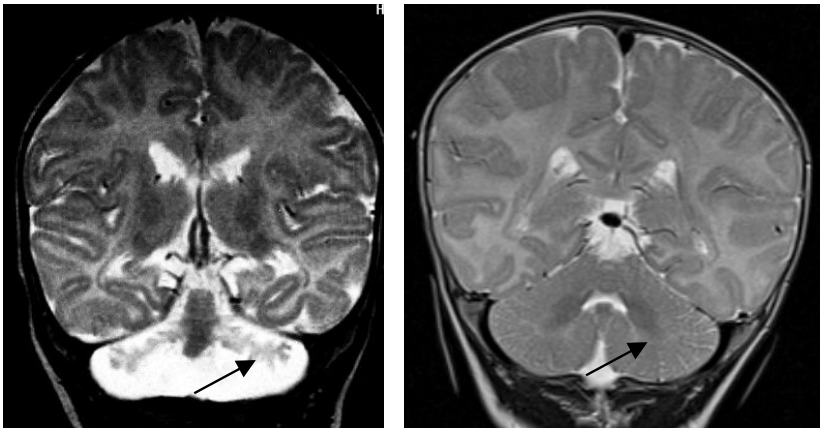


Fig. 3: Magnetic resonance image of a child with PCH2 (left) compared to a normally developed child (right); the arrows point to the cerebellar hemispheres, noticeably underdeveloped in PCH2 (‚dragonfly-like') (Sanchez et al.)

1.6 Prenatal Diagnostics of PCH2

It is possible to have the unborn child genetically tested for the genetic mutation responsible for PCH2A (homozygous pathogenic variant present in the TSEN54 gene) during pregnancy. Genetic testing for PCH2A is only carried out if there is either an affected sibling or if abnormalities are found in the prenatal ultrasound which are indicative of PCH2A. In the case of PCH2A, however, the prenatal ultrasound findings are usually inconspicuous at this time [8, 13]. Genetic testing is technically possible from the twelfth week of pregnancy onwards. For PCH2 parents planning to have another child, obstetric counseling and planning of prenatal testing should take place together with the respective maternity clinic, preferably before a new pregnancy.

If it is already known that both parents are carriers of PCH2, it is also possible to screen embryos after artificial insemination (IVF) before implanting them in the mother‘s uterus. This is known as pre-implantation genetic diagnosis.
In Germany, such a procedure must be approved by the ethics committee of the respective federal state. In the case of a disease as severe as PCH2A, approval is likely, but the process of obtaining the necessary medical reports and approval from the ethics committee will take several months. Health insurance companies only partially cover the costs of pre-implantation genetic diagnosis and the artificial insemination procedure, and only upon application. (Legal frameworks and insurance policies may differ in other countries).

Extensive genetic and obstetric counseling should always take place before a new pregnancy in order to educate and inform families about all available options early on.

2 The 2014 and 2023 Studies – Scientific Background

The first questionnaire study „Natural course of pontocerebellar hypoplasia type 2“ (Sanchez-Albisua et al 2014, Ekert et al 2016, 9,12), which was conducted in 2012 and published in 2014, is a product of the parents‘ initiative in consultation with medical experts headed by Ingeborg Krägeloh-Mann (University Hospital Tübingen). The aim was to collect standardized data on the disease, in particular its progression. Families of altogether 33 children were interviewed by telephone. Data from medical reports was also included.

In 2020, a team of parents and researchers revised the existing parent questionnaire, which had been the basis of the „Natural course of pontocerebellar hypoplasia type 2“ study from 2012-2014. The revised version was then reviewed and improved together with five parents of affected children as part of a preliminary study, allowing the final version of the parent questionnaire to be finalized for the survey in early 2021 in digital form. The second „Natural History Study“ was headed by Wibke Janzarik (University Hospital Freiburg)

One inclusion criterion for both the first and second study was the genetic confirmation of PCH2A (see 1.4. Inheritance) in order to study a group that was genetically as homogeneous as possible. From a clinical perspective, the results can be applied to PCH2 in general.

Participants in the study were mainly recruited via the German-speaking parents‘ initiative (PCH-Familie e.V.). However, some families were also brought on board through further network contacts and pediatricians/pediatric clinics. Parents who were interested in taking part in the study were asked to contact the researchers and - following a medical consultation - were given the link to the digitized questionnaire. They also authorized the researchers to request medical reports and MRI scans of their children or sent these directly to the scientists. After completing the digital questionnaire, the results were briefly cross-checked with the available medical information and any remaining questions were clarified in a final interview between parents and researchers. In total, data was collected

from 53 affected children (some of whom were already adults). Of these 53 children, 21 had already participated in the 2012 Tübingen study and returned to take part in this survey. Twelve children from the 2012 Tübingen study could not be surveyed again, but their data was made available to the researchers in pseudonymized form, so that a total of 65 individual children could be included in the present study. The data does not always refer to all 65 children. As the questionnaires were not completely identical, the answers to some questions are only available for 53 children. Some questions could not be answered by the parents, which is why there are sometimes less than 53 responses. Do not be confused if you see, for example, that epileptic seizures occurred in 43/62 children. In this case, only data from 62 families was available.

3 Pregnancy, Birth, Neonatal Period and Life Expectancy

3.1 Pregnancy, Birth and Neonatal Period

In most cases, the unborn child is not diagnosed with PCH2 during pregnancy (see 1.6. Prenatal diagnostics). There are usually no obvious disease-specific abnormalities during pregnancy with a child with PCH2. Abnormalities such as polyhydramnios (excessive amniotic fluid), irregular movement patterns (e.g. trembling) of the child in the womb, or a reduced head circumference, which are associated with PCH in literature, occur in around half of all pregnancies. However, almost half of all pregnancies with a child with PCH2 progress without significant complications. Sonographic examinations of the brain, which are usually carried out in the second half of pregnancy, only reveal abnormalities such as microcephaly (reduced head circumference) in rare cases [8, 13]. However, according to recent literature, prenatal MRI scans (from the 29th/30th week of pregnancy) are more likely to reveal pathological changes in the cerebellum and the pons [14].

Children with PCH2 do not show any unusual patterns in terms of prematurity or the rate of cesarean sections. Most children are born as full-term babies and the cesarean section rate is not above the average for all births.

At birth, children with PCH2 have a normal weight and body length. The head circumference is mostly within the normal range or microcephaly (reduced head circumference) has already developed at the time of birth. Although the values indicating the well-being of a newborn, i.e. the APGAR score and umbilical cord arterial pH measurement, are also normal in children with PCH2, many of them have to be transferred to a pediatric clinic for further treatment within the first few days of life. The main reasons for this are breathing problems, feeding difficulties or a general adaptation disorder. Within the first month of life (neonatal period), almost all affected children show typical PCH2 symptoms such as feeding difficulties, increased restlessness or noticeable muscle tension, sleepiness or breathing problems.

Data of the Current Natural History Study

Pregnancies and births: The pregnancies lasted an average of 39.6 weeks. There were no multiple births. A total of three children were born prematurely, which corresponds to a premature birth rate of 4.6 %. Four children were delivered by cesarean section. The mean birth weight of the full-term babies was 3457.5 g, the mean birth length was 51.7 cm and the mean head circumference was 33.9 cm. APGAR scores taken at five and ten minutes were nine to ten in most cases. The umbilical cord arterial pH value averaged 7.28.

Neonatal period: Out of 53 children, 39 children had to be hospitalized in a pediatric clinic within their first month of life. Of these, 36 were transferred to a pediatric clinic within 72 hours after birth. A nasogastric tube was required in 22 cases (in 13 cases, tube feeding was still required after discharge from hospital) and 15 children were discharged home with a portable vital signs monitor. 14 children required oxygen (in two cases still after discharge from hospital), four children had to be ventilated. Antibiotic treatment was provided in eleven cases.

The most common problems encountered in the neonatal period were, in descending order: Feeding difficulties, restlessness/irritability, muscular hypertonia (excessive muscle tension), sleepiness, abnormal movement patterns, excessive crying, muscular hypo-

tonia (insufficient muscle tension), apneas (breathing cessations), excessive weight loss and, in five cases, epileptic seizures.

3.2 Survival and Causes of Death

To this day, parents are still being told that their child will only live for a few years when they are first diagnosed with PCH2. Yet Steinlin et al. reported in 2006 [8] that survival into the second decade of life is possible and Namavar et al. described a 31-year-old patient in 2011 [5].

While it is true that some children with PCH2 don‘t survive beyond a few years, more and more children are reaching at least the second decade of life or even adulthood. This was also observed in the first study; although nine of the 33 children had already died (on average at 6.5 years old), the oldest of the 24 living children was 19.5 years old [12]. It is likely that continuous improvements in the care of children with severe multiple disabilities are the reason for this, as well as better knowledge and earlier diagnosis of PCH2, which has only been known for around 25 years, while the genetic mutation has only been known for 15 years. Frequent causes of death are complications in the respiratory system such as pneumonia or aspiration (inhalation of food particles). Thermoregulatory disorders and sudden infant death syndrome are also possible causes of death.

Data of the Current Natural History Study

Fig. 4 shows the survival of each individual patient. Each line represents a child. The graph starts at birth for all children and ends when the data was collected or at the time of death. The researchers of the 2023 study were unable to contact some of the children whose data was collected for the 2014 study, so their path after 2012 is unknown and therefore marked with an empty arrow. Children of the same age can also be shown as different ages in the chart, as the first data collection of the newer study began in December 2020, while the last data was collected in the fall of 2022.

A child with PCH2 has a probability of 88 % to 92 % to experience their fifth birthday and a probability of 66 % to 72 % to experience their tenth birthday (Fig. 5, Fig. 6). The differing probabilities come from a different method of statistical evaluation of the data. The lower value in each case is obtained if only those children are considered who reached at least age ten (or five) or died before that. The higher value is obtained if all 65 children are considered. The actual survival probability falls somewhere in between. Figures 5 and 6 show the ten-year survival. Due to the small number of children over ten years old at the time of the survey, it is not practical to graphically represent survival beyond this age.

Causes of death: 16 out of 65 children had already died by the end of the study. The main causes of death were aspiration in four cases (food entering the airways and obstructing them; in two patients this occurred unnoticed at night) and, in four cases, a gradual deterioration over several weeks. The presumed definitive causes of death in the children affected by the deterioration process were hypothermia in one case and heart failure in another. The second most common causes of death were pneumonia and respiratory failure. Organ failure was reported as the cause of death in one case. In three cases, the cause of death was unclear, including one suspected case of heart failure.

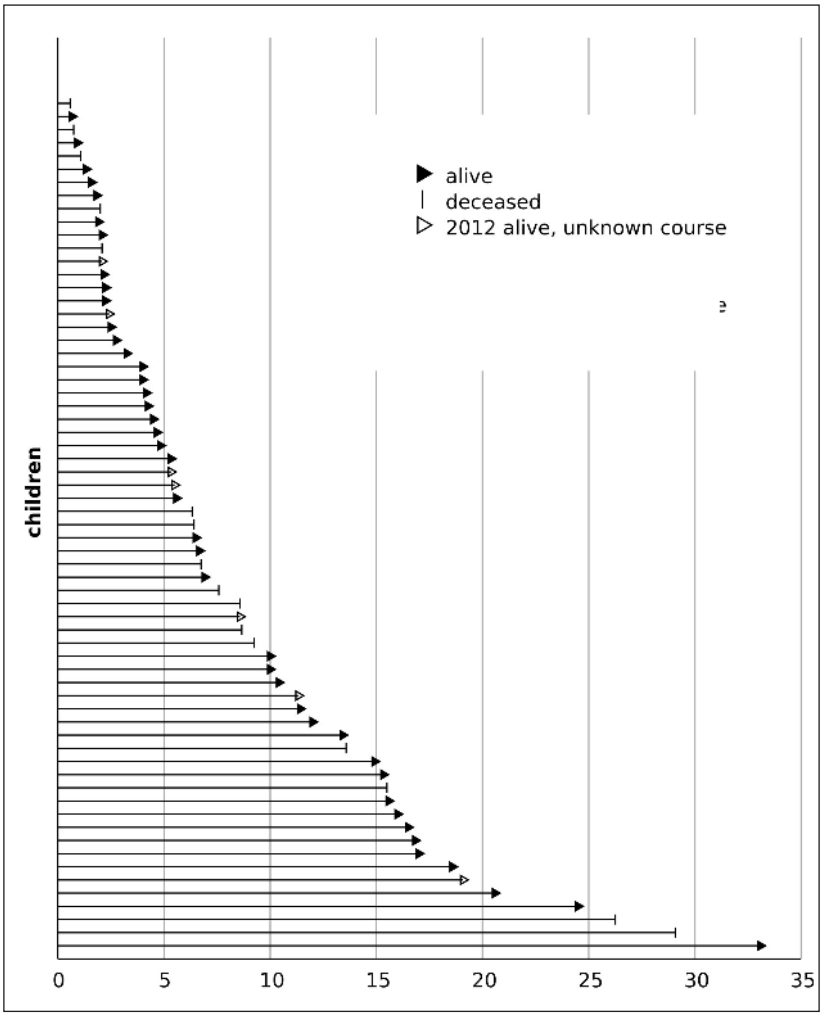


Fig. 4: Graphical representation of the children‘s lifespan.

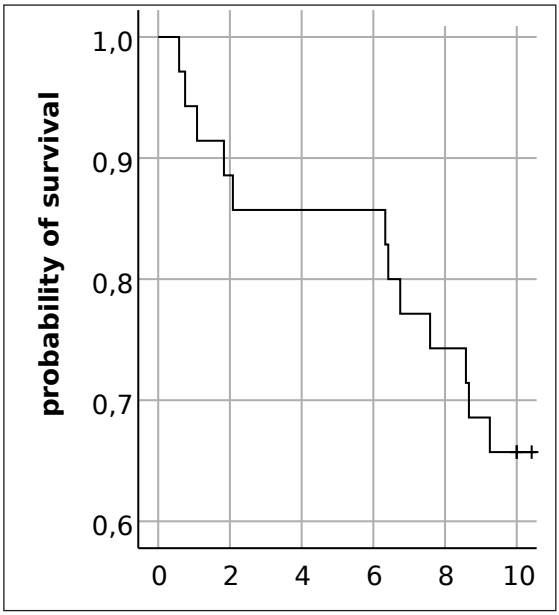


Fig. 5: Ten-year survival, taking into account children who reached the age of ten or died before that.

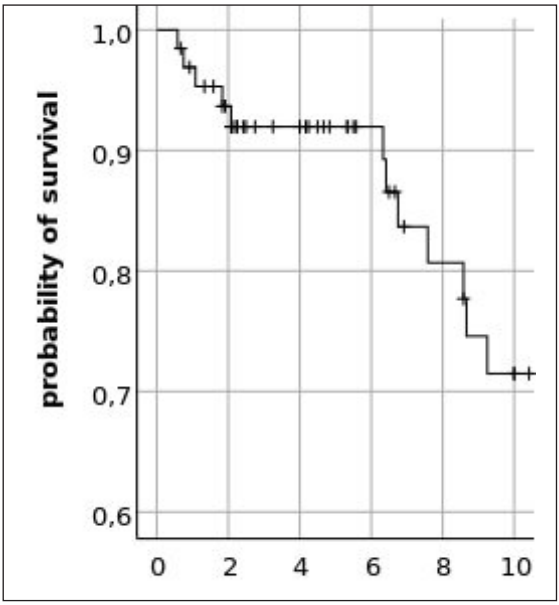


Fig. 6: Ten-year survival, taking all children into account.

4 Symptoms of PCH2

This chapter contains information on symptoms, as mentioned and cited in the introduction, as well as information on their medical treatment in the form of figures and tables. The indications are based on what the parents stated, not on the indications of the medication in general. The bar charts only list medication that was given to at least three children to treat the corresponding symptom. The tables only contain information on medication that was given to at least five children or that is important in the context of PCH2, for example because it has already been discussed in studies. If the study found that the recommended maximum dose of a drug was exceeded, this is marked with an asterisk. However, you should always consult your treating physician to find out which medication is being used on your child and in what dosage.

4.1. Motor Disorder

A motor disorder in the form of frequent, involuntary movements and a significant impairment of voluntary motor skills is one of the main symptoms of PCH2. This motor disorder may consist predominantly of fast, sweeping, twisting (choreoathetosis) or slow movements, the last of which are characterized by abnormal postures and distorted voluntary motor skills with increased muscle tone (dystonia). These movement patterns often occur simultaneously and are collectively characterized as dyskinetic. The motor disorder is particularly noticeable in the extremities (arms and legs), but also affects the muscles of the face and eyes. This can, for example, make targeted grasping or eye movements as well as swallowing very difficult. Affected children always make these movements when awake. The symptoms only cease when asleep. Over the course of the disease, a spastic motor disorder often develops, which can lead to muscle contractures and, in the long term, joint deformities.

Therapy

There is no known causal therapy for the motor disorder associated with PCH2. The effects of the spastic motor disorder described above can be prevented by physiotherapy and, in some cases, braces.

Tips to Try Out

- A change in the familiar movement patterns (e.g. significant intensification/relaxation) can indicate discomfort or may be an expression of emotions (joy, anger) or relaxation. Good observation and knowledge of your child‘s movement patterns can therefore contribute to a better understanding of their needs.
- Physiotherapy/stretching exercises to prevent muscle contracture and maintain muscle mobility
- Make sure your child is protected in their immediate vicinity so that they cannot injure themselves as a result of their sweeping movements

Data of the Current Natural History Study

The motor disorder was subdivided into sweeping movements (corresponding to hyperkinetic choreoathetoid movement disorder), restlessness, dystonic attacks of the entire body, and episodic localized (focal or segmental) abnormal postures (dystonia).

Furthermore, a large number of the children showed a change in **muscle tension**. For example, 23 out of 52 children showed reduced muscle tension and 33 out of 52 children showed truncal instability. 45 out of 52 children had increased muscle tension up to spasticity, the majority of which occurred only when awake or intermittently; few children experienced this permanently.

The **sweeping movements** occurred in almost all children (62 out of 65). Of the three children who were not experiencing these movements, all had spasticity. On average, the sweeping movements first occurred at around two months of age, with the earliest time of occurrence being 0 months and the latest 18 months. There was only one case in which the sweeping movements stopped at around two years of age due to an overall deterioration following a case of successful resuscitation of the child. The majority of children exhibited these movements daily. Overall, there was no change in the sweeping movements with age. Half of the families had tried to treat the sweeping movements with medication, of which around a third stated that the symptoms were partially improved or could be treated effectively. The parents who observed an improvement in their children‘s sweeping movements were more likely to give phenobarbital (Luminal ®) and levomepromazine (Neurocil ®) for motor disorders than those who did not observe any improvement in symptoms following the use of medication.

Dystonia was defined as the persistent abnormal posture of a body part that did not affect the whole body (c-shaped), lasting from a few seconds to hours (this is in contrast to generalized C-shaped dystonic attacks, which are listed separately below). Dystonic motor disorders occurred in 24 out of 53 children, on average from the age of six months (earliest immediately after birth, latest at almost five years). The dystonic motor disorder ceased in only one affected

child over time. In the majority of children, dystonic episodes occurred weekly or daily, mostly while awake. The causes, according to the parents, were often pain, followed by reflux, constipation and emotions. However, in many cases the cause remained unclear. Medication had little to limited effect on the dystonias in the majority of cases. Microklist ®, diazepam and midazolam were used effectively as a medical therapy in one case each. In addition, two families reported that their child regularly adopted an opisthotonic posture (hyperextended backwards) through a negative feedback loop that they were unable to break.

4.2 Dystonic Attacks

Parents of affected children have reported that their children assume a persisting C-shaped posture over a longer period of time, sometimes for several hours, that can not be externally influenced. The children seem to feel highly uncomfortable; they cry a lot and sometimes also vomit. These episodes are referred to as dystonic attacks (also known as dystonic crises or episodic dystonia). Dystonic attacks were different from epileptic seizures in the affected children and, if examined, were not associated with specific changes in the EEG.

