Contents: Care pathway for CAMK2-related disorders

Introduction

Preface

The care pathway for CAMK2-related neurocognitive disorders is outlined below.

Care pathways are developed by a team of physicians specializing in this particular or a related disorder, based on the most recent available scientific research.
In the case of CAMK2, this team included the following members: a paediatrician specializing in genetic and congenital disorders; a child neurologist; and a child and adolescent psychiatrist. Two paramedics – a speech therapist and a child physiotherapist – were also closely involved in developing this guideline.

Care pathways are designed to provide support to both parents and practitioners in delivering the highest-quality medical treatment of the disorder in question. It is important to note that this guideline serves as a general framework and that there may be valid reasons to pursue alternative treatments for individual patients. Differences in the organization of healthcare (local and otherwise) may also constitute reasons to choose an alternative approach.

It is also important to be aware that this CAMK2 guideline is based on information about a relatively small number of patients whose disorder is caused by a variety of genetic factors, i.e. patients with different DNA variations in different subtype CAMK2 genes. The clinical study into CAMK2-related disorders is currently in the nascent stage, as the first patients were described only in 2017. The number of identified patients worldwide is currently small: in 2021, a total of approximately 85 patients had been diagnosed, of whom fewer than 15 live in the Netherlands. In other words, it is an extremely rare disorder, although we expect the number of cases to increase over the next several years, as some existing patients have likely not yet been genetically tested. We also see clear similarities with other genetic disorders that affect cognitive function (and which are part of the same neurotransmitter pathway, e.g. GRIN/NMDAR, SynGAP, IQSEC2, SHANK). We firmly believe that, through close collaboration with the CAMK2 gene experts in the neurosciences lab, we will be able to boost clinical research into CAMK2. The input of parents and/or guardians and international cooperation will be vital when it comes to further refining the guideline in the coming years.

ENCORE Expertise Centre – Genetic NDD

The term ‘genetic neurodevelopmental disorder’ (NDD) describes a heterogeneous group of children and adults where intellectual disability is the principal common factor.

It is particularly challenging for this group of individuals to carve out a space for themselves in our increasingly fast-paced society, characterized by information overload. Due to the complexity of their disorder, many of these patients also end up in hospital, where they are generally treated by several different physicians who tend to view the condition through the prism of their own professional silos.
There is often no doctor or case manager available to oversee the process and to help maintain coherence. Owing to the rare nature of the disorder, knowledge of sometimes unexpected complications or side effects and contraindications for medications are vital to ensuring high-quality preventive and other care, i.e. *disorder-centred medical follow-up.* Centralizing care in a national and international context is also crucial for this patient cohort when it comes to making progress in the scientific research, particularly due to the rare nature of the disorder and the concomitant smaller pool of patients. In addition, the time required to make a genetic diagnosis can be significantly reduced, with fewer essential or non-essential research studies carried out in an expert centre.

The ENCORE – expertise centre for neurodevelopmental disorders at Erasmus MC is dedicated to improving the quality of life of patients with specific genetic cognitive developmental disorders. Their priority is to make or confirm the diagnosis and detect complications or problems in time. This is ensured by a multidisciplinary approach, i.e. a close-knit team of medical specialists who can provide continuity of care from a variety of disciplines and can share their expertise with individual patients' local practitioners.
Our organization is also responsible for supervising the transition to experts working in adult medicine. The centre also conducts substantial scientific research (fundamental, translational and clinical) as an integral part of the care provided, with the objective of developing new treatments. The ultimate objective is to allow this patient cohort to function as successfully as possible and once again become active members of society.

The CAMK2 expertise center is part of ENCORE which also comprises centres specializing in the following disorders:

- Angelman syndrome
- 15q11q13 duplication syndrome
- Fragile X syndrome (FXS)
- Neurofibromatosis Type I (NF1)
- Tuberous Sclerosis Complex (TSC)
- Rasopathies
- CNS malformation
- SynGap syndrome
- GRIN/GRIA syndromes
- DNA repair syndromes
- Ultra genetic disorders

Some of these expertise centres within ENCORE have been in existence for 35 years. For further information, see https://encore-expertisecentrum.nl/en.

