Infantile Neuroaxonal Dystrophy

Information Leaflet

Names used for this condition:

- Infantile Neuroaxonal Dystrophy (INAD)
- Neurodegeneration with brain iron accumulation (NBIA)
- Typical PLAN (Phospholipase A2 associated neurodegeneration)
- Seitelberger Disease (term no longer commonly used)

What is INAD?

Infantile neuroaxonal dystrophy (INAD) is a rare, progressive, life-limiting, neurodegenerative disorder. It is caused by mutations in the PLA2G6 gene. There are other diseases caused by PLA2G6 mutations but INAD is the most common.

Unfortunately there is no cure for INAD but a team of medical professionals can help to improve symptoms of the disease and quality of life for the child and family.

Sadly, INAD is a life-limiting condition. Death commonly occurs before the 10th birthday; children are starting to live longer as doctors learn how to care for them better during the latter stages of disease.

Symptoms and Signs:

The symptoms of INAD usually begin between the ages of 6 months and 2 years. There are usually no features of concern to parents, carers and professionals prior to the onset of symptoms.

INAD is a ‘neurodegenerative’ disorder. This means that nerves throughout the body and the brain begin to breakdown because the PLA2G6 gene isn’t working properly.

Developmental Regression:

A child who has been previously reaching developmental milestones normally will lose some of these skills. For example, they may stop talking/babbling, stop crawling or become unable to sit. This loss of skills is often the first thing that parents notice. Developmental regression is not specific to INAD and occurs in many other neurodegenerative conditions. Sometimes the child will first start to slow down in attaining milestones or reach them late, then eventually starts regressing.

Vision Loss:

Vision is commonly affected quite early in INAD. The eyes may ‘jerk’ from side to side - this is called ‘nystagmus’. The child may develop a squint (crossed eyes or “strabismus”). Because the nerves at the back of the eye degenerate, often affected children cannot see as well as previously.


**Deterioration in Movement and Motor function:**

The nerves controlling the muscles in the arms, legs, trunk and neck degenerate. The trunk may be weak and wobbly and it may be difficult for the child to hold their head up properly. Symptoms of INAD often begin before the child is walking independently. If they have learned to walk, they may begin to fall over frequently or begin to walk in an unusual way. Eventually they will be unable to walk.

Over time, the legs and arms become stiff and may develop contractures - this is when the knees/elbows/wrists/ankles, become permanently fixed in certain positions. The contractures develop because the tone in the muscles is too high (because of abnormal messages from the degenerating nerves in the brain and the limbs).

The increased tone and abnormal nerve signals also cause the ‘reflexes’ to become abnormal. Initially the reflex-jerks may be excessively brisk, and repetitively jumpy - this is called ‘clonus’. When clonus is very severe it can be elicited by merely touching the foot. It is not painful but can look unusual. Over the course of time, progressive neurodegeneration leads to reflexes no longer being present at all (arreflexia).

**Feeding Problems:**

As the disorder progresses (over months to years) the child may begin to drool and may be unable to feed and swallow as previously.

**Seizures:**

Some children develop seizures, though this is relatively uncommon and again is due to the degeneration of the nerves in the brain. Seizures are often late in the disease course.

**Microcephaly (poor head growth):**

The affected child’s head size is usually normal at birth and until signs of the disorder become apparent. However, over time, because of the neurodegeneration, sometimes the head stops growing. Pediatricians and health professionals may measure the child’s head and plot it on a chart to see its rate of growth.

**Cognitive Decline:**

Due to the neurodegeneration, there is a decline in intellect. In INAD, this deterioration in cognition occurs during childhood.

**What Causes INAD?**

INAD is an inherited genetic condition caused by a faulty gene. It is due to mutations (abnormalities) in the **PLA2G6** gene. It is an autosomal recessive disorder, which means that an affected child has inherited 2 copies of the mutated (faulty) gene- one from each parent. Both parents usually have one faulty copy of the gene and one normal copy of the gene, which renders them as unaffected “disease carriers” without disease symptoms. 2/3 of the affected child’s healthy brothers and sisters
(siblings) are likely to be unaffected carriers, with one copy of the ‘faulty’ gene and one normally functioning copy. 1/3 of the affected child’s healthy siblings are likely to have two normal copies—they will not be carriers of the faulty PLA2G6 mutation.

In terms of risks for future pregnancies, there is a 25% (1 in 4) chance that a future child born to the same parents will be affected (with two copies of the faulty gene), a 50% (1 in 2) chance that a future child will be an unaffected ‘carrier’ (one copy of the faulty gene and one normally functioning copy), and a 25% (1 in 4) chance that they will be unaffected with two copies of the normal PLA2G6 gene.