Dystonic attacks often occur without a recognizable cause. In some cases, however, dystonic attacks occur more frequently after certain triggers such as left-sided lying, prone lying or physiotherapy. There is no known effective treatment for these dystonic attacks. The previous study reported that natural, non-drug-induced sleep leads to the cessation of dystonic attacks. The attacks usually began to occur in infancy and, in many cases, seemed to subside or disappear completely as the child grew older.

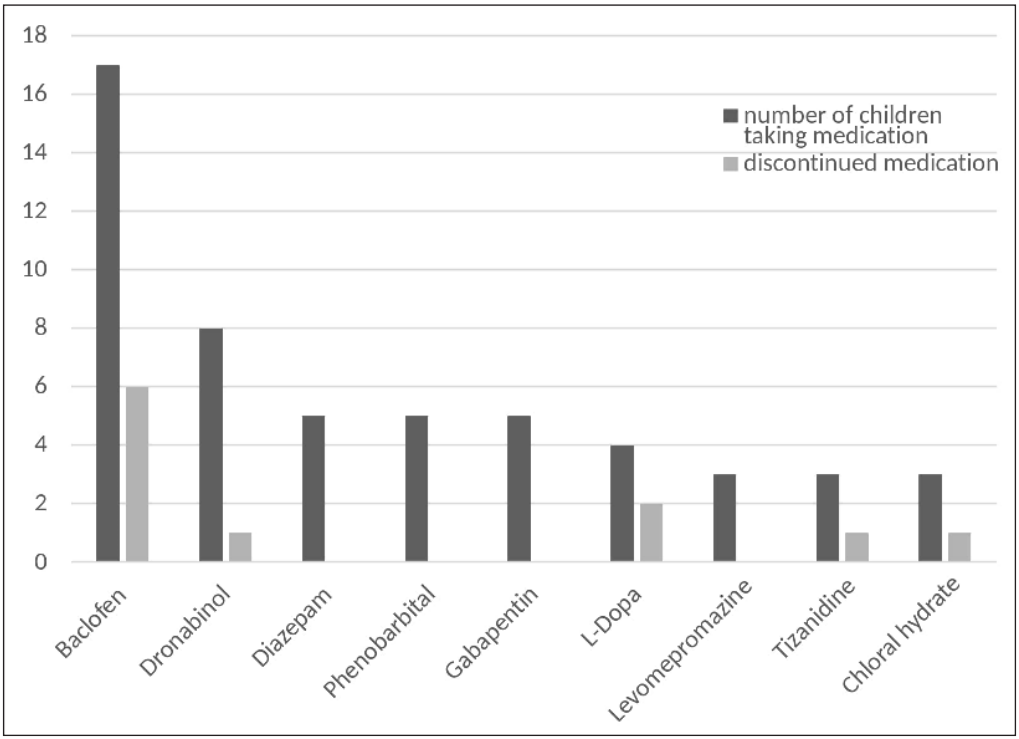


Fig. 7: Medication used to treat motor disorders.

Tips to Try Out With Dystonic Attacks

- Pay attention to potential triggers and minimize them if possible.
- Stay calm during dystonic attacks and create a calm environment.
- Try to help the child fall asleep naturally.

Data of the Current Natural History Study

In the questionnaire, a dystonic attack was defined as “C-shaped hyperextension of the whole body for more than 30 minutes that is hard to interrupt from the outside”.

Table of Medication Used to Treat Motor Disorders

Substance		General Information	Natural History Study
Baclofen (Lioresal ®)	Administration form	Tablets, injection solution, infusion	Orally or via tube
	Indications	Muscle relaxant: generalized spasticity and dystonia	Motor disorder, spasticity, dystonia
	Dosage		15 reports: average 0.94 mg/kg/d (0.14–2.27 mg/kg/d) in 1-4 single doses
	Adverse reactions/ reasons for discontinuation	Sleepiness, sedation, nausea	Sedation/fatigue, no or decreasing effect
	CAVE!	Avoid abrupt withdrawal	
Dronabinol	See 4.11 Restlessness		
Diazepam	see 4.11 Restlessness		
Phenobarbital	See 4.3 Epilepsy		
Gabapentin	see 4.3 Epilepsy		
L-Dopa = Levodopa (Madopar ®)	Administration form	Tablets, gel, dry-powder inhalation, hard capsules; usually in combination with another medication that inhibits the breakdown of L-dopa	Orally or by tube
	Indications	Parkinson's and related diseases	Motor disorder, spasticity, dystonic attacks, dystonia, epilepsy
	Dosage		Insuffient reports
	Adverse reactions/ reasons for discontinuation	Urinary tract infection, weight loss, anxiety, depression, sleeplessness, dyskinesia, orthostatic dysregulation, nausea, constipation	Ineffectiveness

25 out of 65 children were affected by generalized dystonic attacks. Here, too, the onset age was within the first six years of life and in about half of the children (10/22) the dystonic attacks ceased eventually (on average at the age of 5.5 years; at the earliest at ten months, and at the latest at 16 years). The dystonic attacks occurred mostly weekly or monthly and in one case daily (the child was five years old at the time). The cause of the dystonic attacks was mostly pain or remained unclear, followed by reflux, constipation and emotion. In a few children, different body positions (prone position, lateral position, changing positions) also seemed to trigger dystonic attacks. In three cases, natural sleep had a therapeutic effect. Approximately one third of the children had either not tried any medication for dystonic attacks, their attacks were untreatable, or the medication had little effect, respectively. In three cases, the dystonic attacks could be at least partially treated with medication, but in none of the cases were they treated effectively. There were no significant results on substances that might be used to treat dystonic attacks. Overall, a decrease in dystonic attacks was observed with age.

Medication that parents reported using in more than two cases for motor disorders is shown in Fig. 7.

4.3 Epilepsy

Epilepsy is defined as the occurrence of chronic recurrent seizures that are unprovoked. During an epileptic seizure, brain cells suddenly discharge excessively, which is clinically accompanied by seizure symptoms. The clinical picture depends on the extent and localization of the affected neuronal networks. A circumscribed malfunction results in a focal seizure, a generalized malfunction results in a generalized seizure. In addition to the occurrence of clinical seizure symptoms, specific EEG changes must also be identified for diagnosis (EEG = electroencephalogram, recording of brain waves). Generalized seizures can manifest themselves, for example, as tonic seizures (severe cramping), atonic seizures (sudden loss of muscle tone) or absence seizures (sudden loss of consciousness). So called grand mal seizures are also classified as generalized seizures

and may consist of both tonic and clonic (twitching, repetitive movements) components. Epileptic seizures can also manifest themselves solely in the form of respiratory arrest or facial twitching.
The term status epilepticus refers to an epileptic seizure that either lasts for an unusually long time (longer than five minutes) or a series of seizures between which consciousness is not regained.

Epileptic seizures (convulsions) are common in children with PCH2. They are considered one of the main symptoms of PCH2. The types of seizures in PCH2 vary greatly. In addition to generalized tonic-clonic seizures, absences or atonic seizures can also occur. Seizures during fever have also been observed; this is because fever lowers the seizure threshold in children with epilepsy. Status epilepticus also occurs more frequently in children with PCH2.

The earlier study already indicated that the onset of epilepsy tended to be after infancy, with an average age of onset of 2 ½ years. It proved to be difficult to treat; phenobarbital and topiramate were reported as the drugs most likely to be effective. Epileptic seizures in children with PCH2 are difficult for both parents and healthcare professionals to distinguish from the existing motor disorder, especially at their onset. Focal seizures in particular cannot be clearly identified as such at first. As seizures become more frequent and generalized seizures start to occur, this changes and seizures can be easily identified.

Febrile seizures are epileptic seizures in children (aged six months to five years) that are provoked by fever but are not caused by an infection of the brain. They are divided into simple and complex febrile seizures. Complex febrile seizures are characterized by the following criteria: focal symptoms, duration > 15 minutes, several febrile seizures within 24 hours. Complex febrile seizures combined with an underlying brain disorder increase the risk of epilepsy; this applies to children with PCH2. Fever may increase the risk of seizures in children with epileptic seizures.

Therapy

The treatment of epileptic seizures in PCH2 is difficult and only rarely leads to a complete cessation of seizures. Nevertheless, it is essential to attempt to manage the epilepsy as best as possible, as this not only has a direct impact on the well-being of the children and their families, but in many cases also allows for progress in other areas (such as cognitive and motor development, care, fun experiences, etc.).

Long-term Seizure Suppressant Therapy

In the 2014 natural history study, treatment with phenobarbital and topiramate proved to be the most successful. When asked directly about this, numerous parents mentioned phenobarbital as one of the most beneficial drugs for their children, with hardly any side effects like sleepiness/sedation being observed. Phenobarbital is one of the first and therefore best known seizure suppressant drugs. It has sedative and sleep-inducing properties, a long duration of effect, and must be phased out very slowly when discontinued. It accelerates liver metabolism which means that other medications (e.g. valproate or thyroid hormones) are broken down more quickly and their effect is weakened. For this reason, initial treatment attempts are often made with “modern” medications. Based on the many reports from parents and the two natural history studies, children with PCH2 often benefit from taking phenobarbital so that early treatment with this medication can be considered as part of antiepileptic therapy.

Tips to Try Out

- Ensure sufficient daily fluid intake.
- Reduce fever early and adequately.
    - Seizures often occur at the onset of infection and therefore during a rise in temperature. For this reason, fever-reducing therapy is often unable to prevent them. Nevertheless, it is advisable to reduce the fever at an early stage in order to alleviate the children's suffering in general.
- Aim for optimal management with anti-epileptic medication. This requires patience and perseverance, as it is often a lengthy process.
- In the event of a prolonged seizure (longer than three minutes), it is advisable, in addition to administering medication, to measure the oxygen saturation if possible. If it is below 90 %, an O_2 mask is recommended.

Data of the Current Natural History Study

Epileptic seizures had occurred in 43 of 62 children for whom such data was available. In ten out of 62 children, no epileptic seizures had occurred; in nine out of 62 children, the parents were unsure whether epileptic seizures had already occurred. On average, the epileptic seizures first occurred at the age of two. In the majority of children affected by epileptic seizures, these were persistent, while in five children no more epileptic seizures occurred. In three cases, the cessation of seizures was associated with medication. Two of these children received long-term therapy with levetiracetam, while one child received a multidrug therapy of valproate and L-dopa. In one case, unusually severe seizures were triggered by the analgesic fentanyl.

Most of the epileptic seizures occurred weekly. The majority of children with epileptic seizures had already undergone an EEG, for the first time at an average age of four months. The EEG showed abnormalities for the first time at an average age of approx. 1.5 years. Around two thirds of the children had been diagnosed with epilepsy at an average age of two years and five months. One third of the

children had already experienced at least one status epilepticus. On average, the children with status epilepticus had already experienced 2.25 status epilepticus seizures in their lifetime and had received intensive medical treatment for an average of one status epilepticus seizure. The most common types of seizure were tonic seizures (29 children), followed by convulsions (27 children), generalized tonic-clonic seizures (24 children) and absence seizures (23 children). Less frequent were facial muscle twitching (18 children), atonic seizures (ten children) and focal seizures in the form of isolated respiratory arrest (nine children). The probability of developing epilepsy increased with age, i.e. an increase in epileptic seizures with age has been observed.

Slightly more than half of the children had febrile seizures, on average for the first time from the age of around 22 months. These were often complex, i.e. prolonged or recurring. 60 % of children with epileptic seizures had their first seizure during a fever.

Nine out of 52 children were suspected of having so-called infantile spasms. This is a type of seizure characterized by abrupt muscle twitches or flexion spasms in which the hands cross in front of the chest. This epilepsy is also known as West syndrome after the person who first described it. Infantile spasms usually occur in series and often after waking. They are accompanied by typical EEG changes, the so-called hypsarrhythmia – a continuous, diffuse and irregular epileptic discharge in the brain. Only four of the children with suspected infantile spasms were treated with conventional medication for such seizures, i.e. glucocorticoids, which led to the cessation of spasms in two cases. The majority of children who were not treated with glucocorticoids did not show the EEG pattern typical for infantile spasms.

Figure 8 shows which seizure-suppressive drugs were used and how often.

Acute Seizure Suppressant Therapy

For acute seizure suppressant therapy (recommended for seizures lasting longer than three minutes, usually administered rectally or buccally, i.e. in the cheek pouch), 26 children were given midazolam, 23 children diazepam and ten children clonazepam. Diazepam was discontinued in six cases, midazolam in five cases and clonazepam in three. In these cases, the majority of children were switched to another emergency drug due to ineffectiveness. There were no indications of serious side effects.

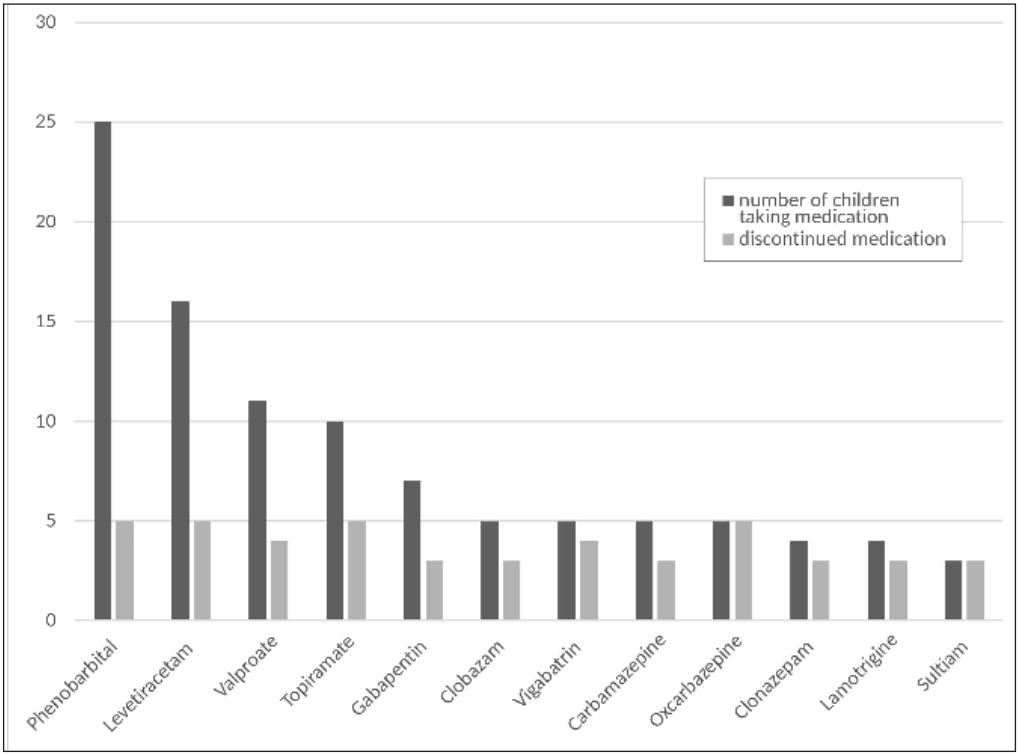


Fig. 8: Frequency of use of seizure suppressants.

Table of Antiepileptic Drugs

Substance		General Information	Natural History Study
Phenobarbital (*Luminal ®, Luminaletten ®*)	Administration form	Tablets, injection solution	Orally or by tube
	Indications	Sedative, seizure suppressant	Seizures, restlessness, sleep, motor disorder
	Dosage		24 reports: average 5.62 mg/kg/d (1–14.16* mg/kg/d) in 1-3 single doses
	Adverse reactions/ reasons for discontinuation	Confusion, headache, motor disorder, cognitive disorders, strong sedation, fatigue	Strong mucous congestion, strong fatigue, lack of necessity, ineffectiveness
	Monotherapy and multidrug therapy		7x monotherapy, 13x multidrug therapy (most frequently combined with levetiracetam)
	CAVE!	Complex interaction potential with other drugs; influences the blood levels of these drugs, including other seizure suppressants; discontinuation only possible by very slow reduction	
Levetiracetam (*Keppra ®*)	Administration form	Tablets, syrup, solution, infusion, granules/mini tablets	Orally or by tube
	Indications	Seizure suppressant	Seizures, restlessness
	Dosage		16 reports: average 49.6 mg/kg/d (20–125* mg/kg/d) in 2-3 single doses
	Adverse reactions/ reasons for discontinuation	Inflammation of the nose and throat region, sleepiness, rarely: dyskinesia	Ineffectiveness or reduced effect, increased sleepiness, tense and skewed posture
	Monotherapy and multidrug therapy		5x monotherapy, 11x multidrug therapy (most frequently ocmbined with phenobarbital)

Table of Antiepileptic Drugs

Substance		General Information	Natural History Study
Valproic acid (*Ergenyl ®, Orfiril ®*)	Administration form	Tablets, syrup, injection solution	Orally or by tube
	Indications	Seizure suppressant, bipolar disorder	Seizures
	Dosage		8 reports: average 29.89 mg/kg/d (10.71-58.7 mg/kg/d*) in 2-3 single doses
	Adverse reactions/ reasons for discontinuation	Elevated ammonia levels, possibly with neurological symptoms, tremors, nausea	Ineffectiveness, strong nausea
	Monotherapy and multidrug therapy		Only given as multidrug therapy (most frequently combined with carbamazepine)
Topiramate (*Topamax ®*)	Administration form	Tablets, capsules	Orally or by tube
	Indications	Seizure suppressant, migraine	Seizures
	Dosage		No calculation possible due to incorrect data
	Adverse reactions/ reasons for discontinuation	Inflammation of the nose and throat region, depression, somatosensory disorder, sleepiness, vertigo, diarrhea, nausea, weight loss, occasionally: restlessness	Ineffectiveness or reduced effect, increased sleepiness, weight loss, intolerable phases of restlessness
	Monotherapy and multidrug therapy		Only given as multidrug therapy (most frequently combined with phenobarbital)

Table of Antiepileptic Drugs

Substance		General Information	Natural History Study
Gabapentin (*Neurontin ®*)	Administration form	Capsules, caplets, solution	Orally or by tube
	Indications	Antiepileptic, neurogenic pain	Seizures, restlessness
	Dosage		7 reports: average 40.76 mg/kg/d (13.1–60* mg/kg/d) in 2-3 single doses
	Adverse reactions/ reasons for discontinuation	Viral infection, sleepiness, vertigo, ataxia, fatigue, fever	Ineffectiveness
	Monotherapy and multidrug therapy		1x monotherapy, 3x multidrug therapy (most frequently combined with phenobarbital)
	CAVE!	Antacids reduce agent absorption; increased liver function in combination with other antiepileptic drugs	-
Clobazam (*Frisium ®, Epaclob ®*)	Administration form	Tablets, suspension	Orally or by tube
	Indications	Seizure suppressant, states of tension, excitement and anxiety	Seizures, restlessness
	Dosage		Insufficient reports on dosage; given in 2-3 single doses
	Adverse reactions/ reasons for discontinuation	Sleepiness, fatigue, in children often paradoxical restlessness	Better efficacy of other drugs, mucous congestion, paradoxical restlessness
	Monotherapy and multidrug therapy	Usually only in combination with other antiepileptic drugs	1x as two-drug therapy, 1x as four-drug therapy

Table of Antiepileptic Drugs

Substance		General Information	Natural History Study
Vigabatrin (*Sabril ®*)	Administration form	Tablets, granulata	Orally or by tube
	Indications	Seizure suppressant	Seizures
	Dosage		Insufficient reports on dosage; given in 2-3 single doses
	Adverse reactions/ reasons for discontinuation	Agitation, sleepiness, visual field deficits, joint pain	Ineffectiveness; in combination with Gabapentin dose escalation: increased restlessness
	Monotherapy and multidrug therapy	Usually only in combination with other antiepileptic drugs	1x given in combination with clobazam
Carbamazepine (*Timonil ®, Tegretal ®*)	Administration form	Tablets, suspension	Orally or by tube
	Indications	Seizure suppressant, neuralgia, neuropathy, non-epileptic seizures, alcohol withdrawal syndrome, bipolar disorder	Seizures, restlessness
	Dosage		5 reports: average 26.13 mg/kg/d (12.82-40.9* mg/kg/d) in 2-3 single doses
	Adverse reactions/ reasons for discontinuation	Hemogram changes, sleepiness, sedation, vertigo, ataxia, nausea, vomiting, increased liver function, allergic skin reactions, occasionally: restlessness	Low effectiveness, restlessness
	Monotherapy and multidrug therapy		two-drug or three-drug therapy, always in combination with valproic acid (among others)

Substance		General Information	Natural History Study
Oxcarbazepine (*Trileptal* ®)	Administration form	Tablets, suspension	Orally or by tube
	Indications	Seizure suppressant	Seizures
	Dosage		Insufficient reports on dosage; given in 2-3 single doses
	Adverse reactions/ reasons for discontinuation	Sleepiness, headache, vertigo, double vision, nausea, vomiting, very rarely: angioedema	Ineffectiveness, sleepiness, facial swelling, increased salivation, neurologist's advice after taking it for ten years
	Monotherapy and multidrug therapy		As the medication had been discontinued in all cases at the time of data collection, no results were available.