Patients' association

While no official CAMK2 patients' association has been established at the time of drafting this guideline, there are four CAMK2 parent representatives (two in Europe [Ireland and England] and two in North America [Boston and Palo Alto]) who are in the process of founding such organizations. These parent representatives have been consulted in all research efforts organized to date. They run a private Facebook group they created for parents of children with CAMK2-related disorders, *CAMK2 Gene Related Disorders* and can be found via the following website: http://camk2.org/

Reading guide

To improve the readability of this document, the various terms used herein have been abbreviated and are used consistently throughout. This means that, throughout the document:

- 'parents' refers to 'parents and guardians',
- use of the masculine form also includes the feminine form,
- 'paediatrician' refers to 'paediatrician specializing in genetic congenital disorders',
- 'primary practitioner' refers to 'paediatric internist specializing in genetic and congenital disorders' in conjunction with a neurologist/paediatric neurologist.

Disease presentation

Description of disease

CAMK2 is an abbreviation of 'Calcium/calmodulin dependent protein kinase 2'.
It denotes a group of four proteins in our brain (alpha [CAMK2A], beta [CAMK2B], gamma [CAMK2G] and delta [CAMK2D]). CAMK2A and CAMK2B are the most common of these four proteins.

There has been a substantial amount of basic scientific research into the role of CAMK2A and CAMK2B in our brain, which has taught us that these proteins play a very important role in *learning*, *memory* and *motor skills*. It is therefore understandable that the first children and adolescents described with this disease (CAMK2A + CAMK2B) have moderate-severe learning disabilities (i.e. are developmentally delayed), have weaker memories and often also exhibit motor problems. Some of the patients developed epilepsy and/or demonstrated psychiatric symptoms. We also refer to this as a 'neurodevelopmental disorder', i.e. complications related to the nervous system and cognitive ability. In addition to an

intellectual disability, a poorly functioning CAMK2G also causes *muscle* issues, and CAMK2D is very important for both the brain and the *heart*. Combined, we refer to this as 'CAMK2-related disorders where an intellectual disability is the main common denominator'.

Aetiology
CAMK2-related disorders are caused by *pathogenic varieties* in one of the CAMK2 genes (alpha [CAMK2A], beta [CAMK2B], gamma [CAMK2G] or delta [CAMK2D]). These flaws in the CAMK2 DNA cause a defective CAMK2 *protein* to be created that is either *overactive* or *no longer functions properly*. CAMK2 is an *Autosomal Dominant* (AD) genetic disease. A defect in the paternal or maternal CAMK2 gene is sufficient to develop the disorder. This defect usually occurs just after fertilization, meaning that most parents are not a carrier of the mutations. For more information about AD, we refer to the national Dutch website devoted to clinical genetics (erfelijkheid.nl) or similar English websites such as the one of the American Genetics association (https://www.ashg.org/discover-genetics/inheritance-health/).

Epidemiology
There is currently no reliable data available on the prevalence and incidence of CAMK2. In the initial papers published on the disorder, a total of 24 CAMK2A and 2B patients were identified after genetic screening (more specifically, *exome sequencing*) of patient cohorts with intellectual disabilities (ID) and/or autism among a total of 21,438 individuals. This is equivalent to a prevalence in this risk population of 1.2 CAMK2 cases in every 1,000 patients with intellectual disabilities.

Prognosis
Based on the current literature, CAMK2 is part of the group of *static* neurodevelopmental disorders; in other words: *no further decline* in cognitive function is expected to occur over time. However, the differences with age peers will become more pronounced among the majority of young children with this disorder. This is sometimes referred to as 'growing into deficit'. This phenomenon can be explained by the fact that in healthy children, some parts of the brain only start developing at a later stage, which means the reduced functioning of these sections of the brain is likely to be revealed later in life. The differences also become more apparent because of the growing demands on and expectations of young people from school, college and society in terms of their skills. This overall prognosis is based on a small number of known adult CAMK2 patients, as well as on CamK2 mouse models.

Evidently, it is also relevant to the prognosis to identify and treat factors with a negative impact, such as epilepsy, in time.

The life expectancy of the group of CAMK2D patients is determined largely by the condition of the cardiac muscle, making this an exception to the above.

