EpiCARE

Infantile Epileptic Spasms Syndrome

Also known as: IESS, Infantile spasms, West Syndrome

Overview

IESS is a rare epilepsy syndrome characterized by onset of epileptic spasms in infants between 2 and 12 months of age, and rarely up to 24 months. Infants may have no medical history before the onset of epileptic spasms, or may have a medical history reflecting the underlying cause. The classical triad of epileptic spasms, hypsarrhythmia and developmental stagnation or regression is historically referred to as West syndrome, but it is not mandatory to have all three for the diagnosis of IESS.

Incidence and prevalence

The incidence is estimated in 1 in 2500 live births (UK). Both sexes are affected, with a higher incidence in males.

Aetiology

The underlying causes include many different structural, genetic and metabolic conditions. The main ones are hypoxemic ischaemic encephalopathy (HIE) with/without hypoglycaemia and pathogenic gene variants/chromosomal abnormalities of which the most frequent include TSC1, TSC2 (tuberous sclerosis complex), ARX, CDLK5, STXBP1, and trisomy 21 (Down syndrome). Structural abnormalities include acquired antenatal and perinatal lesions and malformations of cortical development.

Diagnosis of IESS

Diagnosis is based on the observation of typical epileptic spasms in clusters (home video evidence is very useful) and EEG findings (hypsarrhythmia or other focal/multifocal epileptiform discharges).The typical epileptic spasms occur in clusters (usually at awakening) with a sudden and brief tonic contraction of axial muscles (flexor, extensor or mixed), but they may also be very subtle, as eyes rolling up. Suspected infantile spasms should be considered a neurological emergency and rapid diagnosis and treatment is very important for the developmental outcome. Prior to onset of spasms, development can be normal or abnormal depending on aetiology. Developmental delay, arrest or regression is typically seen with the onset of spasms, and parents may report regression of skills, delayed development or behaviour change.

Brief paroxysmal events which occur in clusters, both epileptic and non-epileptic, should be differentiated from epileptic spasms. The most frequent conditions in the differential diagnosis include myoclonic epilepsy in infancy, hyperekplexia, shuddering, infantile self-stimulation and gastro-oesophageal reflux (Sandifer syndrome). In the absence of the classic triad of West syndrome, the presence of spasms should be confirmed by electroencephalography (EEG)/video-EEG with electromyography (EMG) which helps to distinguish epileptic spasms from myoclonic seizures and tonic seizures.

Careful clinical examination (including head circumference, dermatological, eye and neurological examination) is crucial at diagnosis as it may result in findings suggestive of an underlying aetiology.

Neuroimaging is useful to determine the syndrome aetiology: brain MRI may show acquired or congenital focal, multifocal or diffuse abnormalities in half to two-thirds of children with IESS. Genetic studies may include chromosomal microarray, gene panel or whole exome/genome sequencing and should be considered in all patients mainly those without a known acquired structural aetiology. Metabolic investigations are important to exclude metabolic diseases in the absence of other aetiology or in the presence of additional evocative symptoms.

Age of onset

First symptoms occur between birth and two years old but typically within the first year of life (2-12 months).

Seizure types at presentation

Epileptic spasms are the typical type of seizures observed. The typical epileptic spasms occur in clusters (usually at awakening) with a sudden and brief tonic contraction of axial muscles (flexor, extensor or mixed). The spasm will often consist of the head dropping forward with both arms brought forward and the legs drawn towards the torso in a 'crunch' but can also be extensor spasms where the limbs are flung outward and the head is thrown back. These usually occur in series or clusters, with a pause of several seconds in between each spasm and increasing prominence of the motor features through the cluster, often over a period of minutes (though clusters may last 30 minutes or longer), and are often seen on awakening. Spasms may be symmetric or asymmetric (often in case of unilateral brain lesion) and some might be extremely subtle, with minor head nods, eye or chin movements.

How do seizure types change over time?

If untreated, spasm clusters tend to become more frequent and the individual spasms more pronounced. Children with infantile spasms may go on to develop other seizure types related to their underlying

condition. Infantile spasms may also evolve to other epilepsy types and syndromes such as Lennox-Gastaut syndrome and drug-resistant focal epilepsy.