4.4 Feeding Difficulties

Ensuring an adequate fluid and food supply, as well as administering medication orally if necessary, is a key aspect of caring for children with PCH2.

Feeding difficulties are seen in almost all children with PCH2 and have been described early on [15]. They usually occur from a young age, partially neonatal, and improvements with age have only been reported in individual cases.

Feeding difficulties is a broad term. Overall, a feeding situation is considered abnormal if the duration of a meal exceeds 30 minutes, if very frequent meals are necessary (more than every two hours) or if there is increased choking/coughing when eating. In PCH2, impaired oral motor skills (e.g. closing the mouth around the spoon)

and swallowing difficulties are particularly evident, so that some of the food flows out of the mouth again. In addition, the patients may choke along with coughing and gagging, and be affected by general restlessness and the motor disorder, which makes eating more difficult. In severe cases, choking can lead to aspiration, i.e. food or liquids entering the airways. If the coughing stimulus is not sufficient to clear the airways, this can lead to inflammation of the lungs (pneumonia).

Many parents report that their children are only able to eat finely pureed, mushy food. They also reported that their children find it easier to swallow thickened food/liquids rather than more runny purees or plain liquids.
In the earlier study, two thirds of the patients had already been PEG-fed, and the parents reported a relaxation of the eating situation due to the placement of a PEG tube. A PEG (percutaneous endoscopic gastrostomy) tube is an endoscopically created access from the outside through the abdominal wall into the stomach used for artificial feeding. This allows a continuous and sufficient intake of fluids and nutrients (and medication if necessary) but it can also be used only as required while the child continues to be fed orally. However, the risks associated with the surgical procedure of inserting a PEG tube must be considered individually by parents and doctors.

Another option for tube feeding is a nasogastric tube which is mainly used as a temporary measure in infants. However, nasogastric tubes are usually poorly tolerated by children and are usually not a permanent solution.

Tips to Try Out

- Routines before mealtimes to prepare the children for the upcoming meal (song or slogan, showing and explaining spoon and food, etc.).
- Despite the difficulties mentioned above, try to create a relaxed and calm eating environment and adapt to the child's eating pace.
- Keep the child securely in place while eating to minimize problems caused by uncoordinated movements.
- Have regular meals (possibly smaller and more frequent)
- Use thickened liquids instead of plain liquids
- Finely puree food
- Avoid highly acidic foods (see reflux)
- Use special cups with a soft rim
- Speech therapy to improve oral motor skills and swallowing (if practical)
- Nasogastric tube or PEG tube
- Prepare the child for feeding through rituals and the smell of food, even if a feeding tube is in place
- A PEG tube can be used to give not only tube feeds but also finely pureed family meals.

Data of the Current Natural History Study

Feeding difficulties occurred in 52 out of 53 children within the first few months of life. Only one child (aged three) showed no feeding difficulties. In four cases, the feeding situation improved significantly within the first two years of life. Overall, all parents reported an improvement of feeding difficulties through targeted training and that the problem depended on the respective day. Still, feeding difficulties remained a fundamental problem for all children.

4.5 Gastro-Esophageal Reflux and Vomiting

Reflux comes from Latin “refluxus” and means backflow. Gastroesophageal reflux occurs when (acidic) stomach contents flow back into the esophagus. This happens when the sphincter muscle between the esophagus and the stomach does not function properly. The backflow of stomach content into the esophagus leads to symptoms such as heartburn, pain in the upper abdomen and chest area, acid reflux and, in some cases, vomiting. Reflux is exacerbated by eating foods that increase stomach acid production, such as spicy or fatty foods. In addition, lying flat or having high intra-abdominal pressure can physically increase reflux. If acidic stomach contents are allowed to flow back into the esophagus over a longer period of time, this can irritate the esophagus and lead to painful inflammation of the esophageal mucosa (reflux esophagitis).

Diagnosis: If there are typical symptoms, the condition can be confirmed by gastroscopy or by measuring the pH values of the esophagus and stomach.

Therapy: Home remedies such as sitting upright after eating, no consumption of foods that stimulate additional acid production in the stomach.

Medical therapy with antacids (proton pump inhibitors) [16– 18]. These are drugs that reduce acid production in the stomach (e.g. omeprazole or pantoprazole). This usually helps the affected children quickly and effectively, although it should be noted that children with this condition usually require an increased dose [19]. A daily dosage of two to four mg/kg body weight, divided into several doses, has proven to be effective.

A Nissen fundoplication can be used to reduce reflux surgically. This involves forming a type of sleeve from the upper stomach area, which is placed around the lower end of the esophagus to better seal the connection between the esophagus and stomach.

Children with PCH2 often experience increased vomiting and gastroesophageal reflux. According to many parents, this leads to a severely reduced quality of life due to the children‘s discomfort and pain. PCH2 children cannot express their symptoms to us directly. The parents often recognize reflux symptoms in the form of severe restlessness and hyperextension, crying and an acidic smell when burping, and obvious signs of pain in their children, who do not respond to the usual painkillers. As the symptoms (and secondary conditions) of gastroesophageal reflux can often be treated relatively easily using the above-mentioned medications, sparing children pain in the process, parents and doctors of children with PCH2 should be mindful of this condition early on and treat it if necessary. However, some special dosage considerations should be made (see tips and literature). Many parents consider omeprazole or other proton pump inhibitors to be the key drugs in the treatment of painful PCH2 symptoms.

Tips to Try Out

- Avoid foods that stimulate stomach acid production (spicy food, very hot or cold food, fatty foods)
- Sit upright for 30 minutes after eating
- For children with PEG tubes: de-airing of the stomach via the tube
- Consider gastroesophageal reflux early on if the child‘s symptoms are unclear and initiate medical treatment if necessary (make sure the dosage is sufficiently high and adjust the dose as the child grows!) Treatment with significantly higher doses of proton pump inhibitors has proven to be effective (two to four mg/kg body weight, up to five mg/kg body weight if necessary)

Data of the Current Natural History Study

Reflux and vomiting were queried separately. Reflux was seen as a passive “rising” of stomach contents into the esophagus, while vomiting was defined as a forceful expulsion of stomach contents.

Symptomatic reflux was observed in 48 of 53 children, and according to the parents, it began on average at the age of one year. The formal diagnosis of "gastroesophageal reflux" was given to 25 of these 48 children. All children who, according to their parents, did not show signs of reflux in the study were younger than two years at the time of data collection. In seven cases, children no longer experienced reflux as the study progressed; in five cases, the parents associated this with fundoplication. 43 children were treated with a proton pump inhibitor (mostly omeprazole). The children received an average dosage of 3.1 mg/kg body weight divided into three doses daily. 34 parents stated that they considered the proton pump inhibitor to be one of the key medications for their children and that it had led to significantly improved symptoms such as crying, reflux, restlessness and vomiting.

Increased vomiting affected 39 out of 53 children; this occurred less frequently than reflux and subsided again in a third of the children. Overall, a decrease of vomiting was observed with age.
Other medications that were used in rare cases to treat reflux and vomiting were so-called antiemetics such as domperidone (Motilium®) and ondansetron as well as antihistamines such as dimenhydrinate (Vomex®).

4.6 Additional Gastro-intestinal Symptoms

Besides reflux and vomiting, children with PCH2 have other symptoms affecting the gastrointestinal tract [20], which can be understood either as part of the clinical picture or as indications of food intolerances or infections. These symptoms are discussed below.

4.6.1 Constipation

Constipation refers to a condition where spontaneous defecation occurs too infrequently or is very difficult. It is usually characterized by hard stools and pain during defecation, as well as abdominal pain and bloating.

Constipation is a common problem in children with PCH2. The reasons for this may be a lack of physical activity, insufficient fluid intake, a low-fiber diet, the use of medication, but also unidentified medical causes. Maintaining regular bowel function is a challenge in the care of children with PCH2 and has a direct impact on their well-being, as they usually suffer greatly from the aforementioned symptoms. Regular laxative treatment is often necessary for this purpose.

Therapy

In addition to home remedies such as drinking enough fluids and eating stool-softening foods, both oral and rectal laxatives are also available for treatment. Oral laxatives include, for example, macrogol (Movicol®, Laxbene®, Kinderlax®), that help soften the stool. Rectal laxatives are enemas such as Microklist® or Microlax®, or suppositories such as Lecicarbon®.

Some parents report that their children sometimes need painkillers or sedatives due to the discomfort and pain caused by constipation.

Even though constipation is common in children with PCH2, parents should always verify whether there is an anatomical or other treatable cause.

Tips to Try Out

- Ensure sufficient fluid intake and a high-fiber diet (e.g. tube feeds with the addition „fiber“)
- Avoid constipating foods such as bananas and carrots
- Some stool-softening foods are: pears, plums, applesauce, whey
- Keep stools soft with macrogol
- Gentle abdominal massages
- If necessary, regular laxative treatment with medication in consultation with the pediatrician

Data of the Current Natural History Study

Constipation occurred in 31 of 53 cases from an average age of two years. Only in four cases did the constipation disappear again over time. Overall, however, an increase in constipation with age was observed. In the majority of cases, the parents stated that the constipation could be partially or effectively treated with medication. 22 children received at least one oral laxative. The most commonly used medication was macrogol, which was usually prescribed as a long-term medication. 28 children received at least one rectal laxative. In most cases, Microklist®/Microlax® or Lecicarbon® was used (in twelve cases each), and glycerol was also given in eight cases. The latter mostly as a PRN medication. In addition, most of the children required assistance with defecation through rectal stimulation.

4.6.2 Bloated Stomach

Many children with PCH2 repeatedly experience severe abdominal distension (meteorism). This is defined as both a bloated abdomen and gas inside the stomach. Uncoordinated swallowing and uncoordinated defecation are the most likely causes.

The 2023 questionnaire was evaluated in a preliminary study in collaboration with some of the affected parents. One mother raised the issue of excessive abdominal air, and so it was included as part of the gastrointestinal symptom complex. In fact, the majority of parents stated that their children suffered from excessive bloating and were also extremely sensitive to it (pain, restlessness).

If a combination of bloating, abdominal pain and, in particular, diarrhea occurs in children with PCH2, you should consider a food intolerance, e.g. lactose intolerance, and undergo diagnostics or avoid certain foods in consultation with the attending physician.

Data of the Current Natural History Study

Bloating was observed in 46 out of 53 children. On average, this occurred for the first time at the age of five months (at the earliest directly after birth, at the latest at the age of four). In two of the affected children, the symptoms disappeared over time. The children affected by bloating usually experienced it on a daily basis. The bloating was caused, in descending order, by swallowing air while eating (aerophagia), reduced expulsion of air through burping or farting, unclear causes and poor tolerance of food. Further information on intolerances can be found in 5.2 Nutrition. The effects of bloating were restlessness, flatulence, abdominal cramps, upper abdominal pain, increased reflux and vomiting. The majority of children affected by bloating reacted extremely sensitively to it. Medication could rarely provide any relief in most cases. Antifoaming agents such as dimethicone (SAB SIMPLEX®) and simethicone (Espumisan®) were administered most frequently. Carum carvi® was also used as a P.R.N. medication in three cases. In the case of Carum carvi, it should be noted that they are not pure caraway suppositories, but also contain small amounts of nicotine and atropine and should therefore not be used in newborns.

4.6.3 Abdominal Pain

Episodic, convulsive abdominal pain is frequently observed in children with PCH2. These episodes of abdominal pain can occur “out of the blue”. The children will cry and scream in pain and exhibit severe restlessness that can hardly be controlled. The episodes are often accompanied by loud peristalsis sounds, i.e. you can clearly hear the bowel movements.

Data of the Current Natural History Study

Convulsive/episodic abdominal pain occurred in 39 of 53 children, for the first time at the mean age of one year. These symptoms disappeared only in a few children later in life. They usually occurred at approximately weekly intervals. They could hardly or only partially be treated with medication. Butylscopolamine (Buscopan®) as well as ibuprofen and metamizole (Novalgin®) were most frequently administered as needed.

4.7 Susceptibility to Infection

As a parent, you may often feel that your children are constantly ill. However, frequent infections in (small) children are completely normal. The immune system still has to adapt to different pathogens. Even in healthy children, four to ten respiratory tract infections per year are considered normal for children under the age of two – and even up to 13 infections per year if the children are already attending community facilities. On top of this, there are around one to four gastrointestinal infections per year. For older children, four to eight respiratory tract infections and one to two gastrointestinal infections per year are still considered normal [26].

Warning signs of an impaired immune system are more frequent infections than those listed above, an increase in serious complications (pneumonia, sinusitis, ear infections) or an increase in severe types of infection (blood poisoning, meningitis). A frequent need to take oral antibiotics over a period of two or more months or the need for intravenous antibiotic therapy may also indicate an impaired immune system.

In the previous study, parents reported frequent infections for half of the children with PCH2 (at the upper limit, i.e. ten per year, as defined above). The infections appeared to be more severe. Attention should be paid here in particular to respiratory tract infections, which often develop into pneumonia requiring antibiotic therapy.

Tips to Try Out

- If necessary, prophylactic inhalation with nebulizers (e.g. pariboy ®)
- In consultation with the treating pediatrician, consider regular vaccinations against influenza and Covid-19 in addition to the standard vaccinations

Data of the Current Natural History Study

Pneumonia had already occurred in just over half of the children with PCH2. The cause of pneumonia was either an infection or food or saliva that had entered the airways as a result of the swallowing disorder. Some parents attributed the pneumonia to their children‘s increased mucus production compared to healthy children. The pneumonia often had to be treated with antibiotics, and some children had to be hospitalized. The majority of children affected by pneumonia had developed it less than once a year. Some children had only had pneumonia once in their lives.

Medication that parents reported using in more than two cases for breathing problems is shown in Fig. 9.

Salbutamol (*Sultanol* ®) and ipratropium bromide (*Atrovent* ®) are drugs that are inhaled and widen the airways to facilitate breathing. Budesonide (*Pulmicort* ®), fluticasone (*Flutide* ®) and prednisolone (*Klismacort* ®) are substances similar to cortisol. They are usually also inhaled and used for inflammatory diseases of the airways such as asthma. There are also compounds for rectal administration.

Xylometazoline (*Otriven* ®) is usually administered as a nasal spray and leads to decongestion of the mucous membranes. The lowest possible dosage should be used for decongestant nasal drops / nasal sprays, especially for infants and young children, as breathing interruptions can occur as a side effect.

Salbutamol was mostly used as needed and administered by inhalation, e.g. via a nebulizer. In two cases, salbutamol was discontinued

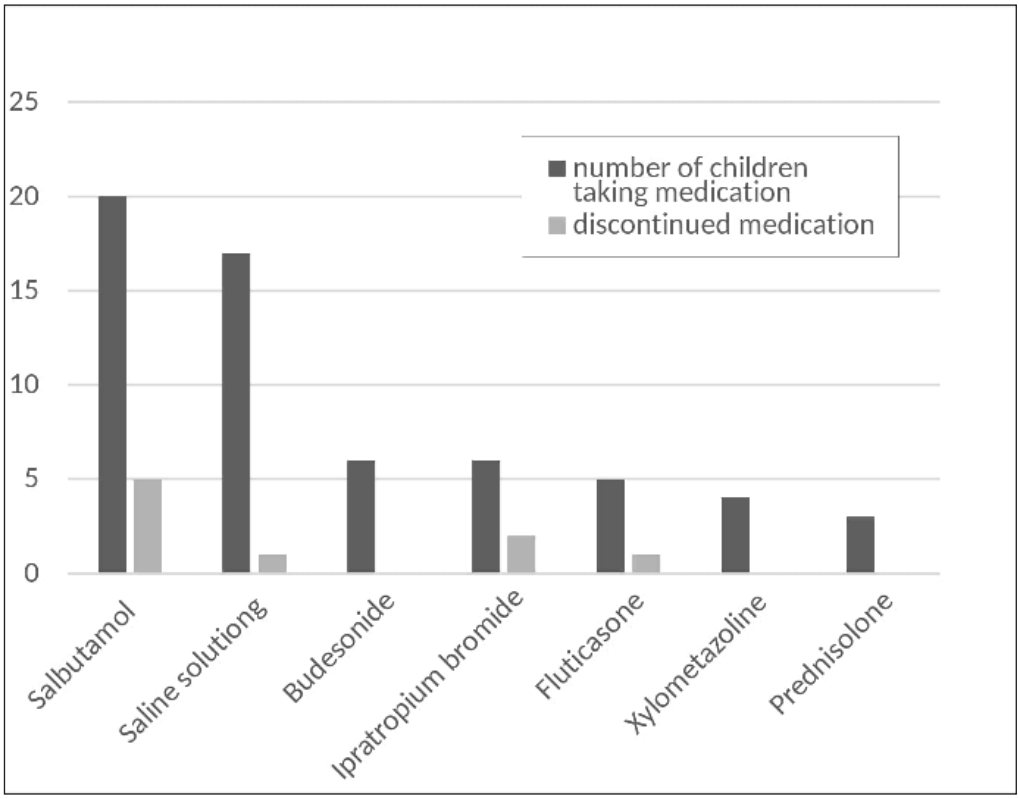


Fig. 9: Table of Medication Used to Treat Breathing Problems

because it led to increased restlessness, and in one case because the parents had read that it could lead to increased seizures. Saline solution was used for infection prophylaxis; both 0.9 % and 3 % saline solution were used. One family pointed out that inhalation should take place in the morning to allow the child to cough up during the day rather than at night. Budesonide was administered both as a long-term medication and as needed for respiratory tract infections or severe mucus production. Ipratropium bromide was also administered both as a long-term medication and as needed for respiratory tract infections or severe mucus production. It was discontinued in one case because it led to restlessness. Xylometazoline was used as recommended and only when needed to impro-

ve nasal breathing. Prednisolone was also only given as needed for respiratory infections.

Non-pharmacological measures for respiratory problems include inhalation (usually performed daily), physical therapy, e.g. a shaking vest, suctioning, oxygen (only if blood oxygen saturation is low), ventilation at home during sleep and a cough assist. A tracheostoma may also be placed in case of problems with the airways, but this was only necessary in a few children.

According to the parents, 29 out of 65 children showed an increased susceptibility to infections. However, the average number of infections per year was only 4.4 even though some children had more than eight infections per year. The average number of antibiotic treatments per year was 1.8. This means that formally there was no increased susceptibility to infections. Nevertheless, half of the parents still reported that their children suffered more frequently from infections.