Symptoms

Core symptoms of CAMK2A and 2B (occurring among the majority of patients)
- Global developmental delay (GDD) – intellectual/learning disability
- Slower processing of information; problems maintaining attention and focus; memory problems
- Developmental problems – developmental disorders/psychiatric problems
- Significantly delayed speech and language development
- Motor disorders such as limpness at birth and trouble maintaining balance (based on data from a subgroup)

Other symptoms
- Epilepsy
- Gastrointestinal (motility) problems
- Range of non-syndrome-specific symptoms, including strabismus (crossed eyes)

It is important to note that there is a wide variety in the number and severity of the various symptoms between different individuals with CAMK2. Further research will need to demonstrate what part is determined by the differences at the DNA level (i.e. the genotype).

Treatment

The treatment of CAMK2-related medical problems is based completely on controlling symptoms and providing adequate psychosocial support to the child and its guardians.

The various types of treatment approaches are explained below, broken down by organ system.

<u>Neurological</u>

<u>Cognitive/intellectual disability</u>

All patients with CAMK2 identified to date have an intellectual (learning) disability. However, the level of cognitive impairment may vary from mild to severe. These individuals take longer to process new information, have more trouble committing new information to memory, and greater difficulty retrieving information from memory. This is further compounded by related problems in maintaining attention and focus. In addition, some children with CAMK2 are irritable and physically restless: they refuse to settle or lie down, which further complicates learning. The level of intellectual disability determines to a large extent how dependent adults and young adults will remain on third parties for their everyday care and in order to be self-sufficient members of society.

In order to ensure that a child is referred to the appropriate school or day-care facility, we recommend that they undergo a psychological/neuropsychological examination at certain critical ages (i.e. 3-4, 7-8, 11-12 and 15-16) at a

credentialled centre, preferably one experienced in conducting examinations of children and adolescents with intellectual disabilities. This makes it possible to conduct a reliable analysis of the child's strengths and weaknesses, which can then be used to draft a personalized development plan in order to create an optimum learning environment for the child.

MRI scan

Children with severe developmental delays will nearly always undergo a standard MRI scan in order to rule out any congenital or acquired cognitive abnormalities. The MRI scans of the vast majority of children with CAMK2 appear completely normal. In other words: the coarse structures of the brain have a normal morphology and are not damaged. However, a standard MRI scan does NOT provide information on how various parts of the brain communicate with each other – i.e. interact – or about how the brain *functions*.

While MRIs revealed irregularities among a small portion of the CAMK2 population, this is more prevalent among children with other syndromes (i.e. they are not specific to CAMK2). It is possible that there are flaws in the way the current MRI scans look at the brain, and that newer functional scan techniques could identify specific CAMK2-specific differences. However, these types of scans are currently only produced for research purposes, and they are also very difficult to use on children who cannot lie still long enough without being administered an anaesthetic.

Note that, while it is NOT necessary to make an MRI scan in order to diagnose a CAMK2-related disorder, a paediatric neurologist may find this necessary in order to rule out *other* (additional) causes of intellectual disability, or due to the severity of the developmental delay or to an unexplained decline in cognitive functioning.

Epilepsy (and suspected epilepsy)

A 30-40 percent of children with CAMK2 are affected by epilepsy. Difficult-to-treat epilepsy appears to be more prevalent among the group of children with a CAMK2A variant, although this data must be interpreted with great care owing to the low patient population.

- If a child suffers from epilepsy (or if epilepsy is suspected), it is helpful to see a paediatric neurologist in order to perform an EEG (i.e. a test to record electrical activity of the brain)

- If the child turns out to have epilepsy, the neurologist can prescribe medication to reduce the frequency or severity of the seizures.

  We recommend treatment by a specialised neurologist/paediatric neurologist, i.e. a physician who is knowledgeable about rare neurocognitive disorders and epilepsy. Many of these physicians are affiliated with a university medical centre. Choosing a university hospital is also related to the need for centralization and knowledge acquisition being concentrated in one place.

There is currently no evidence (or insufficient evidence) that we can *confidently* choose a specific type of anti-epileptic drugs (anticonvulsants). In making this choice, however, the *type* of mutation (i.e. loss of CAMK2 protein or an overactive CAMK2 protein) is considered, as basic research has demonstrated that the glutamate receptors 1, 2A & 2B 1, 2A & 2B are downstream from CAMK2. In this case, we recommend consulting an expert neurologist/paediatric neurologist specializing in rare diseases/epilepsy. Finally, there is currently no evidence that specific anti-epileptic drugs are counterproductive. This is another one of the key research areas of our ongoing CAMK2 'Natural History' project.

