

PACS2 Related syndrome / Developmental and epileptic Encephalopathy 66

Patient journey



EpiCARE

First symptom

Timeline: 1st year of life (usually within 1st month)

Clinical Presentation / Symptoms

One of the first symptoms is epilepsy, often with different seizure types (most seizures have focal origins, and secondary generalization is common). These seizures are not triggered, and clusters and prolonged seizures i.e. status epilepticus may appear as well. Infantile epileptic spasms and evolution into Lennox-Gastaut syndrome have also been reported. Other symptoms that may be present at onset are: hypotonia, mild dysmorphic features, global development delay and/or cerebellar dysgenesis, brain cortical malformations, defects of the heart and urinary tract.

Diagnosis

Timeline: 1-31 y. o.

Clinical Presentation / Symptoms

Diagnosis is usually possible only after performing whole exome sequencing or genetic panels including PACS2 gene. The latter is rare however, as PACS2 is commonly included in epileptic encephalopathies panels, while encephalopathy is usually not suspected in patients at an early stage. Symptoms are not specific and phenotype is wide: seizure types differ heavily, patients may have intellectual disability ranging from mild to severe, with or without autism spectrum disorder. In addition to epileptic seizures, patients with PACS2 mutations may present with cerebellar dysgenesis and facial dysmorphism. For many patients, dysmorphic features are not evident (long eyelashes, broad nasal roots, thin upper lips, down-turned lip corners), while for others they are clear, however strongly individual (limb distal malformations, monkey furrow, a tuft of hair of different colour). Postnatal growth delay, coloboma, cortical malformations, Vein of Galen malformations, atrial sept defects, urinary tract defects, and cardio-myopathy were also reported. Most patients are children, and adults might be heavily underdiagnosed. Adults experiencing this type of disease manifestation living without diagnosis, who performed genetic test before 2019, should be offered genetic test's reanalysis as PACS2 mutation was firstly described in 2018.

Identify Patient Needs

- Parents need information about the availability of publicly covered genetic testing costs.
- Parents need to be offered a genetic test, especially because majority of cases are caused by de novo mutation.
- Parents need proper explanation of diagnosis, prognosis and psychological support.
- Parents need to understand that development varies from child to child, and how to support it.
- Parents need to be offered magnetic resonance imaging (MRI) or MRI reanalysis as changes in MRI are not severe but cerebellar dysgenesis is commonly present among affected individuals, and reanalysis connected with genetic results offers new information both for parents and clinicians on patient's perspectives.
- Parents need instructions on how to treat seizures and what other non-pharmacological therapies their child may benefit from.
- Parents need to know how to keep their child safe (managing seizure triggers, protection from falls).
- Parents need to know what social help is available from government in their country.

Ideal Outcome / support

- Family is explained that a prognosis is difficult to give.
- Family receives genetic counselling with explanation of cause and chances of reoccurrence.
- Family receives professional support to cope with diagnosis and family is referred to patient group/advocacy organization and physicians experienced in following and treating patients with DEE66.
- Parents receive clear instructions, emergency protocol, and explanation of risks and how to minimize them.
- Family is explained that education and rehabilitation are extremely important for child's development and should be closely monitored, as children can benefit from early intervention – time matters!
- Family is given a document that summarizes the social support that may be required and offered in their country.

Treatment

Timeline: Depending on seizure control; in general, lifelong

Clinical Presentation / symptoms

Seizure treatment is critical in the first year of life when seizures are hardest to control. The clinical course of epilepsy is highly variable and while some patients suffer from drug-resistant seizures, others might have well-controlled epilepsy. Some children may wean off anti-seizure medications after being seizure free for 2-3 years. According to cases reported to date, most effective are following antiseizure medications: carbamazepine/oxcarbazepine, phenobarbital, and valproic acid (important: there was a case in which valproic acid worsened symptoms). Levetiracetam may be supportive but usually does not control seizures entirely. There are patients who effectively managed seizures with ketogenic dietary treatment, after 1st year of life. As symptoms vary and can be wide, each patient might need care of additional specialists. Commonly involved specialists are cardiologist, gastroenterologist, nephrologist, otolaryngologists or endocrinologist. Global development delay, intellectual disability, speech delay and autism spectrum disorder or autistic traits are observed, however severity of symptoms differs among patients. Seizure control is critical to unlock development potential.