EEG features

The interictal EEG is abnormal with high voltage chaotic patterns (hypsarrhythmia, modified hypsarrhythmia) that can be observed in the awake and/or sleep recording. It may also show focal and multifocal epileptic anomalies with a less disorganized background. The ictal recording is characterized by a fast activity that might precede a high amplitude, generalized sharp or slow wave followed or super-imposed by low amplitude. In some cases, if the EEG is performed in the early stages of the epilepsy onset, then a short EEG recording in wakefulness may be normal and if this is the case a longer recording to include sleep and spasms cluster recording is necessary to rule out the diagnosis.

Treatment

Treatment should be introduced as early as possible when the diagnosis is established. First line pharmacological treatment options include hormonal treatment (either ACTH or high dose oral prednisolone), vigabatrin or a combination of corticosteroids and vigabatrin. Other antiseizure medication may be used in cases where the combination is not successful or the child relapses as treatment is weaned. The ketogenic diet can be useful option in suitable patients, and early referral to a tertiary epilepsy centre should be considered in order to identify candidates suitable for surgery. In a small subgroup, patients can have a full recovery with freedom from spasms and no cognitive impact.

Individualized emergency protocols

Rescue medication is not usually required for infantile spasms.

Comorbidities - course of illness

IESS in the majority of cases is associated with developmental delay and difficulties related to brain function and skills. Isolated regression in visual attention or altered social responsiveness may occur in the days or weeks preceding onset of spasms. Developmental plateauing and regression typically worsen without rapid, effective treatment.

The majority of infants have a poor developmental outcome, not always related to the seizure outcome. Severity of developmental delay relates predominantly to aetiology and time to treatment from spasm onset. The underlying cause of the spasms has a significant bearing on outcomes and on comorbidities. Common aetiologies with frequent developmental and other comorbid conditions would include hypoxemic ischaemic encephalopathy, tuberous sclerosis complex, Down syndrome, inverted duplicated chromosome 15 syndrome, and rarely metabolic diseases. The resulting difficulties can be global development delay or specific difficulties affecting speech and language, gross motor function, fine motor function, cognition, presence of autism spectrum disorder, ADHD, and sensory processing disorder. There may be issues with muscle tone, posture or movement control including cerebral palsy or dystonia.

In a small subgroup, usually including patients with no identified underlying aetiology, prior normal development and short-lag to treatment, patients can have a full recovery with freedom from spasms and no major cognitive impact.

Review the impact of seizures, drugs and comorbidities on:

- Development
- Quality of life for the child and the family
- Ability to participate in education

Provide patient and/or carer with:

- Accurate information regarding the syndrome and its course
- Accurate information regarding compliance to treatment and potential side effects
- Plan for monitoring of response to treatment and side effects
- Plan for follow up of developmental progress
- Details of allied health professionals/services e.g., occupational therapy, physiotherapy, speech and language therapy etc.
- Details of support organisations
- Genetic counselling, if genetic cause is confirmed
- Individualised habilitative program

Authors: Jenny Rawling (UK Infantile Spasms Trust), Dr. Alice Goldhill and Dr. Maria Papadopoulou (Hospices Civils de Lyon, France).

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How common is IESS?

IESS occur in about 1/2500 live births. Both sexes are affected, with a higher incidence in males.

What causes IESS?

There are more than 200 different underlying conditions (structural, genetic, metabolic) e.g., hypoxemic ischaemic encephalopathy, tuberous sclerosis complex, Down syndrome, inverted duplicated chromosome 15 syndrome, which lead to development of an abnormal brainwave pattern (frequently corresponding to a chaotic background pattern called hypsarrhythmia) and the visible seizures called epileptic spasms. In some case, the underlying cause is not found even following several investigations.

When do symptoms first appear?

IESS can start at any age from birth to 2 years but most commonly in the middle of the first year of life (4-8 months old) and rarely after 12 months. Typical symptoms include epileptic spasms in clusters (home video evidence is very useful) and abnormal EEG findings (hypsarrhythmia or other). Prior to onset of spasms, development can be normal or abnormal. Developmental delay, arrest or regression is typically seen with the onset of spasms, and parents may report regression of skills, delayed development or behaviour change.

What are the types of seizures seen in IESS?

Epileptic spasms are the typical type of seizures observed. Seizures are presented as brief spasms (lasting less than 3 seconds) in clusters with a pause in between each spasm. The typical movement is a whole-body crunch with the head dropping forward, arms brought inwards and legs drawn towards the trunk, but sometimes spasms are extensor – with arms and legs flung outwards and the head backwards. The movements can sometimes be extremely subtle with just a small head drop or eye roll.