Extremely severe (i.e. difficult-to-treat) forms of epilepsy can sometimes be alleviated by following a special diet known as the 'ketogenic diet'. However, there is no specific data regarding its efficacy in treating CAMK2, although a small number of patients have been treated through this diet. In exceptional cases of therapy resistance, the option of Vagus Nerve Stimulation (VNS) may be considered.

Motor delays

The majority of babies with a CAMK2-related disorder have abnormal muscle tension from birth. They suffer from hypotonia (decreased muscle tone) to a lesser or more severe extent. Parents will notice that they need to provide extra physical support for their baby and that their baby has trouble moving against gravity.
Children with CAMK2 will experience delays in achieving developmental milestones such as rolling over for the first time, sitting up without assistance, crawling, and walking. A number of children with CAMK2 will, unfortunately, never learn to sit up without support, or learn to walk. CAMK2 children therefore develop more slowly than their age peers; this tends to be main reason for parents to contact the primary practitioner following a referral from a child and family centre. However, there is also a group of children who experience relatively few motor problems. Unfortunately, we are currently unable to make any predictions based on the flaw in the DNA, although this should become clear for individual children over time. One exception is the CAMK2G variations. Since this CAMK2 subtype also impairs *muscle strength*, these children cannot sufficiently make up for their low muscle tone and tend to have even more motor problems.

Limp babies may eventually become more rigid (i.e. hypertonic). This rigidity is then mainly noticeable in the arms and legs, while the neck and back tend to remain limp (i.e. axial hypotonia).

It is very important that children with motor development problems start seeing a paediatric physiotherapist at an early age.

A paediatric physiotherapist can support parents in encouraging their child's motor development through advice and exercises adapted to the child's current level of development. The physiotherapist assesses the child's current motor skills (i.e. what they can do and how they do it) and supports them in making progress in motor development through advice and exercises. At a later stage, support from a

paediatric physiotherapist can also contribute to preventing contractures (i.e. delaying stiffness of the joints).

Periodic evaluation by a paediatric rehabilitation specialist is recommended for children who are permanently hypo/hypertonic.

Their expertise in, and knowledge of, areas such as mobility aids and tools for everyday activities in and around the house and at school is necessary in order to support the child in fulfilling these basic needs as much as possible. In the Netherlands, paramedic support services (e.g. paediatric physiotherapy, speech therapy, dietetics, and sometimes education) are based in a paediatric rehabilitation centre, which facilitates communication between the various practitioners and the parents.

Finally: a subgroup of children with CAMK2 experience balancing problems or problems with fine motor skills; this is most likely the result of reduced functioning of the cerebellum, where CAMK2 plays an important role during embryonic development and beyond and which is responsible for many motor-related behaviours. The medical term for this disorder is *cerebellar ataxia*; it manifests – in addition to gait disorders – in problems pronouncing (articulating) words, in impaired manual dexterity, in difficulty swallowing, and in double vision. Aside from balance problems, patients with CAMK2 often exhibit difficulties in executing complex motor tasks, which in medical terms is called Motor dispraxia

Speech and language delays

All children with CAMK2 experience speech and language delays, without being affected by congenital deafness. This includes not only *delayed language comprehension*, but also (especially) problems *forming words correctly*.
The latter (speech, i.e. verbal communication) is the result of a complex process where all parts of the body – ranging from the brain to the nervous system to oral muscles – must function properly. If there is any part of this cascade reaction that does not function as it should, this can potentially lead to delayed speech or permanent speech difficulties and trouble forming sentences. The medical community refers to this as ‘developmental verbal dyspraxia’ (DVD): a phonological disorder, motor-speech disorder, or dysarthria. For a more detailed explanation, see the website www.hersenletsel-uitleg.nl, the main difference being that with CAMK2, the language-speech disorder is a *result* of the CAMK2 genetic defect rather than of any *acquired* impairment. The inability to formulate language (aphasia) also appears to play a significant role in our initial observations of CAMK2 patients.