4.8 Sleep Disorders

Problems with sleeping in general are very common in (small) children. This is considered normal in the first year of life, as the sleep-wake cycle is still developing and waking up at night is important for feeding. While toddlers tend to struggle with sleeping through the night, children aged three to four years and older mainly have difficulties falling asleep. Even children who have already found a stable sleep-wake cycle will develop periodic sleep problems, which may indicate acute illnesses, developmental changes or emotional stress.

Sleep disorders are separate from “normal” sleep problems, in that they occur regularly, frequently and are stressful for the affected child.

Distinctions are made between sleep onset disorder/middle-of-the-night insomnia, problems with sudden wake-up (e.g. night terrors) and daytime sleepiness. Sleep disorders are not uncommon in chil-

dren with physical or mental disabilities. They are also frequently associated with PCH2. Here they mainly manifest as sleep onset disorder or middle-of-the-night insomnia. By definition, a sleep disorder cannot be diagnosed in the first year of life. From the age of two, a sleep onset disorder is diagnosed if falling asleep is only possible with extensive help from parents/caregivers and if it takes more than 30 minutes to fall asleep for at least five times a week for more than a month. A child is diagnosed with middle-of-the-night insomnia if they wake up at least 5 nights a week for at least a month and cannot fall asleep again within 30 minutes without assistance.

In children with (mental) disabilities, there are further difficulties beyond the usual causes of sleep disorders (disruption of the circadian rhythm, irregular daily routine, emotional stress).
In the case of children with PCH2, frequent restlessness, pain (e.g. due to reflux), breathing problems or the inability to adjust their position during sleep are major contributing factors. Sleep routines and, if necessary, sedatives can be used to tackle sleep problems, which are very stressful for both the children and their families. However, there is no cure-all. Many families report success using chloral hydrate as a P.R.N. medication. If P.R.N. medication is required frequently, the use of long-term medication should be considered together with the attending physician. This may include e.g. chloral hydrate or diazepam, but must be discussed and tested in each individual case.

Tips to Try Out

- Establish a sleep routine (darken the room, read a story or sing a song)
- provide optimal support for children with existing breathing problems (ventilation, inhalation, monitoring breathing during sleep)
- Adjust the sleeping position during the night if necessary
- A lack of sleep has a major impact on the health and psyche of caregivers, so seek help if possible and take turns
- In consultation with the attending physicians, determine individual long term and P.R.N. medication for severe restlessness and sleep disorders

Data of the Current Natural History Study

Sleep disorders occurred in almost all children (61 out of 65) from a mean age of 6 months. They stopped only in five cases at a mean age of 8.5 years. Sleep disorders occurred daily in most children. Most of the children (50) experienced both a sleep onset disorder and middle-of-the-night insomnia, six children only had middle-of-the-night insomnia and four children only had a sleep onset disorder. The parents of 35 children stated that their children would wake themselves up at night due to their movement disorders. Overall, no significant difference in sleep disorders was found between different age groups.
The most commonly administered medications for sleep disorders were melatonin, chloral hydrate and levomepromazine. Of three children who received gabapentin, one family stated that it was a fantastic medication because it made the child sleep through the night.

Medication that parents reported using in more than two cases for sleep disorders is shown in Fig. 10.

Table of Medication Used to Treat Sleep Disorders

Substance		General Information	2023 Study
Melatonin (*Slenyto* ®)	Administration form	Tablets	Orally or by tube
	Indications	Sleep Disorders	Sleep Disorders
	Dosage		11 reports: average 5 mg/d (2–10 mg/d) in 1-2 single doses
	Adverse reactions/reasons for discontinuation	Somnolence, exhaustion, mood swings, headache, irritability, aggressiveness, morning fatigue	predominantly lack of efficacy

Table of Medication Used to Treat Sleep Disorders

Substance		General Information	2023 Study
Chloral hydrate (individual compounding; no approved medicinal product for children exists)	Administration form	Oral aqueous solution (100 mg/ml), rectal oily solution (200 mg/ml)	Orally, by tube or rectally
	Indications	Sleep disorders, to calm states of agitation	Sleep disorders, motor disorders, restlessness, constipation
	Dosage		5 reports: average 30.9 mg/kg/d (14.3-66.7 mg/kg/d) in 1-3 single doses
	Adverse reactions/reasons for discontinuation	Sleepiness, dizziness, headache, paradoxical reactions (increased agitation), mild respiratory depression, disorientation, confusion, anxiety, vertigo	Nasty taste, respiratory depression, ineffectiveness
Levomepromazine (*Neurocil* ®)	Administration form	Tablets, drops, injection solution	Orally or by tube
	Indications	Restlessness and agitation, severe and chronic pain	Sleep Disorders, restlessness
	Dosage		8 reports: average 2 mg/kg/d (0.2-10.5 mg/kg/d) in 1-2 single doses
Levomepromazine (Neurocil ®) continued	Adverse reactions/reasons for discontinuation	Weight gain, fatigue, motor disorders, occasionally: seizures, disorders of the eye, cardiac arrhythmias, circulatory disorders, feeling of nasal congestion, gastro-intestinal problems, problems with urinating	Low efficacy, increased epileptic seizures
Phenobarbital	see 4.3 Epilepsy		
Promethazine	see 4.11 Restlessness		
Diazepam	see 4.11 Restlessness		
Gabapentin	see 4.3 Epilepsy		

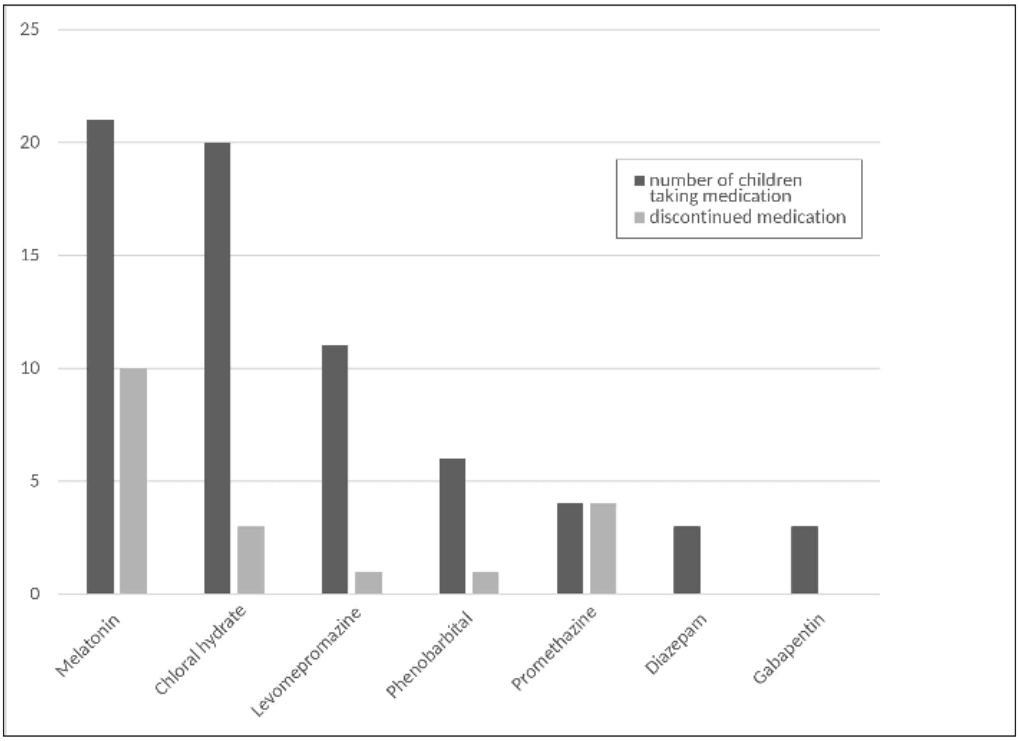


Fig. 10: Medication Used to Treat Sleep Disorders

4.9 Thermoregulatory Disorder

The normal body temperature of a child depends on several factors (age, measurement method, time of day, activity level, etc.). On average, the normal rectal temperature is measured between 36.6°C and 37.4°C. A temperature above 37.5°C is considered elevated temperature, between 38.1°C and 38.5°C mild fever and above 38.6°C fever. The point at which a patient begins to feel subjectively ill or unwell varies from person to person.

A thermoregulatory disorder in terms of hypothermia (body temperature too low) or hyperthermia (body temperature too high) has been observed repeatedly in children with PCH2. In this context, it has often been reported that high or low (usually too high) body

temperature does not have a clear infectious cause. This suggests that children with PCH2 may have a so-called central thermoregulatory disorder, in which the hypothalamus fails to regulate body temperature properly.

In addition, many PCH2 children show a rapid rise in temperature during infections, accompanied by severe restlessness and crying; in some cases, the restlessness occurs before a measurable rise in temperature. Many parents therefore recommend closely monitoring the child‘s body temperature if increased restlessness is observed.

In isolated cases, so-called rhabdomyolysis has been described in children with PCH2 [22]. This refers to the breakdown of skeletal muscle and the resulting release of muscle constituents. This may occur during epileptic seizures, but also during extreme physical exertion such as high fever or during an infection. The released muscle constituents damage the kidneys, which may eventually lead to kidney failure.

Therapy

Antipyretic medication (e.g. ibuprofen, paracetamol) is not always effective in lowering the body temperature of children with PCH2, but combined with sedative medication, it can help improve the restlessness of a child with fever. In contrast, physical cooling (cool bath, cold compresses) often helps to reduce the body temperature.

Tips to Try Out

- In case of unexplained, increased restlessness or discomfort of the children, measure body temperature regularly
- If body temperature is high, try giving a cool bath and/or a cold compress (caution: not too cold, rather lukewarm)
- Ensure sufficient fluid intake
- Give antipyretics in consultation with the pediatrician
- Consult a physician early if the above options do not provide adequate relief or if you are unsure

Everyone reacts differently to an increased body temperature.
Even a slight fever can lead to severe discomfort.
A child with PCH2 is unable to communicate this, so pay more attention to other signs of discomfort and react accordingly!

Data of the Current Natural History Study

A thermoregulatory disorder occurred in 38 of 65 children, on average for the first time at the age of two years. The thermoregulatory disorder only ceased in three children later in life. Overall, the thermoregulatory disorder seemed to become less severe as the children got older. The thermoregulatory disorder mostly occurred daily. Fever without a clear infectious cause occurred in 28 children and a low body temperature in eleven children. Half of the children showed no fluctuations in their state of health depending on the season or ambient temperature. Twenty children had a better state of health in summer, only one child in winter. Twelve children showed a deterioration in cold weather, while eleven children showed a deterioration in hot weather.
Three families independently reported in the free text field that their children were very weather-sensitive; in all three cases, the epilepsy worsened depending on the weather.
In addition, three families also used the free text field to describe very rapid temperature rises without an identifiable cause.
Paracetamol or ibuprofen were frequently given for fever, whereby one child reacted to both medications with a paradoxical rise in temperature. In one case, it was stated that a fever without an identifiable cause was not alleviated by the typical antipyretic medication.

4.10 Interrupted Breathing (Apnea)

The word apnea comes from Greek apnoia, which means non-breathing. Apnea is therefore a stoppage of breathing. This stoppage of breathing can last just a few seconds up to a few minutes and can lead to a shortage of oxygen in the blood. If the interruptions occur predominantly during sleep, this is known as sleep apnea.

Children with PCH2 usually have breathing problems, including apnea, from an early age. The apneas usually occur at night. There used to be somewhat frequent reports of children with PCH2 dying inexplicably in their sleep. It is not clear whether apnea was always the cause of these deaths. Nevertheless, many children are now monitored at night using a pulse oximeter, which measures the pulse and oxygen saturation in the blood and triggers an alarm if there are irregularities. Unexplained nocturnal deaths are now rare due to increased monitoring at night.

The respiratory situation worsens during periods of heavy mucus production or acute upper respiratory tract infections. Inhalations, suitable medication for colds or the suctioning of mucus may provide relief.

Tips to Try Out

- If (sleep) apnea occurs or is suspected, set up nocturnal monitoring using a pulse oximeter in consultation with the attending physicians
- CAVE: simple pulse oximeters are usually sufficient. More complex devices, such as those that also record an ECG, lead to frequent false alarms and can therefore significantly disturb people's sleep
- Try out different sleeping positions (e.g. slightly elevating the upper body)
- Consult your pediatrician whether it is advisable to have oxygen and suction equipment on hand for emergencies and to be instructed in their use.

Data of the Current Natural History Study

Apnea occurred in 46 of 65 children, on average for the first time at the age of eleven months (at the earliest immediately after birth, at the latest at around twelve years). The apnea also occurred mainly at night; only five children had apneas exclusively during the day. Seven children had apneas that ceased again, on average at the age of 13 months. In one case, the cessation of apneas was associated with caffeine citrate treatment. In another child, who was born prematurely, apnea had only occurred during the period of prematurity.
The apneas were caused mainly by seizures, followed by mechanical obstruction of the airways, unclear causes, impaired respiratory drive and emotion.

Thirteen children were given oxygen (five daily, eight only in case of infection) and eight children received home respiration (seven only during sleep, one child continuously). Six out of 65 children had received a tracheostomy, on average at the age of six. According to the parents, the advantages of the tracheostoma were the suctioning of foreign material and the reduced need for anesthesia during surgical procedures (as intubation is not required for ventilation). A better quality of life due to easier breathing and easier inhalation were further advantages. Disadvantages included the resulting

mechanical disturbance, increased difficulty in swallowing and the permanent dependence. A pulse oximeter or home monitor was procured for 25 of 52 children, and was used at least once a week in the majority of cases. Therapies mostly used prophylactically for respiratory problems can be found in section 4.7 Susceptibility to Infection.

4.11 Crying / Severe Restlessness

Parents are often left helpless and desperate by the screaming, crying and obvious discomfort of their own child, which they are unable to explain. If only they could understand what the problem is and how to help their child. At the same time, frequent and prolonged crying or screaming can also lead to high levels of stress for caregivers.

The Situation With PCH2 Children

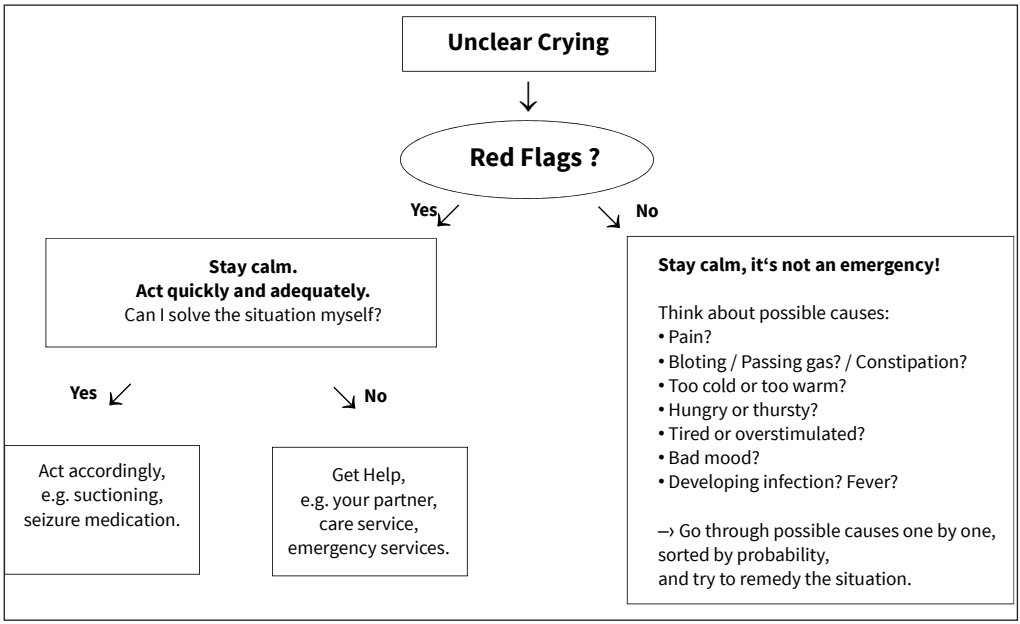
Parents of a baby with PCH2 initially face similar challenges to the parents of a healthy child. Why is my child crying? Is it hungry, does it need comforting, is it overwhelmed, is it in pain? However, there are some more specific reasons for continuous crying that parents of PCH2 children always have in mind.

These are challenges that persist in PCH2 children as they get older. The children are unable to communicate verbally and therefore cannot explain the reason for their current discomfort. Even at an older age, they can usually only communicate this through crying, screaming or changes in their movement pattern.

Over time, most parents become experts on their own children and are usually able to identify problems relatively quickly. PCH2 parents learn to understand the non-verbal language of their children increasingly well. While a motor disorder in the form of uncoordinated movements is part of PCH2, many parents are able to recognize discomfort, pain, joy or other emotions in their children, e.g. based on changes in their movement patterns.

Still, even experienced parents can reach their limits in the face of persistent crying or severe restlessness from their children when all previous remedies fail.
What helps here is a little mental checklist (or on paper) that you can work through in such cases. A checklist like this can also help others who provide care for your children (relatives, care services, etc.) who are not yet familiar with their "non-verbal language".

Checklist for Unclear Crying / Strong Restlessness



What Are Red Flags?

Red flags are warning signs – in the case of unclear crying they are something that should make you alert beyond the normal level. Parents often develop an instinct for this over time. Listed below are some red flags related to unclear crying:

- blue discoloration of the skin, especially on the face
- seizure (current, imminent or just passed)
- severe choking or gasping

> Of course, these red flags do not necessarily have to occur in combination with crying – they should always lead to immediate action.

In such cases, immediate and appropriate action must be taken. In the case of a seizure and if the parents have experience treating it, appropriate medication may be administered (see 4.3 Epilepsy).
If the child is struggling to breathe, e.g. because of heavy mucus build-up over the past few days, suctioning can be attempted. If the breathing difficulties could be caused by choking on an object or by the aspiration of food into the airways and if they cannot be rectified immediately, no time should be lost and the emergency services should be called.

The same applies to all other situations that cannot be brought under control quickly and safely.

Other Causes for Unclear Crying / Strong Restlessness

First, you should take a moment to determine what the child is trying to communicate by crying. A child does not cry to irritate their parents, they do so because it is the only way they can communicate in this situation and they want to draw attention to a problem.

The most likely reasons, which can often be quickly resolved, are hunger, thirst, excessive warmth or cold, an uncomfortable position or a full diaper.

Could the child be tired? Maybe the sensations experienced during the day were simply too much?
Perhaps they are bored or in a bad mood (which everyone is entitled to sometimes)?
Could it be a developing infection? If so, it is advisable to take the temperature and repeat it every 10-15 minutes to avoid a rapid rise in temperature that would require immediate intervention.

Is the child in pain, and if yes, where?

- When did the child last pass stool?
- If it is burping frequently, acid reflux could be the reason.
- If their belly appears bloated, it could be gas.
- Too much gas in the stomach can cause discomfort and pain. Maybe the child needs to burp or the gas can be sucked out through the feeding tube?
- Has the child hit something, been stung by an insect or injured themselves in some other way?
- Pain caused by an infection (such as earache or sore throat, pain when urinating) is often more difficult for parents to recognize. The only help here is to take the temperature and consult your pediatrician.

Note: The severity of the restlessness or crying does not always directly indicate the severity of the discomfort or pain. A child with PCH2 lives in the present. The most important thing to them is what is annoying or painful right now. It is not possible for them to assess the intensity ("I've had more severe pain before") or the time frame ("It'll pass in a minute", "I'll eat in a minute, I can hold out this long").

Sometimes you may not find a reason for the crying or restlessness. It's important to be patient and compassionate, to reassure or comfort your child (take turns, if possible, to get some rest for yourself).

Administering a painkiller or sedative that you already have experience with can sometimes calm the situation even if the exact cause is unknown, thus helping both the child and the family.