Identify Patient Needs

- Parents need support and respite care from professionals.
- Parents need information about prescribed medication, side effects, how to monitor long-term side effects.
- Parents need advice on how to deal with seizure triggers and illness.
- Parents need help/medical advice concerning the non-epileptic symptoms and information that individual need for additional specialists may occur.
- Parents need rehabilitation plan tailored to individual patient's needs and age.
- Parents need school advice/advice for respite care.
- Patient needs access to clinical trials and/or new treatment options.

Ideal Outcome / support

- Patient achieves satisfying seizures control.
- Parents receive plan for the use antiseizure medication, and potential future weaning-off.
- Parents receive information about non-pharmacological treatment options like ketogenic dietary treatment.
- Parents are informed about medication side effects and the timing for control blood test and EEGs.
- Patient has a team of specialists coordinating individualized care, including neurologist and neuropsychologist, and other specialists that patient may require.
- Parents receive defined rehabilitation plan (speech therapy including feeding training, physiotherapy, psychologist support, sensory integration therapy, social skills training) with cooperating therapists supporting multidisciplinary development.
- Parents receive information about ongoing clinical trials where their child might be eligible with detailed explanation of risks and benefits.
- Parents receive regular counselling with professionals.
- Up to date information is available for parents at any time.
- Parents receive help finding a school/daycare and respite care.
- Family nurse is offered to educate family to manage seizures, if available.

Follow-up

Timeline: 1-18 y. o.

Clinical Presentation / symptoms:

Seizures are usually easier to control after 1st year of life. Seizure potential should be regularly monitored with EEGs and weaning-off the antiseizure medications could be considered if there is no seizure potential. If seizures are hard to control, ketogenic dietary treatment supporting antiseizure medication should be considered. Psychomotor development is delayed, however many children make progress, which is also seen in speech and cognitive development. Some children could catch up with speech and enter low norm for cognitive development. Some children can still learn words when they are 6 y. o. or older. Multidisciplinary support and seizures control is critical to unlock development potential. Hypotonia impacts motor function, and most children are characterized with a wide-based gait. Some patients may need additional support of wheel chair. Most children are able to achieve independence in feeding and movement. Potty training is usually delayed, in some cases not possible what is connected both with cognitive function and proprioception disorder.

Identify Patient Needs

- Parents need evidence-based advice and expertise when it comes to these additional symptoms.
- Potential individual needs for additional specialists can occur.
- Parents need emotional support.
- Parents need help in creation and adjustment of development plan with special focus on: speech therapy (including feeding training), physiotherapy, psychologist support, sensory integration therapy, and social skills training.

Ideal Outcome / support

- Patient has regular EEGs especially in first 3 years of life.
- Patient has MRI examination to assess myelination development.
- Developing guidelines.
- Developing standards for quality of life adult patients.
- Limiting number of antiseizure drugs to minimum and weaning off, if possible.
- Patient has team of specialists coordinating individualized care.
- Patient has cooperating therapists supporting multidisciplinary development (speech therapy including feeding training, physiotherapy, psychologist support, sensory integration therapy, social skills training)

Adult follow-up

Timeline: 18 y. o. +

Clinical Presentation / symptoms:

Not much is known about adults with this condition. Some patients can achieve some level of independence (usually with assistance) but most will need lifelong daily support in basic daily tasks. Neurodegeneration and/or increasing seizure potential can occur. Close neurological monitoring is necessary, and MRI and annual EEGs might be needed. Some additional observations may be valuable. Reporting those publicly can have tremendous impact on disease understanding, guidelines development and quality of life of other diagnosed patients.

Identify Patient Needs

- Parents need advice (including legal advices) and support during transition to adult care.
- Parents need advice on possible options of daily care centres for adults.
- Patient needs regular monitoring of seizures and development, new therapeutic opportunities, neuropsychological behavioural situation etc.
- Parents need additional support when caring for an adult person.

Ideal Outcome / support

- A process of transition from paediatric to adult physician should be put in place.
- Rehabilitation path for maintenance is defined.
- Patient received occupational therapy and/or support for semi-independent patients.
- Possible aggravation of the various motor, behavioural, social and cognitive problems is monitored, and treatment offered when possible.
- Patient receives regular monitoring of seizure potential even if it was not present for years with regular neurological follow up.
- Family's needs and concerns are re-evaluated.
- Support and advice on later stages of adulthood and in case the primary caregivers become unable to provide is offered.