Based on this information, we strongly recommend that the child start seeing a speech therapist at an early age, *including both verbal language support and alternative forms of communication* (e.g., use of speech devices and pictograms) in order to present the child with as many modes of expression as possible. We refer to specialized speech-therapy centres for further details.

Special support by a speech therapist is highly recommended for all children with CAMK2 and delayed speech and language. This involves considering the various options of alternative communication available in time and as part of a gradual approach, and must be adjusted periodically to the child’s developmental age.

Contrary to assumptions made by practitioners in the past, many non-verbal children with intellectual disabilities turn out to display greater language comprehension if they are provided with the right communication tools.

Gastrointestinal motility problems

Our intestines serve a variety of purposes, the main one being the transmission and absorption of nutrients. The intestines also play an important role in protecting the body from threats such as bacteria and viruses. There is an extensive network of nerve cells in the intestines that ensures that signals are transmitted from the intestines to the brain, and vice versa. It is not surprising, then, that colon function is impaired in many syndromes marked by poor or inadequate brain function.
This often manifests in changes in bowel movements, both at rest and when digesting a meal. As a result, children and adolescents may experience a wide range of intestinal symptoms, including vomiting, reflux, abdominal pain, a bloated stomach and changing excretion patterns, ranging from overly frequent and liquid (i.e. diarrhoea) to constipation. Virtually all children with CAMK2 suffer from constipation from a relatively early age, which is fortunately relatively treatable by either following a high-fibre diet and drinking sufficient liquids, or with medication (the laxative macrogol). Unfortunately, a smaller number of children with CAMK2 are so prone to vomiting that it is necessary to insert a nasal-stomach tube (a procedure known as nasogastric intubation) to ensure they ingest enough calories to be able to grow. Some of these children remain dependent on a tube for a longer period of time, after which it may be decided to insert what is known as a Percutaneous Endoscopic Gastronomic Drain (PEG). The advantage of this procedure is that children no longer experience complications when taking food orally, that it remains in place, and that it facilitates overall care/is low-maintenance. For more serious gastrointestinal (GI) motility problems, we recommend referring the child to a paediatric gastroenterologist.

Behaviour, behavioural problems and psychiatric disorders

Unusual behavioural patterns or behavioural problems are prevalent among children and adults with intellectual disabilities, but may vary significantly in severity and over time. Causes may be physical (including pain), mental/psychological or environmental (e.g., side effects of medication, or restlessness/anxiety).
Ongoing evaluation (and elimination) of the cause of the behaviour is particularly important when it comes to breaking these patterns.

However, among a significant number of individuals with CAMK2, behavioural problems are likely to be the manifestation of a change in the functioning of the neural networks in the brain. Basic neuroscientific research, for example, has demonstrated that the CAMK2 protein interacts with important neurotransmitter transporters (known as glutamate receptors) and activates or deactivates these.
A defective or slow CAMK2 protein therefore results in an imbalance of these neurotransmitters and therefore constitutes the biological basis of aberrant behaviour or even psychiatric problems in patients.

An initial analysis of a group of 12 children with CAMK2-related disorders resulted in reports of a very wide spectrum of developmental disorders and psychiatric problems, ranging from autism-like characteristics and autism spectrum disorders to

anxiety disorders, hyperactivity, and psychosis. Additional basic research is required in order to learn more about which DNA CAMK2 variation increases the probability of the above-mentioned problems, and which type. This information can also help in choosing medications if behavioural therapy turns out to be insufficient.

Given the rare nature of CAMK2 and its genetic and biological basis, there is a strong preference for diagnostics and treatment in a specialized child and adolescent psychiatric clinic or department experienced in treating children and adolescents with intellectual disabilities.

There is currently no overall evidence that might serve as a guideline in choosing specific types of behaviour-modifying drugs. However, the type of mutation can be factored in when making this choice (i.e. loss of CAMK2 protein or, conversely, an overactive CAMK2 protein). See our notes under the ‘Epilepsy’ heading for further reference.

Parallel to anti-epilepsy drugs, there is currently a lack of evidence that specific behaviour-modifying drugs may be counterproductive. However, this is one of the main points of concern of our ongoing CAMK2 ‘Natural History’ project.