Data of the Current Natural History Study

Severe restlessness occurred in all children whose families provided information on the issue (52/52). On average, it occurred for the first time at the age of six months, at the earliest directly after birth and at the latest at the age of seven years. The main cause of severe restlessness was pain, followed by reflux, constipation and emotion. In many cases, the cause remained unclear. Most of the children exhibited severe restlessness at least once a week, which could usually be improved with medication.
Medication that parents reported using in more than two cases for restlessness is shown in Fig. 11

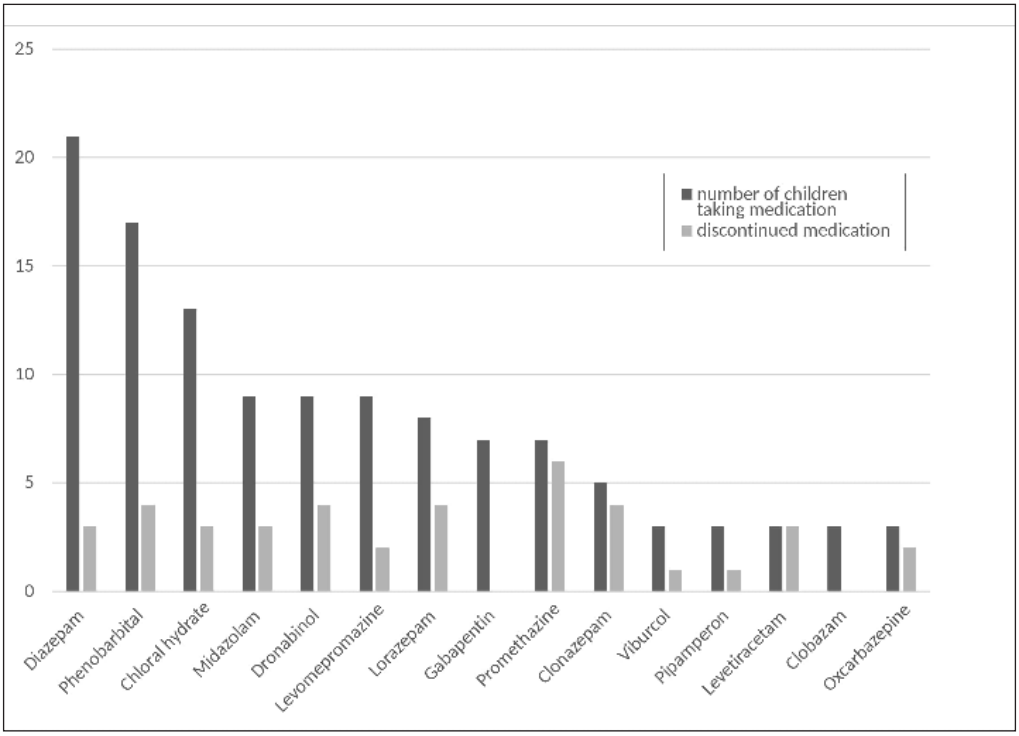


Fig. 11: Medication Used to Treat Restlessness

Table of Medication Used to Treat Restlessness

Substance		General Information	Natural History Study
Diazepam (*Valium* ®)	Administration form	Tablets, drops, suppositories, rectal tube, injection solution, injection emulsion	Orally, by tube, rectally
	Indications	Sedative, muscle relaxant, seizures, febrile seizures, status epilepticus, anxiolytic	Restlessness, motor disorder, seizures
	Dosage		P.R.N. medication, 14 reports: average 3.9 mg/dose (0.5–10 mg/dose)
	Adverse reactions/ reasons for discontinuation	Hypotension, respiratory depression, fatigue, sleepiness; in case of tonic seizures: danger of intensification in combination with benzodiazepine	no substance-specific reasons for discontinuation
Phenobarbital	see 4.3 Epilepsy		
Chloral hydrate	see 4.8 Sleep Disorders		
Midazolam	Administration form	Tablets, injection solution (can also be used nasally), infusion, oral solution	Orally, by tube, rectally, nasally
	Indications	Sedative, seizures, febrile seizures, status epilepticus, anxiolytic	Restlessness, seizures
	Dosage		P.R.N. medication, 9 reports: average 0.24 mg/kg (0.05–0.52 mg/kg)
	Adverse reactions/ reasons for discontinuation	respiratory depression, sleepiness, fatigue, nausea, vomiting	Loss of efficacy, vomiting

Table of Medication Used to Treat Restlessness

Substance		General Information	Natural History Study
Dronabinol (synthetic tetrahydrocannabinol, THC)	Administration form	In Germany only as oily drops (capsules available in the U.S.)	Orally or by tube
	Indications	Pain, spasticity, loss of appetite, nausea in association with severe diseases, epilepsy	Restlessness, motor disorder, pain, spasticity
	Dosage		Long-term medication, 9 reports: average 0.8 mg/kg/d (0.35-1.6 mg/kg/d) in 2-3 single doses
	Adverse reactions/ reasons for discontinuation	Vertigo, sleepiness, concentration disorders, mood swings, gastro-intestinal symptoms	Loss of efficacy, increased abdominal pain, tachycardia, restlessness
Levomepromazine	see 4.8 Sleep Disorders		
Lorazepam (*Tavor* ®)	Administration form	Tablets, infusion	Orally or by tube
	Indications	Short-term treatment of states of anxiety, tension and agitation, as well as sleep disorders caused by it	Restlessness, seizures, sleep disorders, motor disorder
	Dosage		P.R.N. medication, 7 reports: average 0.03 mg/kg/dose (0.02– 0.05 mg/kg/dose)
	Adverse reactions/ reasons for discontinuation	Sedation, fatigue, dizziness, development of dependency, paradoxical reactions such as anxiety and restlessness	Lack of necessity, development of dependency, paradoxical increase in states of restlessness
Gabapentin	see 4.3 Epilepsy		

Table of Medication Used to Treat Restlessness

Substance		General Information	Natural History Study
Promethazine (Atosil ®)	Administration form	Drops, tablets, injection solution	Orally
	Indications	Antihistamine: Restlessness and agitation, nausea, vomiting, sleep disorders	restlessness, sleep disorders, motor disorder
	Dosage		mostly as P.R.N. medication, lack of data for precise dosage
	Adverse reactions/ reasons for discontinuation	Sedation, very rarely: malignant neuroleptic syndrome, seizures, paradoxical stimulation of the central nervous system particularly in children and during infections	Especially malignant neuroleptic syndrome, better efficacy of other substances, paradoxical effects, trigger of seizures, ineffectiveness
Clonazepam (*Rivotril* ®)	Administration form	Tablets, drops	Orally or by tube
	Indications	Antiepileptic: Ancillary therapy or in case of ineffectiveness of other antiepileptics	Restlessness, seizures, motor disorder, sleep disorders
	Dosage	Gradual increase, big differences depending on age	Mostly as long-term medication, lack of data for precise dosage
	Adverse reactions/ reasons for discontinuation	Occasionally: rash, often: central side effects, e.g. sleepiness, muscle weakness	Habituation effect, rash, kept as emergency medication

4.12 Pain

Pain can be the cause of both unclear crying and restlessness without unclear crying.
The pain, in turn, can have various causes already listed in the previous section.

Data of the Current Natural History Study

The parents of the affected children indicated pain as the main cause of restlessness (48/52). Pain was also suspected to be the main cause of dystonic attacks (9/25) as well as dystonic postures that do not meet the criteria for a dystonic attack (17/24).

Medication that parents reported using in more than two cases for pain is shown in Fig. 12.

Fig. 12: Medication Used to Treat Pain

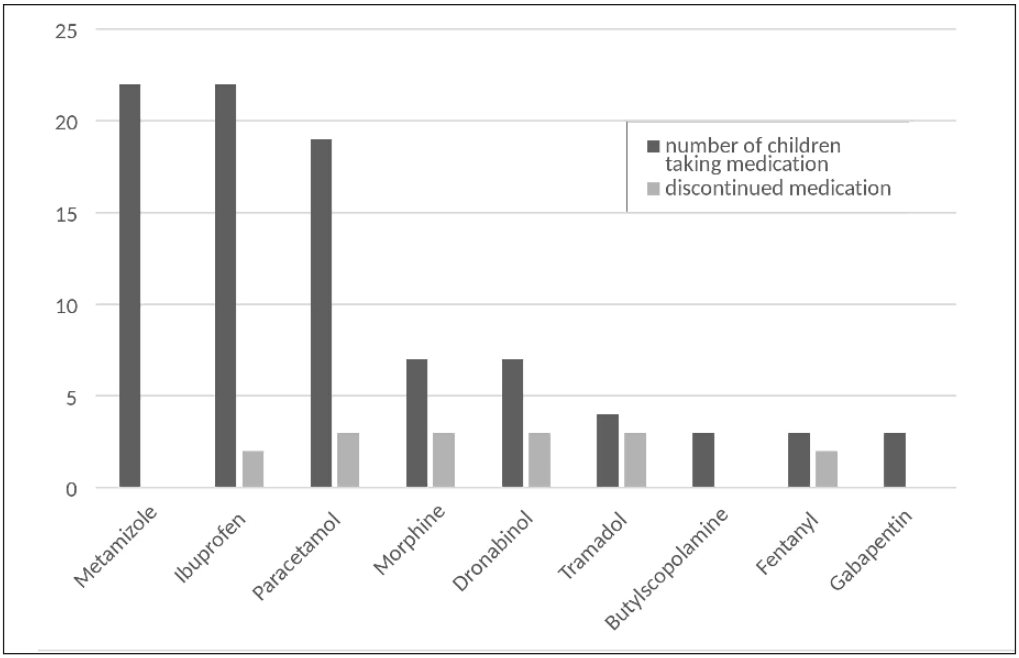


Table of Medication against pain

Substance		General Information	2023 Study
Metamizole *(Novaminsulfon ®, Novalgin ®)*	Administration form	Tablets, drops, injection solution, suppositories	Orally, by tube or rectally
	Indications	Pain, high fever	Pain, restlessness, colic, fever, thermoregulatory disorder
	Dosage		18 reports: average 17.2* mg/kg/dose (0.03–69.4* mg/kg/dose)
	Adverse reactions/ reasons for discontinuation	Reduced number of leukocytes	Not administered for a long time due to ineffectiveness in two cases
	Other		In one case, it was described as a key medication
Ibuprofen (*Nurofen ®*)	Administration form	Tablets, syrup, infusion, creme, gel, suppositories	Orally, by tube or rectally
	Indications	Pain, inflammation, fever	Pain, colics, restlessness, fever
	Dosage		Analysis impossible due to incorrect data
	Adverse reactions/ reasons for discontinuation	Gastro-intestinal symptoms, e.g. reflux → in case of sanguineous vomiting or stool after administration, immediately consult your physician	“Stomach problems”

Table of Medication against pain

Substance		General Information	2023 Study
Acetaminophen / Paracetamol (*Tylenol*®)	Administration form	Tablets, syrup, injection solution, suppositories	Orally or by tube
	Indications	Pain, fever	Pain, restlessness, fever, thermoregulatory disorder
	Dosage		Analysis impossible due to incorrect data
	Adverse reactions/ reasons for discontinuation	Occasionally: inflammation of the liver after long-term therapy with high dosage, otherwise few adverse effects	Lack of efficacy, lack of necessity
Morphine	Administration form	Tablets, infusion, solution, drops	Orally or by tube
	Indications	Strong and extreme pain	Pain, restlessness, colics, dyspnea, anxiety
	Dosage	Different dosages depending on age	Too little information on dosages
	Adverse reactions/ reasons for discontinuation	Mood swings, constipation, nausea	No indication, constipation, increased secretion
Dronabinol	see 4.11 Restlessness		

5 Caring for and Living With a Child With PCH2

5.1 Perceived Severity of Symptoms and Quality of Life

Families of children with a rare neuropediatric disease often experience a reduction in their quality of life.
To date, there has only been one study specifically on PCH2 that has examined the impact of the disease on the quality of life of families in more detail [23]. Parents of children with PCH2 showed a reduced quality of life compared to parents of healthy children, with mothers being particularly affected. Mothers are often restricted in their professional career as a result of caring for the affected child.
Studies on other rare diseases indicate that siblings also experience a reduction in their quality of life, for example because they are less able to take part in leisure activities.

Data of the Current Natural History Study

As part of the study, parents were asked to use a scale of 0-10 to rate the overall impact of the condition and typical PCH2 symptoms on both the affected child and themselves. The results showed a high symptom burden in the children and a correspondingly high overall burden of the disease on the parents. With regard to individual symptoms, parents were always severely affected if they perceived the symptom as distressing and stressful for their child. Parents felt slightly more subjectively burdened than their child only with regard to the child‘s sleeping disorders. The individual symptom “restlessness” was rated as the most stressful (for both the affected child and the parents). Similarly, “episodic abdominal pain” and “gastrointestinal problems” in general also placed a heavy burden on the children (and therefore their parents). The least stressful individual symptom was “epileptic seizures”. This is probably due to the fact that many younger PCH2A children do not have epileptic seizures, in which case the symptom is not a burden for these families. However, epileptic seizures presumably create a high burden for affected families when they are newly diagnosed or during pe-

riods of increased seizures; this burden decreases again when the seizure-suppressive medication has been adjusted to a stable level. The seizures then only become relevant to everyday life in phases. In relation to the different age groups (< 2 years, 2-9 years, > 9 years), there was a clear decrease in the (subjective) burden of the disorder (overall burden and some individual symptoms) at ages > 9 years. This is hypothesized to be due to a habituation effect, better chances of survival for children with less severe symptoms and increased external care as the children get older.

5.2 Nutrition

Children with developmental disorders have different fluid and calorie requirements than healthy children. There are studies on energy expenditure in children with cerebral palsy. Nevertheless, the European Society for Pediatric Gastroenterology, Hepatology and Nutrition recommends using the reference standards for healthy children.

Data of the Current Natural History Study

Infancy: Feeding at the breast was possible for 15/65 infants, on average from 1.5 weeks to six months of age. 48 infants could not be breastfed. The majority of children (45/53) received expressed breast milk up to almost four months of age. Two thirds of the children received exclusively infant formula from around two months of age, while one third were not given infant formula at any point. The majority of the children (48/53) received their first pureed meal at an average age of six months.

Oral feeding: Almost all children were able to feed orally at some point in their lives. The majority of children needed 30 minutes for an oral meal. 17/53 children were exclusively orally fed in their lifetime; they were on average four years old at the time of the survey. Even children who had received a feeding tube were often still fed orally. Four children had never been fed orally at any point in their lives.

Only five children had to be fed via a venous access, most of them only temporarily in hospital.

Diet: Eleven out of 53 children received a high-calorie diet, 7/53 a lactose-free diet, 4/53 a gluten-free diet and 2/53 a diet for children with cow‘s milk protein intolerance (intolerance to dairy products). Three children received a “gas-free” diet. It was not tested whether the children in question actually had an intolerance to lactose, gluten or cow‘s milk.

Food supplements: Trace elements and vitamins were substituted in more than half of the children, most frequently vitamin D, followed by iron, zinc, vitamin B12, folic acid and selenium. Three children received combination supplements containing several vitamins and trace elements.

Fluid and calorie intake: For the three to five age group, fluid intake averaged 76.9 ml/kg/day and calorie intake averaged 80 kcal/kg/day. For the six to ten age group, the average fluid intake was 65.4 ml/kg/day and the calorie intake was 75.8 kcal/kg/day. For the 11-14 age group, the average fluid intake was 33.7 ml/kg/day. Children over the age of 14 were given an average of 42.7 ml/kg/day to drink and 45.3 kcal/kg/day to eat. There was too little data available to calculate a statistically correct average for children under the age of three and those aged 11-14 (only calorie intake).

Fig. 13 shows the calorie intake for children with PCH2, Fig. 14 shows the fluid intake for children with PCH2. The gray bar indicating the recommended fluid and calorie intake for different age groups is taken from the book “Ernährungsmedizin Pädiatrie [Nutritional Medicine in Pediatrics]” by Jochum [21], published in 2013.

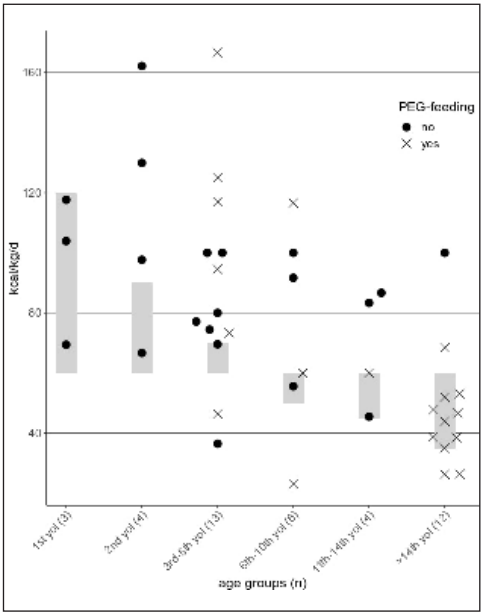


Fig. 13: Calorie intake for children with PCH2 (dots) and reference for healthy children (gray bars)

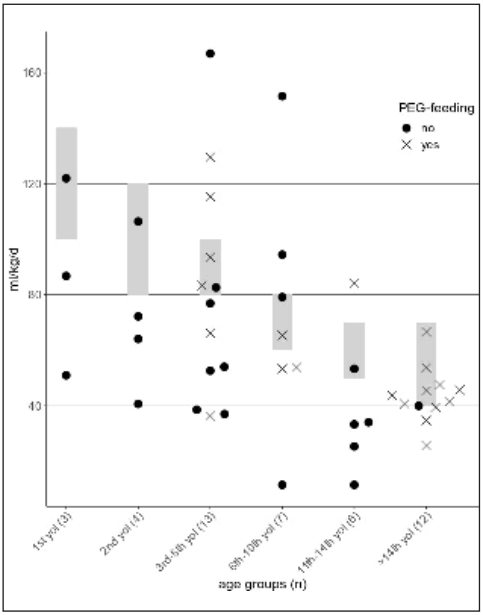


Fig. 14: Fluid intake for children with PCH2 (dots) and reference for healthy children (gray bars)

5.3 Feeding Tubes

Many families initially shy away from using a feeding tube. It may be seen as a further escalation in the care of the child or even as a perceived failure to feed their own child properly, or it may be due to concerns about the surgical risk. In general, it is a personal decision that each individual family makes in consultation with their doctors. It depends on numerous factors and must be continually reconsidered over time. If the current feeding situation of the affected child is perceived as little or only occasionally stressful, the decision for a feeding tube can certainly be delayed. However, if the feeding situation is a persistent burden for the child and the entire family, opting for tube feeding can bring relief. In particular, most families in the first survey felt that the resulting improvement in the feeding situation was a great relief for themselves and their children. (see also 4.4 Feeding Difficulties)

Which Types of Feeding Tubes Are There?

Generally speaking, oral feeding is still possible even with a feeding tube in place. The tube can be used as the sole means of feeding, but does not have to be. There is a difference between nasogastric tubes, i.e. tubes that are inserted into the stomach via the nose and esophagus, and surgically inserted tubes. It is easy to insert nasogastric tubes, but they are not intended for permanent use.

Surgically inserted tubes can be divided into PEG, G-Button/GastroTube and PEJ. PEG is short for percutaneous endoscopic gastrostomy. This means that a feeding tube is inserted through the skin directly into the stomach. Once a stable canal has formed after four weeks, this can be replaced by a GastroTube or a G-button. Unlike the PEG tube, these do not have an inner retaining plate, but rather a locking balloon on the inside. For this reason, the G-button and GastroTube can be changed more easily. In addition, the G-button only protrudes a few millimeters above the skin level, which is why some children find it less irritating.
In the case of a gastric emptying disorder, the stomach tube can be supplemented with a tube that extends into the small intestine.