Medical research teams are working hard to find out more and more about the role of PLA2G6 in disease.

**How will the diagnosis be made? What tests may be required?**

**MRI Brain Scan**

This is done to help with making the right diagnosis and exclude other causes of the neurodegeneration.

In INAD, specific parts of the brain may look abnormal. Brain iron deposition is not usually detected early in INAD but may develop later in the disease course. Earlier in disease there may be atrophy in a region called the cerebellum.

The brain scan provides clues to help the doctors send appropriate tests for specific diagnoses.

**Neurophysiology (EMG/NCS)**

This is an electrical test which is undertaken by a specialist. Again, it helps to provide clues about what might be causing the symptoms in the nerves and muscles before the diagnosis has been made.

**Electroencephalogram (EEG)**

This is a brain wave test which is undertaken if the child is having seizures. Again it is undertaken by specialists and is painless.

**Eye Tests**

If the affected child does not appear to be ‘seeing’ as well as previously, or has abnormal eye positioning or movements, a review by an ophthalmologist will be requested. The ophthalmologist can look at the nerves at the back of the eye and may also do further tests to determine how the electrical connections between the eyes and brain are working.

**Blood tests**

The gene test is done by taking a blood sample from the affected child. If the child has 2 copies of the mutated PLA2G6 gene, doing a gene test on the parents’ blood is important to help to confirm the diagnosis, and provide information for future ‘family planning’.
Nerve Biopsy

Prior to the identification of PLA2G6 mutations as being causative for INAD, nerve biopsies (taking a small sample of nerve tissue from the patient) were common. INAD has specific features on nerve biopsy- ‘spheroids’. A nerve biopsy is a minor surgical procedure but they are now rarely undertaken for INAD because the gene test is available, which is considered to be the gold standard to make a diagnosis.

Treatment

Unfortunately, there is currently no cure for INAD. Treatment is ‘supportive’, aimed at minimizing symptoms and optimizing quality of life for the child and family.

Contractures

Passive stretching exercises and splints can help to minimize the development of contractures and improve muscle tone. Sometimes more invasive treatments (botulinum toxin injections, surgery-tendon lengthening, serial casting) are indicated, but the contractures may return.

Muscle Spasms

Muscle spasms may occur because of episodes of high tone in the muscles and can be painful. The pediatrician and neurologist can prescribe medications (such as baclofen and trihexyphenidyl) to help to minimize them.

Drooling

Patches and medications (hyoscine, glycopyrolate) are available to help control excess saliva and secretions.

Feeding

Because the muscles of feeding (bulbar muscles) degenerate, the affected child is likely to require assistance with feeding.

Affected children are also at risk of ‘aspirating’ food into their lungs- (food going down the wrong way). This happens because the nerves supplying the protective muscles which close the wind-pipe on swallowing are not working properly. It may not be obvious or cause immediate discomfort but can be life-threatening and cause breathing difficulties.

It is therefore, highly important that children with INAD are fed appropriately and safely to maintain nutritional status. They will need regular input from both speech and language therapy and dietetic services.

Children with INAD often require feeding via a tube - this may initially be in the form of a tube inserted in the nostril going into the stomach (NGT). A PEG tube (Percutaneous enterogastrostomy)
is a more permanent means of feeding. This is where a surgeon makes a little hole on the wall of the abdomen and places a ‘button’ there, which can be easily connected to a feeding tube when required, by the child’s parents/carers. Such feeding strategies are aimed at preserving a good nutritional status for these children, as well as preventing complications such as aspiration.

**Gastro-oesophageal Reflux (GOR)**

Because the feeding muscles are not receiving the correct messages from the nerves, children with INAD commonly have gastro-oesophageal reflux (GOR). This means that stomach contents which are acidic have a tendency to come back up the esophagus (food pipe). This can cause discomfort, whole body arching, vomiting and sometimes no obvious symptoms. However, it is important that it is treated if present to prevent complications. Treatments include anti-reflux medications to reduce stomach acid (gaviscon, omeprazole, ranitidine) and sometimes surgery (fundoplication) to prevent stomach acid and food going back up into the food pipe. Sometimes the surgeon may do a fundoplication at the time of PEG insertion.

**Vision**

Unfortunately there are no specific treatments available to improve vision, as the damaged nerves cannot be repaired. However, therapists and play-specialists can provide advice on how to improve sensory stimulation for visually impaired children.

**Seizures**

If the affected child develops seizures they may be started on anti-convulsant medication to treat the seizures (liquids or tablets). This would be monitored by a pediatrician or pediatric neurologist. It is likely that this treatment would be lifelong.