Ophthalmic effects
The vast majority of babies born with CAMK2 pathogenic DNA variations are cross-eyed at birth and remain that way until just after their first birthday. The process of following objects with their eyes, another key milestone during the first few months of life, tends to be substantially delayed. Treatment by a paediatric ophthalmologist is recommended.

Vaccinations
CAMK2 patients are advised to comply with the vaccination regimen prescribed under the government vaccination programme. While no specific restrictions apply, in some children with epilepsy the fever they develop after being vaccinated may induce seizures. Ask your local child neurologist, whether specific measures should be taken for your child.

Medications and foods to be avoided
There is currently insufficient evidence to advise against specific types of medication, and therefore there are no specific restrictions as such. However, if a child is taking behaviour-modifying and anti-epileptic drugs (anticonvulsants), it is recommended to contact an expertise centre, as CAMK2 is known to interact with specific neurotransmitter systems, which could change the first choice of medications for symptom control in individual situations.

Diagnostics

Laboratory findings

Confirmation of diagnosis of CAMK2-related disorder

- DNA diagnostics: targeted CAMK2 mutation analysis or as part of a Whole-Exome-Sequencing panel or open analysis

Children in the Netherlands with diagnosed intellectual disabilities or severe developmental delays are referred to either a paediatrician specialized in genetic and congenital diseases, or to a paediatric neurologist or clinical geneticist to identify the cause of the delay. Genetic tests have been developed over the past 10 years, known as Whole Exome Sequencing and Whole Genome Sequencing (acronyms: WES and WGS). This test can be used to examine all genes involved in intellectual disability (a total of more than 1,500) in a single examination (known as an 'ID panel'). CAMK2 is therefore one of the approximately 1,500 genes in this panel, and the diagnosis CAMK2 is therefore established through a sequencing test. In order to take this test, the attending physician will ask for permission to take a blood sample from your child and from you as the biological parents. It often takes a few months for the results to be released.

If you would like to receive more information, visit the website of Erfelijkheid Nederland (https://erfelijkheid.nl/erfelijk /hoe-werkt-dna-onderzoek) or the website of the Erasmus MC's Clinical Genetics department or similar English websites such as file:///C:/Users/857775/Downloads/OCC1050b%20WES%20Info%20Sheet%20(1).pdf.

Finally, it is important to note that CAMK2 cannot be identified based on external characteristics. All children and adults with this disorder have a regular appearance.

Differential diagnosis

As stated, the differential diagnosis of intellectual disability is very comprehensive and is therefore outside the scope of this document.

Additional research

Please consult the relevant subspecialist or paramedic for:

- Brain MRI (minimum of 1.5 T-scan, including spectroscopy): pay attention to ventriculomegaly, mega cisterna magna, white-matter abnormalities, corpus callosum atrophy, or hypoplasia
- EEG: pay attention to the background pattern and to disorders associated with epilepsy
- Formal developmental neurological or neuropsychological examination, depending on age on presentation.
- Child and adolescent psychiatric examination, including psychological and neuropsychological examination

- Examination by a speech therapist
- Evaluation by paediatric physiotherapist

- Imaging through contrast of gastrointestinal tract in children suffering from severe food intolerance

Supervision and support for children

In addition to the paediatrician and paediatric neurologist, other practitioners are likely to be involved in the treatment of CAMK2-related disorders. The types of practitioners depend on the symptoms which occur or checks that need to be performed. One of the principal practitioners involved is always responsible for referring patients to a co-practitioner.

Treatment team

- Parents/Patient
- Case manager
- Paediatrician specializing in genetic and congenital disorders & paediatric neurologist

Co-practitioners

- Dietician
- Paediatric physiotherapist
- Speech therapist
- Paediatric rehabilitation specialist
- Gastrointestinal and liver specialist
- Paediatric orthopaedist
- Ophthalmologist
- Child psychologist or child and adolescent psychiatrist
- Clinical geneticist
- Social worker

Support

- Outpatient check-ups
- Diet
- Lab research
- Growth and puberty development
- Social situation
- Independence
- Heredity
- Emergency protocol (if applicable)
- Medication
- Vaccine instructions
- Neurological complications
- Transition

- Cognitive development

Multidisciplinary outpatient check-ups are preferred. The frequency of these check-ups depends on various factors, including age, the problems concerned, the type of treatment pursued, and the circumstances of the patient and his/her parents. Checks are generally highly frequent immediately after the diagnosis. This is followed by outpatient check-ups based on the schedule below.