This is called PEJ (= percutaneous endoscopic jejunostomy, because "jejunum" refers to the uppermost section of the small intestine into which the tube is inserted). If a PEG is already in place, a tube can be advanced into the jejunum. Alternatively, the jejunum can be punctured directly. However, since the reservoir function of the stomach is lost when feeding via a PEJ, it is not possible to feed as a single meal; instead, feeding via a PEJ must be carried out using a continuous infusion of food (usually throughout the night).

Different Ways of Placing the PEG Tube

Nowadays, a PEG tube is usually inserted endoscopically using the so-called transillumination method. An endoscope with a light source is inserted into the stomach via the esophagus; it is then pressed against the stomach wall from the inside so that the light illuminates through the skin, where the probe is inserted. In the case of a laparoscopic PEG insertion, the stomach is accessed via the abdominal wall with the aid of a camera and the tube is then inserted. The laparoscopic procedure appears to have fewer complications than endoscopic PEG insertion, particularly in high-risk patients. However, due to the small number of cases, it is not possible to make a general recommendation in favor of or against one type of placement.

Differences between children with and without a PEG tube:

The first study already showed a positive influence of PEG tube feeding on weight and BMI development compared to purely oral feeding. In terms of survival, gastrointestinal symptoms and overall symptoms typical of PCH2, however, there appears to be no difference between children being tube-fed and orally fed.

Data of the Current Natural History Study

Nasogastric Tube: In the course of their lives, 27/53 children had already been fed via a nasogastric tube, mostly temporarily in hospital or directly after birth.

PEG/G-Button/GastroTube: A PEG had been placed in 29/53 children in the course of their lives, on average at the age of two years. Of these, 27 children had also been at least partially tube-fed via PEG.

PEJ: Only 2/53 children were fed via a PEJ tube.

Children who were exclusively tube-fed mostly continued to have taste samples by mouth.

PEG placement: Endoscopic placement resulted in more complications than laparoscopic placement; the difference was not statistically significant and the complication rate was not considerably higher than that reported in literature [27]. Still, there are indications in literature that a laparoscopic placement has advantages in general and particularly in children considered to be high-risk patients [24]. Due to the small number of cases, no recommendation can be made. The type of PEG placement depends on the child and the surgeon‘s experience and is therefore an individual decision.

Thriving with a PEG tube: When compared to children without a PEG, there was no difference in survival, gastrointestinal symptoms, symptom burden and quality of life in children who were at least partially fed via a PEG tube in the long term. However, it was found that weight and BMI development tended to be more favorable in children fed via a PEG tube (although the number of cases was small).

5.4 Hospitalization and Surgery

5.4.1 Hospitalization

Almost all children with PCH2 were hospitalized at least once during their lifetime. The hospital stays were categorized into planned and emergency stays.
The majority of children had one planned and one emergency hospital stay in the first year of life. In the second year of life, the number of hospitalizations decreased. Only few children were hospitalized more than three times annually in the first two years of life. From the second year of life onwards, the children had to be hospitalized

twice a year on average, once planned and once as an emergency. Again, children who had more than three stays in hospital per year were in the minority.
In the first year of life, the average hospital stay was 37 days (minimum one day to a maximum of 240 days). In the second year of life, the average hospital stay was 23 days (minimum one day to a maximum of 192 days).

5.4.2 Surgery and Medical Procedures

Children with PCH2 undergo a wide variety of procedures in the course of their lives. The most common procedures are briefly explained below.
Upper gastrointestinal endoscopies are performed frequently. During an upper GI endoscopy, the esophagus, stomach and the uppermost section of the small intestine, the duodenum, are examined through the mouth using a camera. If necessary, tissue samples (biopsies) can be taken.
During a colonoscopy, on the other hand, the large intestine and the end section of the small intestine are assessed; biopsies can also be taken here if necessary. Colonoscopies are rarely performed in children with PCH2.
Fundoplication is an operation in which the entrance to the stomach is narrowed. This is done in the hope of reducing reflux from the stomach into the esophagus.
A tracheostoma is an artificial access to the airways below the vocal cords. It is created in the case of constrictions above the vocal cords, which can lead to shortness of breath, or if ventilation is required.
A grommet or tympanostomy tube is a tube that is inserted into the eardrum to create a connection between the middle and outer ear. It is used in case of Eustachian tube malfunctions.

Procedures or surgeries were required in 48/65 children. Of 52 children, 19 had at least one diagnostic gastroscopy over the course of their lives, and 11 of the 19 children had another gastrointestinal endoscopy. Only 2/52 required a colonoscopy.
The placement of a PEG tube, G-button, GastroTube or PEJ tube was done in 37/65 children (in the case of endoscopic placement, a gastrointestinal endoscopy was also performed). The feeding tube had to be replaced in eight out of 37 children over time. Detailed information on feeding tubes can be found in section 5.3 Feeding Tubes.
A fundoplication was performed in 15/65 children, three of whom required a second operation for renewed fundoplication. In 11/15 children, information was available on whether postoperative complications had occurred, which was answered negatively in all cases.
Operations in the ENT area were also performed: Placement of a tracheostoma (6/65) and a tympanostomy tube (6/65), and pharyngeal tonsillectomy (9/65).
Seven out of 65 underwent at least one orthopedic procedure, mostly in the pelvis or hips.
Further procedures were performed on 27/65 children. Dental operations, hernia operations and various abdominal operations were the most common.

5.5 Social Pediatric Aspects

This data only refers to a group of 45 children. Their families had completed the new questionnaire and came from Germany. As the survey was designed for the German social system, the questions were difficult or impossible to answer for families from other countries.
The following section therefore reflects the care system and its opportunities in Germany.

5.5.1 Care Levels in Germany

The care level determines which benefits insured persons receive from their nursing care insurance provider. The higher the need, i.e. the greater the restriction of a patient‘s everyday life and independence, the higher the financial and non-cash benefits. As of 2017, Germany has a system that distinguishes between five levels of care. In order to obtain a care level, an application must be submitted to the relevant nursing care insurance provider. This is followed by an assessment procedure by the MD (Medizinischer Dienst; medical advisory service of the statutory health insurance funds) or by MEDICPROOF GmbH for those with private insurance. In this process, the extent to which the patient is restricted compared to a healthy person of the same age is assessed and, if necessary, a care level is recommended. In the case of adults, this particularly focuses on one‘s level of independence. Generally, the same conditions as for adults apply to children in need of care, with a few special aspects:

- Children under 18 months: Because healthy children of this age also need full care from their parents, affected children in this age group are always classified one care level higher.
- Children under 11 years: As the independence and many skills of children only develop over time, the care level is determined at this age by comparison with children of the same age that are developing normally.

The care benefits consist of a monthly care allowance and care allowances in kind. In addition, there are allowances for day and night care, respite care, consumable care products, short-term care if necessary, and others. The amount paid depends on the care level. A detailed overview of this can be found on the German website www.pflege.de. Here you will also find detailed information on care and care levels in general, on application forms, on preparing for the care assessment, templates for any appeal against an assigned care level, a care level calculator and much more.

Generally speaking, a child with PCH2 is entitled to care level five from birth due to the severity of the condition (called a ‚specific needs constellation' with ‚non-usable arms and legs'). Still, some families have to overcome many obstacles in order to receive the benefits to which they are entitled. Exchanging experiences with other affected families can help to identify potential obstacles in advance and to react to them more effectively.

Data of the Current Natural History Study

Of 45 children, 42 had a care level, of which the majority had care level five (32), followed by three (6), four (3) and one (1). On average, a care level was first approved at the age of eight months.

5.5.2 German Disability Card

The Schwerbehindertenausweis is a standardized nationwide proof of status as a severely disabled person and provides information on the severity of the disability. Identification by means of this card is necessary, for example, in order to claim legally defined compensation for disadvantages and to exercise certain rights. From a grade of 50 (on a scale from 20 to 100), a person is considered severely disabled and is entitled to a severely disabled person's pass.

The pass is green in color. An orange-colored area indicates that one of the characteristics "G", "aG", "H", "BI", "RF" or "GI" has been determined.

(G = Beeinträchtigung der Bewegungsfähigkeit; impairment of mobility

aG = außergewöhnliche Gehbehinderung; exceptional impairment of mobility

H = Hilflosigkeit; helplessness

BI = Blindheit; blindness

GI = Gehörlosigkeit; deafness

TBI = Taubblindheit; deaf-blindness

B = Begleitperson; accompaniment by a carer

RF = Ermäßigung des Rundfunkbeitrags oder der Telefongebühren; reduction of the German broadcasting fee or telephone charges

In order to obtain a pass for severely disabled persons in Germany, an application must first be submitted to determine the grade of disability (20-100). The authority to which this application must be submitted varies from municipality to municipality, but the correct place can be obtained from the citizens' office. Many federal states already offer an online download of the application forms; a list can be found on www.einfach-teilhaben.de.

For people with PCH2, the standard disability card has the following classifications: 100 % (grade of disability), aG , H, B (aG also includes the necessary parking permit). As PCH is a genetic disease, the application can be made from birth.

Data of the Current Natural History Study

A disability pass was issued to 41/45 children and was in the process of being issued in one other case. In one case, no information was provided. The two children who did not have a disability pass had died before their first birthday. On average, a disability pass was approved at the age of eleven months. There were 36/41 children with a grade of 100 %, two children each with 80 % and 50 % and one child with 90 %. The majority of children had four characteristics in their pass. The most common characteristic was H (39), followed by G (33), aG (32), B (18), RF (15) and Bl (6). No child had been given the TBl and Gl characteristics.

5.5.3 Care Relief for Families With a Child With PCH2

As caring for a child with PCH2 is very time-consuming, the following options have proven to be very helpful in Germany:

Home nursing care according to §37 SGB V/German Social Act 5 (or currently out-of-hospital intensive care according to §37c SGB V/German Social Act 5): If prescribed by a doctor, the funding body can recognize the need for home care by registered nurses. The care is provided either by an outpatient (pediatric) nursing service or by nursing staff employed under an employment scheme (personal budget).

Specialized outpatient (pediatric) palliative care (§37b SGB V/ German Social Act 5): Multi-professional outpatient support for children and adults with life-limiting diseases. Teams of doctors, nurses, social counselors and psychologists provide systemic support to families not only in the terminal phase. However, they do not provide nursing care.

Outpatient children's hospice services: To assist families with children with a life-limiting disease such as PCH2, outpatient children's hospice services are available nationwide, usually with specially trained volunteers who support the families. The affected children, and sometimes their siblings, are cared for, or the parents are supported in various ways.

Inpatient hospices for children and young people: Children and young people with a life-limiting disease such as PCH2 have a legal right to hospice care in Germany and can visit inpatient children's hospices with their families to relieve the burden of care. Unlike in adult hospices, >90 % of stays there are for care relief and not for care during the terminal phase.

Data of the Current Natural History Study

The families of 25 of the 45 children were supported by a care service. On average, a care service was approved at the age of 24 months, but in some cases it was approved much later. In the majority of cases, the care service was able to cover the approved number of hours, in some cases the majority of the approved hours were covered, and in three cases significantly less than half were covered by the care service.

Nine children were cared for via a personal budget (nurses directly employed by family), on average from the age of around three.
Just over half of the children were already supported by a SAPPV team (specialized outpatient pediatric palliative care). Of these, 13 children had received support in the previous quarter and eleven children had suspended this support in the last quarter.
23 out of 45 children had already stayed in a children‘s hospice at least once. On average, those children had already spent four visits to the children‘s hospice in their lifetime.

5.5.4 Kindergarten

A third of the children were not yet in external care, 30 children were already in external care. In one case, the parents stated that external care for their child had been impossible for its entire life.
The average age at the start of kindergarten was just under three years, the average hours of care per day in kindergarten was 6.5 hours. The majority of the children (16) attended a combined school/kindergarten for children with physical and mental disabilities. Twelve children attended a regular kindergarten and one child each attended an institute for the blind and the inclusive kindergarten run by the German Lebenshilfe association. Twelve children required an accompanying person, eight of them an integration assistant and four a nurse.

5.5.5 School

21/45 children were already of school age. The average age at the start of school was just under seven years, the average hours of care per day in school was seven hours. Fourteen children attended a special-needs school, three children were in an inclusive mainstream school and one child attended the institute for the blind. Twelve children required an accompanying person in school, eight of them a nurse and four an integration assistant.
In one case, the parents commented further that their child had benefited greatly from being taught together with non-disabled classmates.

5.6 Provision of Assistive Devices

Accepting aids is not always easy at first, as it means admitting that your own child needs additional support in everyday life. Each family should therefore proceed at their own pace and consider their needs carefully depending on the situation. In addition, affected children often have difficulties accepting new aids (such as a special seat), as these are perceived as unfamiliar and possibly restrictive. It is therefore advisable to allow the child to get used to any changes slowly. Health insurance companies or other bodies that approve or finance the aids may try to fob you off with blanket statements such as "At this age you don't get a special needs buggy" or "You have to pay for the roof of the buggy yourself". Even if it seems stressful and time-consuming at the beginning, it is worth gathering information first (forums, advice from physiotherapists and other professionals), especially with more expensive purchases, and then sticking to your demands by filing objections and being persistent. Make sure that the prescription contains the exact aid (with all the necessary accessories!) that best meets your needs. Anything that needs to be added or changed afterwards will require a separate approval process from the health insurance company, thus delaying the process and potentially leading to rejection (as a result of a further review).

The **standard equipment** for younger children included: therapy chair, special needs buggy, shower stretcher, car seat (rear-facing car seat also possible for special needs)
Later: wheelchair, nursing bed, lift

Data of the Current Natural History Study

There were 21 checkbox options to choose from, 16 of which were labeled as aids (see Fig. 15), while five checkbox options were labeled "Other" and parents could enter additional aids themselves. Based on these 21 options, the children needed an average of eight aids. Some children were not (yet) dependent on aids, the maximum number was 17. Most children needed between four and eleven aids.

Explanation of Fig. 15 using the example of the therapy chair: 42 out of 52 children had a therapy chair at some point. For 36 of these children, the therapy chair was used at least once a week in the last year (of age).

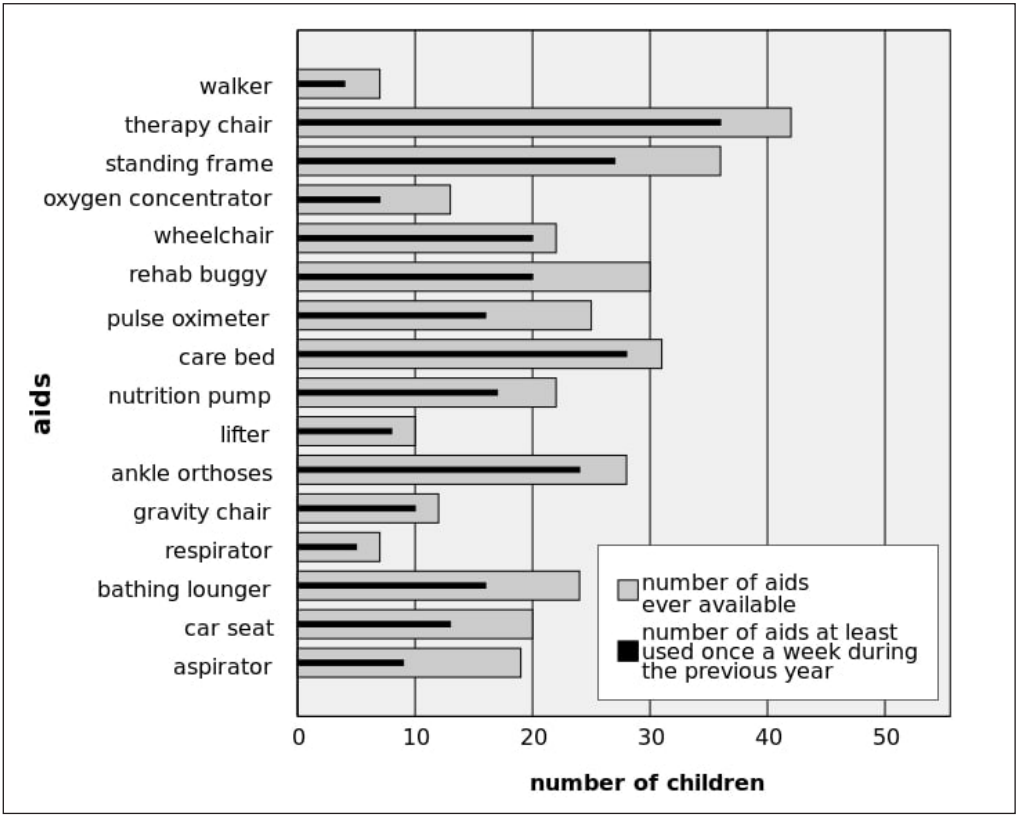


Fig. 15: Possession and use of selected assistive Devices

5.7 Remedies

Data of the Current Natural History Study

All children had received physiotherapy. The majority of children had received physiotherapy according to Vojta (reflex locomotion) and Bobath, followed by only physiotherapy according to Bobath. Only a few children had received just physiotherapy according to Vojta.
The second most frequently used treatment was early remedial intervention (33/52), followed by speech therapy (30/52), early vision therapy (25/52) and occupational therapy (22/52). Six children also received animal-assisted therapy, five each osteopathy and music therapy, and two children went swimming. The most frequently discontinued therapies were early remedial intervention (24/33), followed by early vision therapy (16/25) and speech therapy (14/30). Physiotherapy and occupational therapy were continued in the majority of cases. Early remedial intervention was usually discontinued because the health funds are no longer covering it above kindergarten age or because it is not offered to schoolchildren. The same applied to early vision therapy. There were many reasons for ending speech therapy, including a lack of success, no possibility of home visits or a lack of necessity.

6 Development of Children With PCH2

Child development is often divided into different areas (gross and fine motor skills, language and cognition, as well as social-emotional development). Studies have established average ages at which specific developmental steps, so-called developmental milestones, will be reached. However, every child develops at their own pace. Slight deviations in one direction or the other are therefore completely normal. During check-ups with the pediatrician, the child‘s development is monitored to see whether it is within the normal range (the 90th percentile is usually used for this) or whether individual areas require special support.

In the past, the literature on PCH2 often summarized that affected children do not make any developmental progress (5,15). The first natural history study was already able to demonstrate that children with PCH2, although severely impaired in motor and cognitive development, can still achieve certain milestones, albeit with a considerable delay. For example, the milestone of targeted head movements was achieved by more than half of the children, but not in the same way as in healthy children, where it remains reproducible and constant through changes in position. In many children with PCH2, however, brief periods of head control in a certain direction were clearly present. The milestone of rolling over was also achieved by a large number of children with PCH2, and many children also showed attempts to reach for objects offered to them. However, more complex skills were only achieved by very few children with PCH2. For example, sitting without support, moving forward in a prone position or targeted and secure grasping was only possible for a small number of children with the disease.

In terms of cognitive development, many PCH2 children responded to caregivers with recognition, showed a social smile and fixated and tracked high-contrast objects with their eyes. They also reacted to noises and were able to communicate with sounds. However, few reached the milestone of uttering specific words.

It should also be noted that independent walking or the ability to speak in complete sentences was never achieved, yet only around 10 % of the children later lost the skills they had learned. As the literature often only describes a lack of development, these were important findings.