Is IESS linked to other epilepsy syndromes?

As infantile spasms have many underlying causes the prognosis and progression to other epilepsy syndromes is very varied and dependent on this underlying diagnosis. The underlying causes include many different structural, genetic and metabolic conditions. The main ones are hypoxemic ischaemic encephalopathy (HIE) with/without hypoglycaemia and pathogenic gene variants/chromosomal abnormalities of which the most frequent include TSC1, TSC2 (tuberous sclerosis complex), ARX, CDLK5, STXBP1, and trisomy 21 (Down syndrome). Structural abnormalities include acquired antenatal and perinatal lesions and malformations of cortical development.

Children with uncontrolled spasms will often evolve to fit the criteria for Lennox-Gastaut syndrome or drug-resistant focal epilepsy.

How frequent are seizures typically?

Spasm clusters typically occur at sleep transitions (waking or falling asleep) and will increase in frequency if untreated to having multiple episodes a day.

How may seizures change over time?

If untreated the spasm clusters tend to become more frequent and more pronounced. Children affected with infantile spasms often go on to have other seizure types.

What other problems apart from epilepsy affect children with IESS?

IESS is an epileptic encephalopathy (a condition where the underlying electrical activity causes ongoing damage to the developing brain) with various degrees of developmental impact manifested as a plateauing or regression in skills at onset of epileptic spasms. Isolated regression in visual attention or altered social responsiveness may occur in the days or weeks preceding onset of spasms. Developmental plateauing and regression typically worsen without rapid, effective treatment.

Severity of developmental delay relates predominantly to underlying condition and time to treatment from spasm onset. The underlying cause of the spasms has a significant bearing on outcomes and on comorbidities. Children will often have residual effects including global developmental delay or specific difficulties affecting speech

and language, gross motor function, fine motor function, cognition, visual/auditory or other sensory processing disorder, autism spectrum disorder, ADHD, and in specific cases, tonus/posture and movement disorder. Delay in diagnosis and treatment has been linked to poorer outcomes.

What are the treatment options?

Initial treatment should be with hormonal therapy (ACTH or oral prednisolone), vigabatrin or a combination of those. In cases where this is not successful then the options are other antiseizure medication, epilepsy surgery or ketogenic diet. Children should be thus be referred to tertiary epilepsy centres.

Children with a focal lesion on MRI may be candidates for resection of the lesion. In some children corpus callosotomy or implantation of a VNS (vagal nerve stimulator) may be helpful to control drug resistant seizures.

What is the emergency protocol for seizures?

Rescue medication is not typically needed for infantile spasms as the visible seizure episodes tend to only last for a few minutes. It is important to recognise the urgent need to treat the seizures and the underlying brainwave pattern – the visible spasms are only a marker of the underlying pattern.

What could I ask my doctor or specialist epilepsy nurse about?

- Investigation of an underlying cause should be undertaken and should include brain imaging with MRI, blood tests for metabolic and genetic causes and lumbar puncture.
- The aim of treatment is to completely eliminate visible spasms and clear up the EEG abnormalities and it's important that this is closely monitored until the child is stable.
- Side effects of treatment can be significant and should be discussed with parents.
- Support is usually needed for development. This should follow individualised protocols which may include physiotherapy, speech therapy, occupational therapy etc.
- Genetic counselling, if genetic cause has been identified.
- Surgery options for focal origin spasms/ structural causes should be sought in specialised epilepsy centres when appropriate.

Who should be part of the medical team?

Paediatric neurologist or paediatrician with special interest in epilepsy, epilepsy nurse, community paediatrician to monitor development and refer to support services as appropriate. Physiotherapist, speech therapist, occupational therapist, play therapist may be involved. Support may be needed once the child is old enough to go to school from educational psychologist. Psychological support to caregivers may be needed especially in cases of a genetic or other underlying cause identified. Referral to specialised epilepsy centres when appropriate.

Patient and scientific groups

UK Infantile Spasms Trust
https://ukinfantilespasmstrust.org
ukinfantilespasmstrust@gmail.com

Authors: Jenny Rawling (UK Infantile Spasms Trust), Dr. Alice Goldhill and Dr. Maria Papadopoulou (Hospices Civils de Lyon, France).