Age	Frequency
After diagnosis	
Age 0-12	Once-Twice a year
Age 12-18	Twice a year

During the outpatient check-ups, the principal practitioner establishes the progress of the disease and its impact on the patient.

Supervision and support for adults

Various practitioners are involved in the treatment of CAMK2-related disorders, i.e. in addition to a general internist and a neurologist. If the patient lives in an institution, a physician specialized in treating patients with intellectual disabilities is almost always involved. Which other practitioners are involved in the hospital depends on the symptoms which occur or the checks that must be performed. It is always the internist or neurologist who refers the patient to a co-practitioner.

Treatment team

- Patient
- Case manager
- General internist (specializing in genetic and congenital diseases)
- Neurologist

Co-practitioners

- Physician specialized in treating patients with intellectual disabilities
- Dietician
- Gastrointestinal-liver specialist
- Psychologist and/or psychiatrist
- Clinical geneticist
- Social worker

- Gynaecologist

Supervision and support

- Outpatient examination/monitoring
- Diet
- Lab research
- Social situation
- Fertility and pregnancy
- Heredity
- Emergency protocol
- Medication
- Neurological complications
- Cognitive and social skills

Miscellaneous information

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Quality indicators

This care pathway is designed to provide the best possible care. We use a number of quality indicators to assess and improve the quality of this care. The following factors are important in order to determine, and be able to guarantee, the quality of the care provided:

- All patients have an individual case manager, who coordinates the care process and therefore serves as the initial point of contact for patients. The principal practitioner often also serves as the case manager.

- All patients are seen by a dedicated paediatrician specializing in genetic and congenital disorders, a paediatric neurologist, or an internist specializing in genetic and congenital disorders or a neurologist, depending on who the principal practitioner is.
- The members of the multidisciplinary treatment team are present in, or available to, the UMC
- The following care specialists are always involved in the care process:
    - Paediatrician/internist specializing in genetic and congenital disorders
    - Neurologist/paediatric neurologist
    - Psychologist/child psychologist and psychiatrist/child psychiatrist
- The following healthcare practitioners are involved in the care process if necessary:
    - Occupational therapist
    - Dietician
    - Physiotherapist
    - Rehabilitation specialist
    - Speech therapist
    - Gastrointestinal and liver specialist
    - Orthopaedist
    - Gynaecologist
    - Clinical geneticist
    - Physician specialized in treating people with intellectual disabilities
    - Social worker
- The co-practitioners within the treatment team are carefully briefed by the paediatrician specializing in genetic and congenital disorders and proactively report back to this principal practitioner.
- There is written and/or verbal communication between the paediatrician specializing in genetic and congenital disorders and the internist to ensure a smooth transition of patients from a paediatrician to an internist.
- Approximately once a year, there is written and/or verbal communication between the paediatrician or internist and the GP about the patient's current situation.
- You discuss with the patient and/or parents within what timeframe the results of the study will be released and discussed. If this is not possible, the patient and/or parents will be notified.
- This care pathway will be revised every five years at the behest of the Netherlands Federation of University Medical Centres (NFU) to ensure that the care described is updated with the latest scientific findings.

Consensus

The following departments of the following university medical centres (UMCs) have reached consensus on this care pathway:

Date:

Paediatrician:

Paediatric neurologist:

Child and adolescent psychiatrist

Disclaimer

The information contained in this document was prepared with great care.

This document establishes the optimum support and treatment pathways based on current research. Since scientific research continuously leads to new insights, the information contained in this document may become obsolete after some time. The document is therefore updated every five years (at the behest of the NFU Nederlandse Federatie Universitaire Centra) to incorporate the latest findings.

The care pathway described in this document constitutes an agreement between practitioners and parents of patients regarding the optimum care to be provided to CAMK2 patients. It is important to note that this represents a general guideline and that there may be compelling reasons to pursue alternative treatments for individual patients after discussing this with the practitioner.

The information provided in this document should not be considered a substitute of a consultation or treatment by a physician.

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