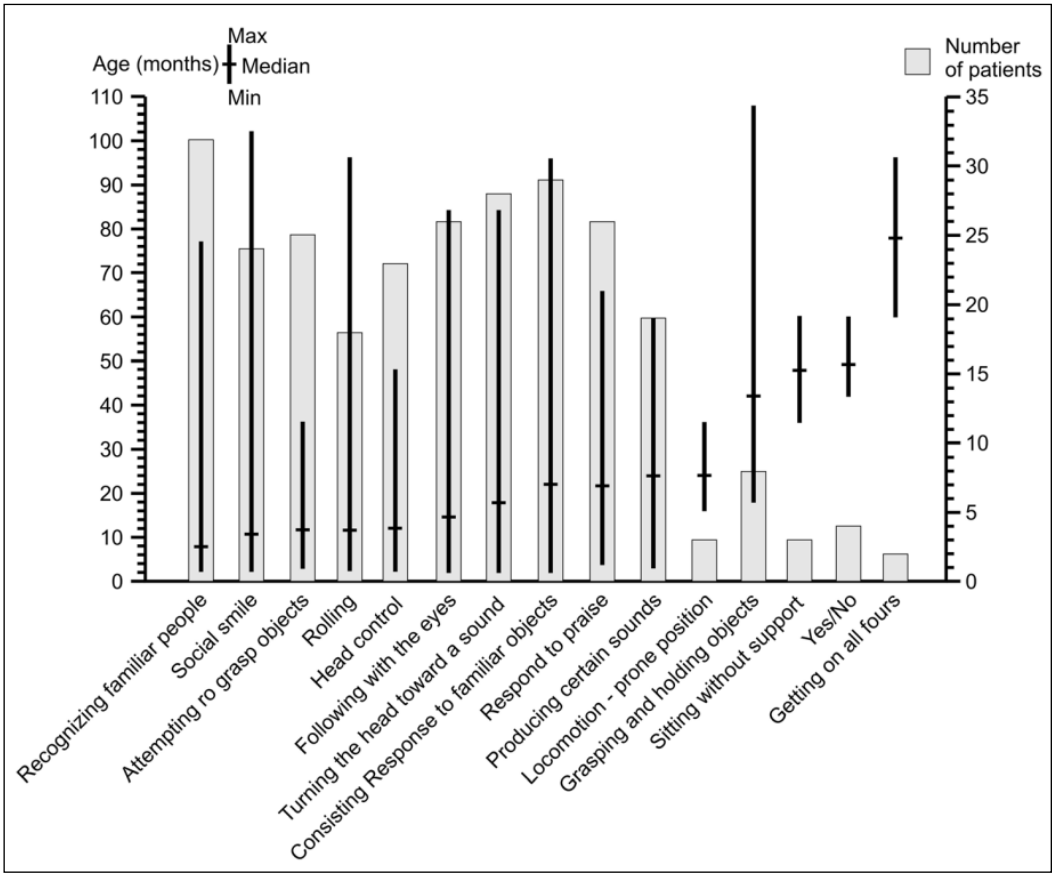


Fig. 16 (taken from the first parents‘ brochure):
Skills learned based on number of children and age

Data of the Current Natural History Study

Tab.: Motor development		
Skills	How many children have learned it? indicated in % and absolute numbers)	Median age at learning (months)
Grasping attempt	69 % (45/65)	12
Head control	65 % (42/65)	9,5
Rolling over	48 % (31/64)	12
Targeted grasping	35 % (23/65)	16,5
Crawling	14% (9/65)	18
On all fours	11 % (7/65)	19,5
Sitting without support	6 % (4/65)	32

The data collected (see table above) shows that the motor development of children with PCH2 is severely limited, but it also emphasizes that children with PCH2 do in fact make developmental progress. Despite the severe motor disorder, two-thirds of children gain head control and half are able to roll over, with a few even able to move in a prone position or achieve sitting without support. The latter is rare, however, and standing or walking (even with support) has never been reported. Nevertheless, more than two thirds of the children attempt to grasp, although only one third can actually accomplish this. This indicates that their cognitive development and their curiosity about the environment are stronger than their severely impaired motor development would suggest.

This is also reflected in the data on communication and social contact (see Data on Communication table). Almost all children recognize their caregivers, smile at them and react to familiar things. Almost 90 % fixate and 80 % follow with their eyes. However, patience is required here, as this is only observed on average at the end of the first year of life. It is also important to note with regard to language development (see Data on Language table) that around half of the children use specific sounds to express themselves, even

if specific words were only observed in a few children and at a later age (in the third year of life on average).

Tab.: Cognitive development		
Skills	How many children have learned it? (indicated in % and absolute numbers)	Median age at learning (months)
Recognition of caregivers	94 % (61/65)	6
"Response to familiar things"	88 % (57/65)	12
Fixation	86 % (56/65)	10,5
Social smile	85 % (55/65)	8
Eye tracking	80% (52/65)	12
Response to sounds	77 % (50/65)	12
"Reaction to visual stimuli "	94 % (49/52)	4,5
Tab.: Language development		
Skills	How many children have learned it? (indicated in % and absolute numbers)	Median age at learning (months)
Response to requests/ praise	69,2% (45/65)	19
Specific sounds	48 % (31/65)	18
Specific words	12 % (8/65)	30

The following figure shows how many children have achieved which motor skills and when.

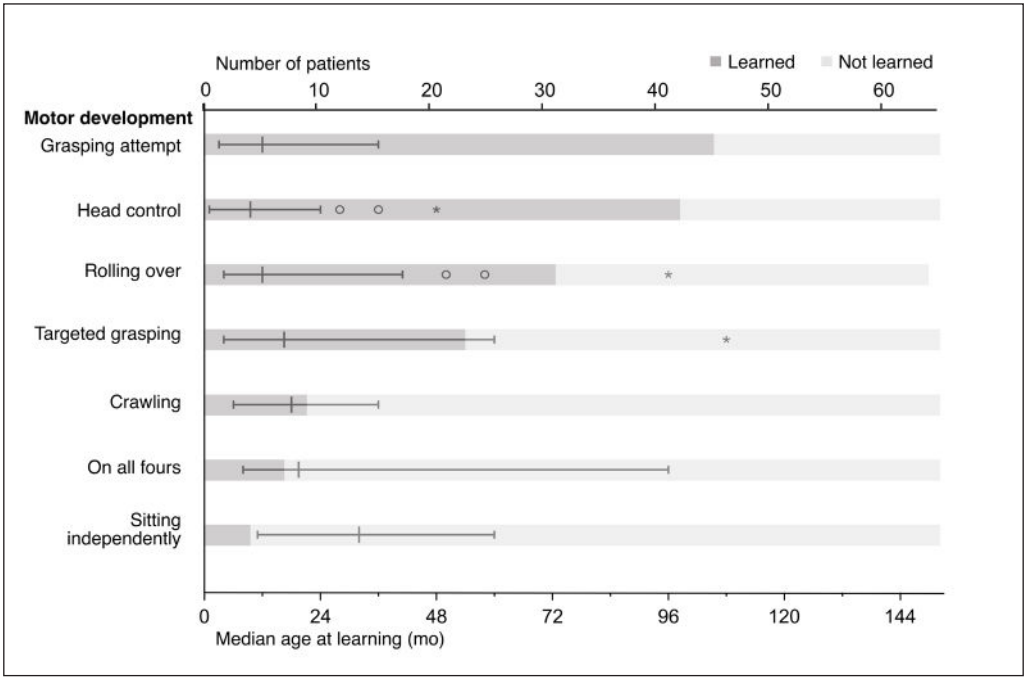


Fig. 17: Number of children who have achieved motor skills and when.

The same type of visualization shows developmental steps in linguistic and cognitive development.

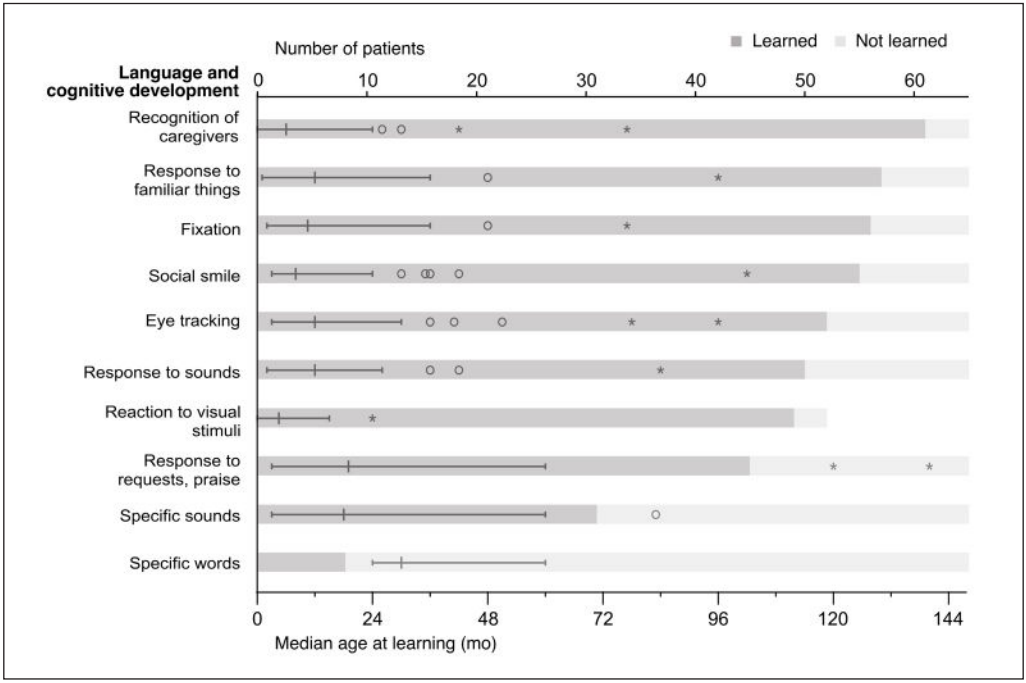


Fig. 18: Number of children who have achieved linguistic and cognitive skills and when.

6.1 Physical Development of Children With PCH2

The growth of a child‘s head and body as well as its weight gain can be tracked using so-called percentiles. The age is shown on the x-axis and the head circumference on the y-axis, for example. Percentiles are percentages that show the head circumference of an individual child in relation to their peers. If a child‘s head circumference is at the 50th percentile, this means that 50 % of all other children have a smaller and 50 % a larger head circumference. Values below the third or above the 97th percentile are considered clearly abnormal and may indicate illness. At birth, children with PCH2 are usually still within the normal range in terms of body measurements, although the head circumference is often relatively small already. In the course of the first years of life, they often fall below the third percentile due to a smaller increase in physical dimensions. This applies to the head circumference in all cases; the children therefore develop secondary progressive (= increasing) microcephaly. Over time, weight and BMI also often fall below the third percentile [12].

Data of the Current Natural History Study

Due to the strong deviation from the normal growth rate, the individual development of a child with PCH2 is difficult to assess using the percentiles of healthy children. For this reason, PCH2-specific percentiles were created. A distinction between male and female PCH2 percentiles could only be made up to the age of two years due to the small number of values. The sex-specific percentiles were each compared with reference values of healthy children; this comparative data was obtained from the 2013 KiGGS study (Study on the health of children and young people in Germany) and was kindly provided by the Robert Koch Institute.