**Scoliosis**

Because of the reduced body tone the child’s spine may become twisted. This may eventually cause discomfort and may impact on breathing if it affects the size or shape of the chest cavity. It is important that carers and professionals are vigilant to the potential development of scoliosis.

A spinal brace/jacket may be provided to prevent further progression of the scoliosis. These are usually custom-made for the child by an orthotist. Sometimes surgery is required and a special spinal surgeon may become involved. However, the decision about surgery for the scoliosis has to be weighed up in terms of the potential benefit and risk to the child.

**Breathing and Chest**

Children with INAD are at increased risk of chest infections. This is for several reasons. Firstly, the muscles which support breathing progressively deterioriate. Secondly, children with INAD are likely to have a weak cough, making it difficult for them to clear infections. Thirdly, children with INAD are at risk of ‘aspiration’. This is why it is important for them to be fed safely - and often this is by nasogastric tube (NGT) or percutaneous enterogastrostomy (PEG) tube. It is difficult for children with INAD to clear secretions adequately, which leads to drooling, but may also lead to aspiration.
For these reasons, whether they are fed orally or by tube, children with INAD are at increased risk of chest infections.

Parents and carers may be taught special chest physiotherapy exercises, to help the child remove build ups of secretions from their lungs and prevent infections. Sometimes over the winter months children are given influenza vaccines, and if infections are frequent a low dose preventative antibiotic may be given (a few times a week) to try and prevent chest infections from developing.

Affected children may require hospital admission when they have even apparently minor chest infections for oxygen and intravenous (IV) antibiotics.

Assistive Communication:

There are excellent assistive technologies available to preserve communication for children with INAD. Speech and language therapists work with experts in assistive devices that can meet the needs of individual children with progressive disabilities and their families.

Professionals Involved:

There are likely to be many professionals involved in the care of a child with INAD. This may include:

**Pediatrician**- A Consultant Pediatrician has specialist expertise in caring for children with complex disorders with multi-system problems like INAD. The consultant pediatrician will oversee and organize all of the services that the child is likely to need.

**Pediatric Neurologist**- A pediatric neurologist is likely to be involved often for diagnosis, and expert management of tone, seizures etc.

**Physiotherapist**- A physiotherapist will help to show carers stretching exercises which can slow down the rate of development of contractures, as well as helping to organise splinting, casting and botulinum toxin as needed.

**Occupational therapist**- An OT may provide equipment, special seating devices, advice on wheelchairs and equipment to make the home safe, accessible and practical for the child and family.

**Gastroenterologists, Dieticians and Surgeons**- Because the muscles of feeding (bulbar muscles) degenerate the affected child is likely to require assistance with feeding. This may initially be in the form of a tube inserted in the nostril going into the stomach. A PEG tube (Percutaneous entero-gastrostomy) is a more permanent means of feeding. This is where a surgeon makes a little incision on the abdomen and places a ‘button’ there which can be connected to a feeding tube by a carer. A dietician can ensure adequate calorie intake. Sometimes gastroenterologists are needed to help with severe reflux and other gut issues.

**Geneticists and Genetic Counselors** - Often, the parents of children affected by rare genetic conditions find it useful to meet with specialists in inherited diseases: these are called geneticists and genetic counselors. Both can provide information about family diseases and can offer advice to couples about planning further pregnancies.
The future

INAD is an irreversible neurodegenerative genetic condition for which there is currently no cure. Researchers and medical professionals are working together to learn more about the precise function of the PLA2G6 gene and how mutations lead to the different features of the disease. This work will be vital in developing more specific, targeted treatments for INAD.

INAD is one of a group of conditions associated with brain iron accumulation. A trial (TIRCON Trial) is currently underway for the use of iron chelating agents in pantothenate kinase-associated neurodegeneration (PKAN). If successful, it is conceivable that similar trials may be undertaken for INAD in the future.

About the Contributors

Dr. Marjorie Illingworth is a Consultant Pediatric Neurologist with a specialist interest in Neuromuscular Disorders at Southampton University Hospitals NHS Foundation Trust

Dr. Manju Kurian is a Wellcome Intermediate Clinical Fellow at UCL-Institute of Child Health and Honorary Consultant in Pediatric Neurology at Great Ormond Street Hospital. She has an interest in movement disorders and neurodegenerative diseases of genetic origin.

Allison Gregory, MS, CGC is a Genetic Counselor and Research Instructor at Oregon Health & Science University.

Dr. Susan Hayflick is Professor and Chair of Molecular and Medical Genetics and Professor of Pediatrics and Neurology at Oregon Health & Science University.

References