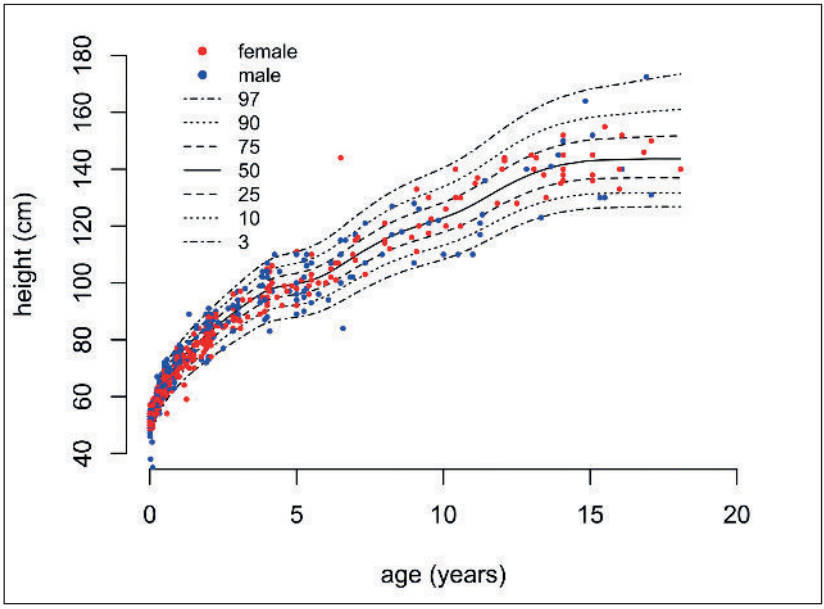


Fig. 19: Height percentiles PCH2

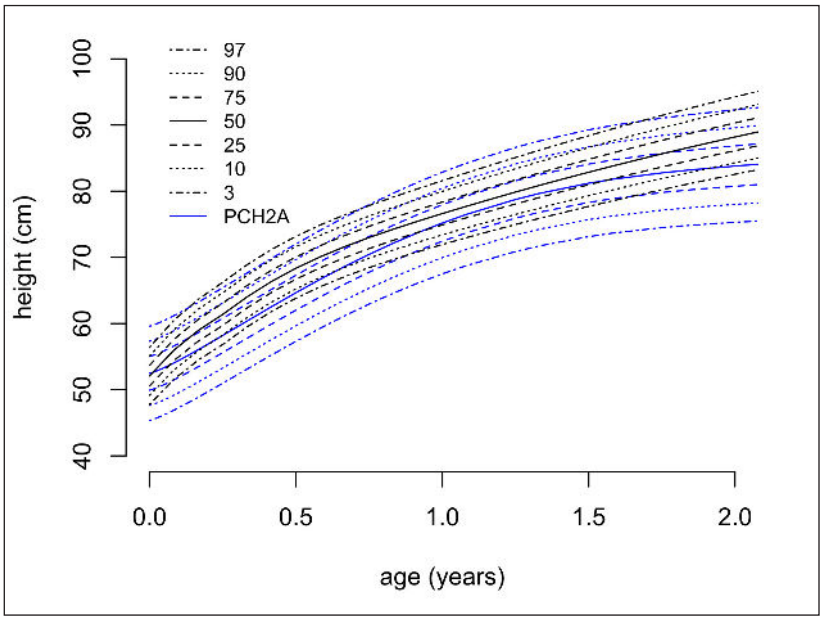


Fig. 20: Height percentiles for boys with PCH2 compared to healthy boys

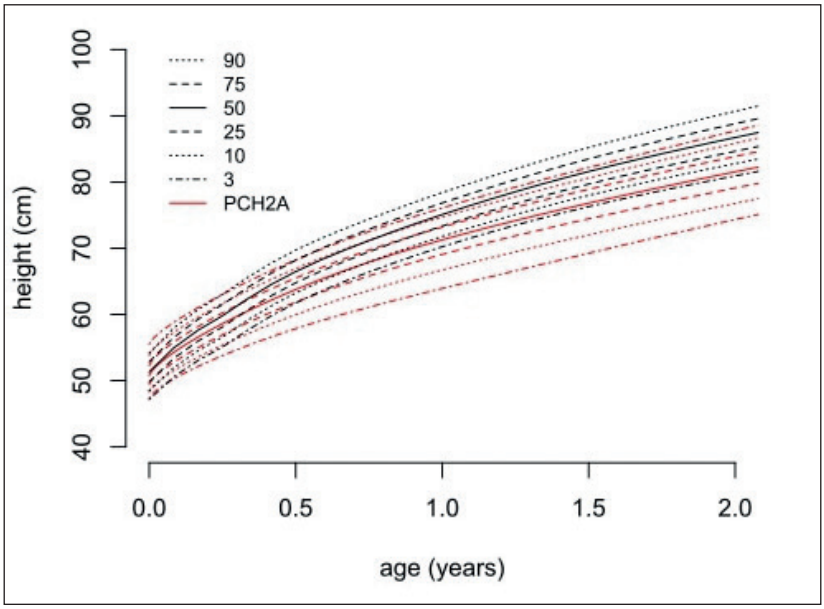


Fig. 21: Height percentiles for girls with PCH2 compared to healthy girls

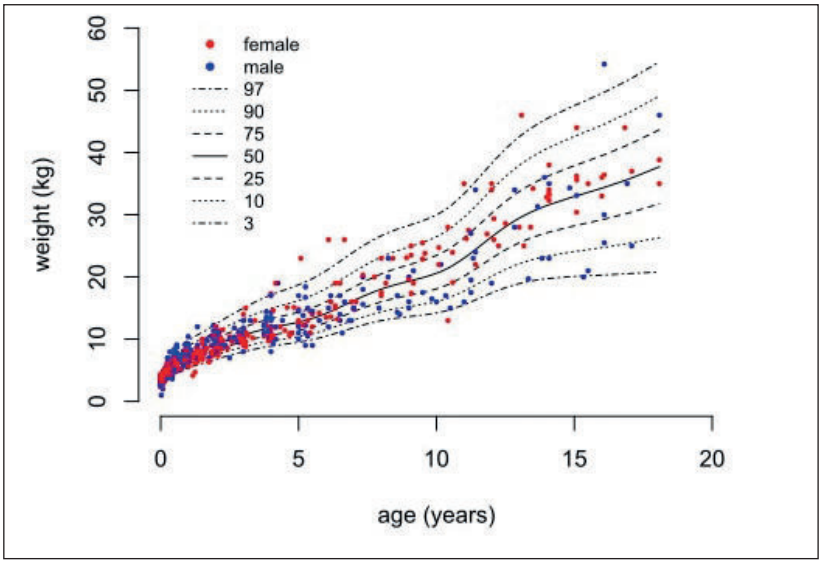


Fig. 22: Weight percentiles PCH2

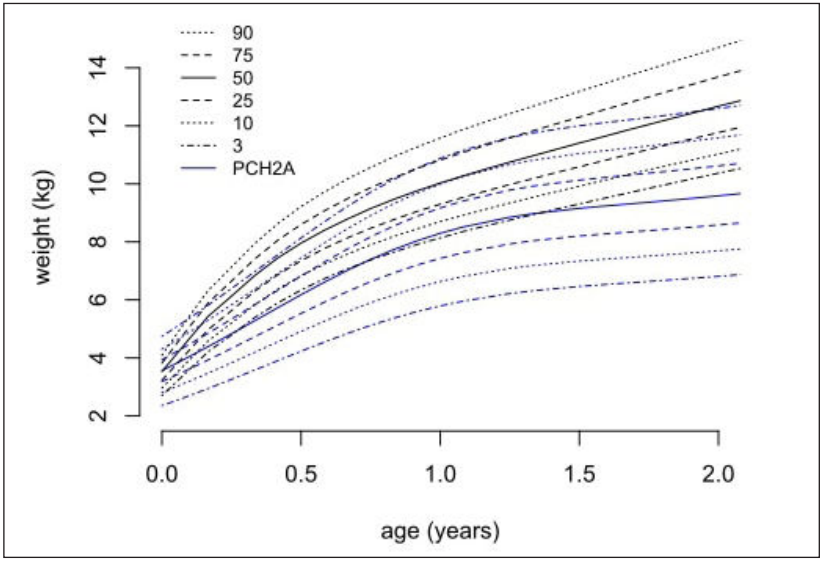


Fig. 23: Weight percentiles for boys with PCH2 compared to healthy boys

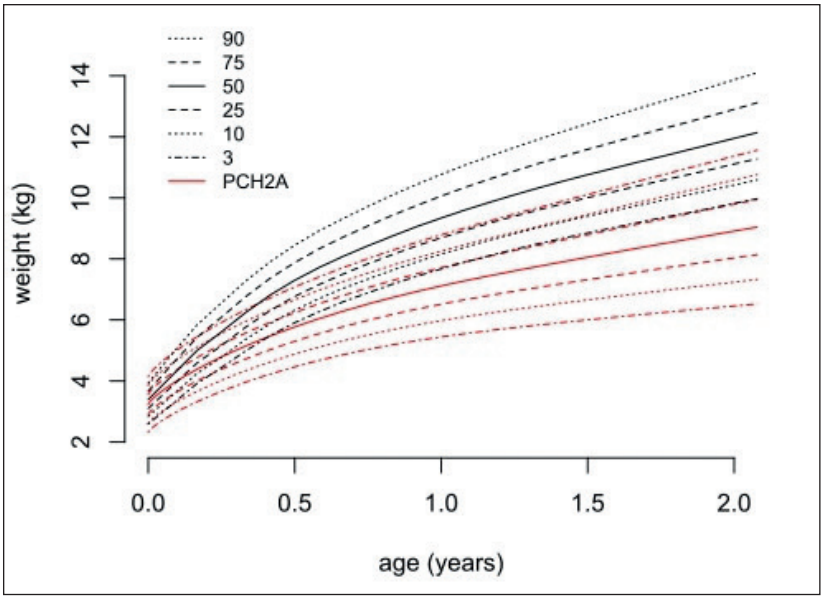


Fig. 24: Weight percentiles for girls with PCH2 compared to healthy girls

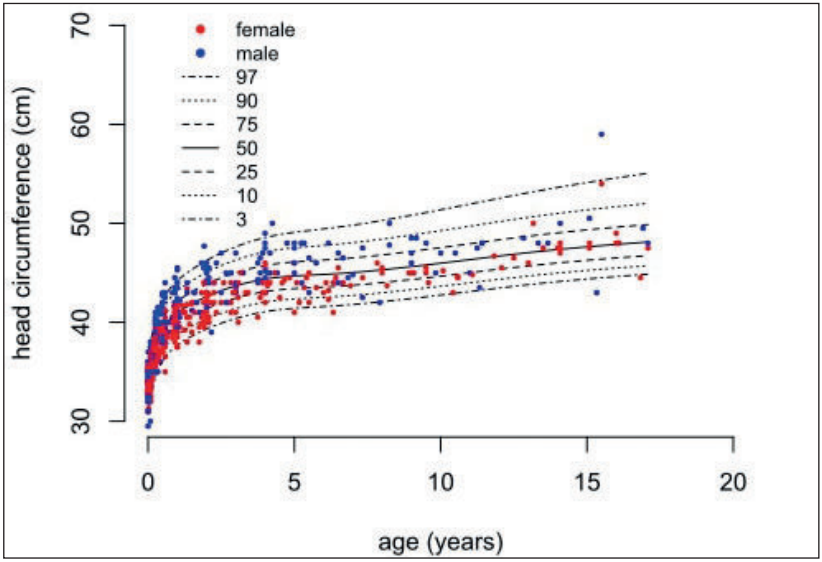


Fig. 25: Head circumference percentiles PCH2

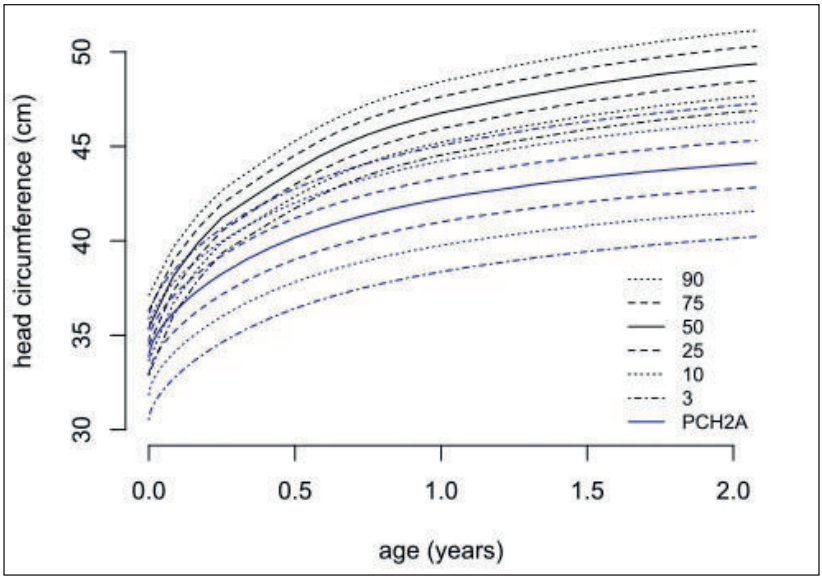


Fig. 26: Head circumference percentiles for boys with PCH2 compared to healthy boys

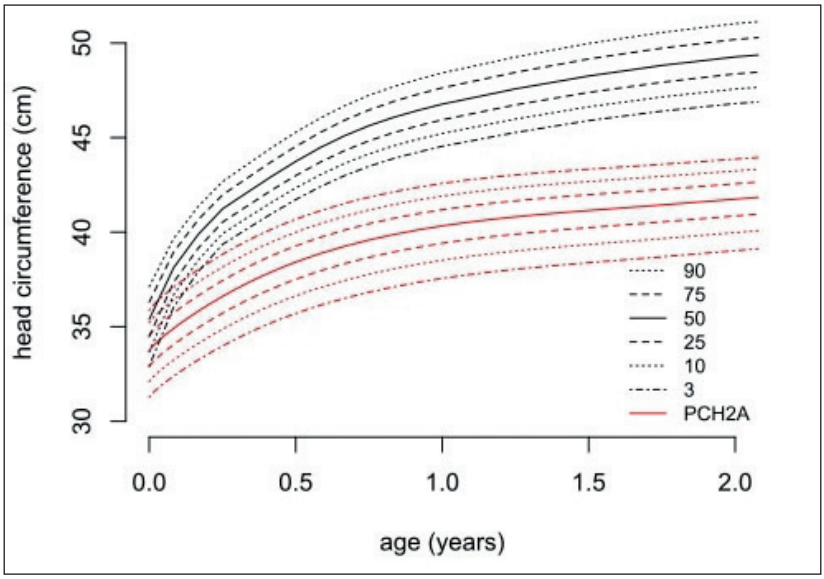


Fig. 27: Head circumference percentiles for girls with PCH2 compared to healthy girls

The available data underlines the results of previous studies. While many PCH2 children are still within the normal height and weight range at birth, the growth rate over the course of their lives is lower than normal for their age. This applies more to weight gain than to growth in length. Up to the age of two years, the 50th height percentile does not fall into the pathological range (i.e. not below the 3rd percentile of the healthy comparison group), in contrast to the 50th weight percentile. The children show pronounced and progressive microcephaly. Some values are still in the lower normal range at the time of birth, but insufficient head growth always occurs in the course of the disease. With the help of the collected data, growth percentiles for head circumference, height and weight of children with PCH2 are now available for the first time, which can be used to assess their growth much better than by comparing them to healthy children [25].

6.2 Puberty and PCH2

Puberty is a time of change. The child turns into an adult, both physically and mentally. With the start of sex hormone production, the bodies of adolescents begin to change.

Secondary sexual characteristics develop in the course of puberty. In addition, there are growth spurts, and the numerous physical and hormonal changes bring emotional ups and downs and insecurities.

In girls, the breasts and pubic hair begin to grow (thelarche and pubarche), the vagina and uterus mature and the first menstruation occurs (menarche). This usually happens two to three years after the onset of puberty.

In boys, the testicles start to grow in volume, as do pubic hair, penis and muscle mass, the first (nocturnal) ejaculations occur, and the voice changes.

The timing of the onset of puberty depends on numerous other factors in addition to genetics. These include, for example, health and nutritional status as well as emotional stress. Typically, puberty begins around the age of eleven for girls and thirteen for boys.

Precocious puberty occurs when external sexual characteristics develop before the age of eight in girls and before the age of nine in boys.

Delayed puberty occurs when girls have not developed pubertal characteristics by the age of 13 and boys by the age of 14.

Children with disabilities may enter puberty either significantly too early or too late. But even if puberty occurs on time, it presents the caregivers with completely new challenges.
New aspects need to be taken into account from a care perspective; orthopedic problems such as scoliosis may worsen as a result of a growth spurt, and existing symptoms may also change due to physical and emotional changes. For example, epileptic seizures may occur more or less frequently.

In girls with disabilities who are unable to communicate clearly enough, menstrual pain must also be taken into account as a reason for restlessness. Finally, there is also the aspect of emotional development and the need for autonomy in young people with disabilities.

Data of the Current Natural History Study

In total, data on puberty was collected from 52 children. Of the 52 children, twelve were already twelve or more years old. With regard to precocious pubertal development, cryptorchidism (undescended testicles) or increased epileptic seizures before puberty, 69.2 % of the children showed no abnormalities.

Of the 26 boys, 42.5 % had cryptorchidism.

Of the 15 children who were already twelve or more years old, 33.3 % showed a higher incidence of epileptic seizures during puberty.
In 3.8 % of cases, precocious puberty occurred (boys before the age of nine, girls before the age of eight).
Delayed pubertal development was observed in only one case.

In free-text responses, several families reported menstrual cramps in their daughters; in one case, the child‘s restlessness subsided after puberty was completed.

7 Summary

This brochure summarizes data from a second, extended study on the natural history of PCH2. It not only describes the main characteristics of the disorder, but also reports on the experiences of the families surveyed, how they are coping and what advice they can give to other affected families. For example, detailed medication lists reflect the experience with symptomatic treatment, which can serve as a basis for disease management. As children with PCH2 have major feeding and growth problems, PCH2-specific percentile curves for weight, height and head circumference have also been compiled to provide guidance. PCH2 is an autosomal recessive disorder caused by changes in the TSEN54 gene. The clinical picture of children with PCH2 is severe and affects many areas of everyday life. Neurologically, the main symptom is a severe, dyskinetic motor disorder. This means that the children are severely impaired in their targeted movements, have little ability to learn motor skills and require considerable assistance. Around a third of children develop dystonic attacks, which are usually difficult to treat. Epilepsy is to be expected in all children; it usually occurs after the age of two and the seizures are difficult to treat. A further characteristic of this severe brain disorder is below-average growth of the head (microcephaly). Despite this, most children develop simple cognitive and communication skills. Non-neurological symptoms also contribute significantly to the severity of the disease and the care required. These include significant feeding problems, which often make a PEG tube necessary, as well as gastro-esophageal reflux, which not only has to be treated with medication, but in some cases also requires surgery. Accordingly, the growth of affected children is significantly below average. Severe sleep problems and frequent infections are also characteristic and determine the amount of care required. Life expectancy is reduced, but it has been reported that the third decade can be reached.

8 Abbreviations and Explanation of Terminology

Apnea = stoppage of breathing
Developmental retardation = developmental delay
Gastroesophageal reflux = backflow of stomach contents into the esophagus
Hyperthermia = body temperature too high
Hypothermia = body temperature too low
Microcephaly = reduced head circumference
Muscle tone = how much tension there is in the musculature
Muscular hypertonia = excessive muscle tone
Muscular hypotonia = insufficient muscle tone
Neonatal period = 1st to 28th day of life
Constipation = defined here as a condition where spontaneous defecation occurs too infrequently
Pneumonia = inflammation of the lungs
Polyhydramnios = excessive amniotic fluid
PRN = Abbreviation meaning „when necessary“ (from the Latin „pro re nata“)
Rhabdomyolysis = muscle atrophy, dissolution of muscle fibers
Status epilepticus = an epileptic seizure lasting for more than 5minutes, or a series of seizures between which consciousness is not regained

9 Bibliography

1. Krause F. Über einen Bildungsfehler des Kleinhirns und einige faseranatomische Beziehungen des Organs. Zeitschrift für die gesamte Neurologie und Psychiatrie 1928; 119: 788-815
2. Pfeiffer J, Pfeiffer RA. Hypoplasia ponto-neocerebellaris. J Neurol 1977; 215: 241251
3. Barth PG, Vrensen GFJM, Uylings HBM, Oorthuys JWE, Stam FC. Inherited syndrom of microcephaly, dyskinesia and pontocerebellar hypoplasia: a systemic atrophy with early onset. J Neurol Sci 1990; 97: 25-42
4. Budde BS, Namavar Y, Barth PG, Poll-The BT, Nürnberg G, Becker C, van Ruissen F, Wetermann MA, Fluiter K, te Beek ET, Aronica E, van der Knaap MS, Hohne W, Toliat MR, Crow YJ, Steinlin M, Voit T, Roelenso F, Brussel W, Brockmann K, Kyllerman M, Boltshauser E, Hammersen G, Willemsen M, Basel-Vanagaite L, Krägeloh-Mann I, de Vries LS, Sztriha L, Muntoni F, Ferrie CD, Battini R, Hennekam RC, Grillo E,

Beemer FA, Stoets LM, Wollnik B, Nurnberg P, Baas F. tRNA splicing endonuclease mutations cause pontocerebellar hypoplasia. Nat Genet 2008; 40 (9): 1113-1118.
5 Namavar Y, Barth PG, Kasher PR, van Ruissen F, Brockmann K, Bernert G, Writzl K, Ventura K, Cheng EY, Ferriero D M, Basel-Vanagaite L, Eggens V R, Krägeloh-Mann I, De Meirleir L, King M, Graham J M, Jr., von Moers A, Knoers N, Sztriha L, Korinthenberg R, Dobyns WB, Baas F, Poll-The BT. Clinical, neuroradiological and genetic findings in pontocerebellar hypoplasia. Brain 2011; 134(Pt 1): 143-156.
6. Van Dijk T, Baas F, Barth PG, Poll-The BT. What's new in pontocerebellar hypoplasia? An update on genes and subtypes. Orphanet J Rare Dis 2018; 13(1):92
7 Barth PG, Aronica E, de Vries L, Nikkels PG, Scheper W, Hoozemans JJ, Poll-The BT, Troost D. Pontocerebellar hypoplasia type 2: a neuropathological update. Acta Neuropathol 2007; 114(4): 373-386
8 Steinlin M, Klein A, Haas-Lude K, Zafeiriou D, Strozzi S, Müller T, Gubser-Mercati D, Schmitt Mechelke T, Krägeloh-Mann I, Boltshauser E. Pontocerebellar hypoplasia type 2: variability in clinical and imaging findings. Eur J Paediatr Neurol 2007; 11 (3): 146-152
9 Ekert K, Groeschel S, Sánchez Albisua I, Frölich S, Dieckmann A, Engel C , Krägeloh-Mann I. Brain morphometry in Pontocerebellar Hypoplasia Type 2. Orphanet J Rare Dis. 2016;11(1): 100
10 Rüsch ChT, Bölsterl BK, Kottke R, Steinfeld R, Boltshauser E. Pontocerebellar Hypoplasia: a Pattern Recognition Approach The Cerebellum 2020; 19:569–582
11 https://www.omim.org/phenotypicSeries/PS607596
12 Sánchez-Albisua I, Frölich S, Barth PG, Steinlin M, Krägeloh-Mann I. Natural course of pontocerebellar hypoplasia type 2. Orphanet J Rare Dis 2014; 9:70, 1-11.
13 Graham JM, Jr., Spencer AH, Grinberg I, Niesen CE, Platt LD, Maya M, Namavar Y, Baas F, Dobyns WB. Molecular and neuroimaging findings in pontocerebellar hypoplasia type 2 (PCH2): is prenatal diagnosis possible? Am J Med Genet 2010; 152A(9): 2268-2276
14 Tortora M, Spaccini L, Lanna M, Zambon M, Izzo G, Parazzini C, Righini A. TSEN54 Gene-Related Pontocerebellar-Hypoplasia and Role of Prenatal MR Imaging: Besides the Common Posterior Fossa Cystic Malformations. The Cerebellum 2023; 22:1023–1025
15 Barth P G, Blennow G, Lenard H-G, Begeer J H, van der Kley J M, Hanefeld F, Peters A C B, Valk J. The syndrome of autosomal recessive pontocerebellar hypoplasia, microcephaly, and extrapyramidal dyskinesia (pontocerebellar hypoplasia type 2): Compiled data from 10 pedigrees. Neurology 1995; 45: 311-317
16 Böhmer CJ, Niezen-de Boer MC, Klinkenberg-Knol EG, Tuynman HA, Voskuil JH, Devillé WL, Meuwissen SG. Gastroösophageale Refluxkrankheit bei geistig behinderten Menschen: Hinweise zur Diagnose und zur Wirkung der Omeprazol-Therapie. J Gastroenterol. 1997; 92(9): 1475-9
17 Böhmer CJ, Niezen-de Boer RC, Klinkenberg-Knol EC, Neuwissen SG. Omeprazol: Therapie der Wahl bei geistig behinderten Kindern. Arch Pediatr Adolesc Med. 1998; 152(11): 1113-8
18 Hassal E, Israel D, Hirte R, Radke M, Dalväg Ein, Sköld B, Junghard O, Lundborg P. Omeprazol zur Behandlung der chronisch erosiven Ösophagitis bei Kindern: eine multizentrische Studie zu Wirksamkeit, Sicherheit, Verträglichkeit und Dosisanforderung. Internationale pädiatrische Omeprazol-Studiengruppe. J Pädiatr. 2000; 137(6): 800-7

19 Andersson T, Hassall E, Lundborg P, Hirte R, Radke M, Marcon M, Dalväg E in, Martin S, Behrens R, Koletzko S, Becker M, Drouin E, Göthberg G . Pharmakokinetik von oral verabreichtem Omeprazol bei Kindern. Internationale pädiatrische Omeprazol-Pharmakokinetikgruppe. Bin J Gastroenterol. 2000; 95(11):3101-6.
20. Janzarik W, Kraegeloh-Mann I, Langer T, van Buiren M, Schaefer HE, Gerner P. Spasmodic abdominal pain and other gastrointestinal symptoms in Pontocerebellar hypoplasia type 2. Neuropediatrics 2021; 52:495–498
21 Jochum F. Empfehlungen für die Nährstoffzufuhr. In: Jochum F, editor. Ernährungsmedizin Pädiatrie. Berlin, Heidelberg: Springer Berlin Heidelberg; 2013. p. 57–74
22 Barth PG, Ryan MM, Webster RI, Aronica E, Kan A, Ramkema M, Jardine P, Poll-The BT. Rhabdomyolysis in pontocerebellar hypoplasia type 2 (PCH-2). Neuromuscul Disord 2008; 18(1):52-58
23. Ammann-Schnell L, Groeschel S, Kehrer C, Frölich S, Krägeloh-Mann I. The impact of severe rare chronic neurological disease in childhood on the quality of life of families-a study on MLD and PCH2. Orphanet J Rare Dis 2021; 16(1):211.
24 Balogh B, Kovács T, Saxena AK. Complications in children with percutaneous endoscopic gastrostomy (PEG) placement. World J Pediatr 2019; 15(1):12–6.
25 Alice Kuhn, Maren Hackenberg, Anna-Lena Klauser, Antonia Herrmann, Julia Matilainen, Simone Mayer, Saskia Frölich, Ingeborg Krägeloh-Mann, Samuel Groeschel, Wibke G. Janzarik. Growth charts for pontocerebellar hypoplasia type 2A. doi: https://doi.org/10.1101/2024.06.23.24307757.
26 Dötsch J, Schoener J. Infekte I: Atemwegserkrankungen. Infekte II: Magen-Darm-Grippe. In ‚Grosswerden, Gesundheit und Entwicklung in turbulenten Zeiten. Die ersten 10 Lebensjahre'. DuMont, Köln, 2024, S. 157-167.
27 Kargl S, Deluggi S, Pumberger W. Gastrostomie im Kindesalter. Paediatr. Paedolog. Austria 2015; 50(5):192–5.
28 Romano C, van Wynckel M, Hulst J, Broekaert I, Bronsky J, Dall'Oglio L, Mis NF, Hojsak I, Orel R, Papadopoulou A, Schaeppi M, Thapar N, Wilschanski M, Sullivan P, Gottrand F. European Society for Paediatric Gastroenterology, Hepatology and Nutrition Guidelines for the Evaluation and Treatment of Gastrointestinal and Nutritional Complications in Children With Neurological Impairment. J Pediatr Gastroenterol Nutr. 2017; 65(2):242–64.

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