Investigation of progressive neurological impairment in children with epilepsy

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Whether epilepsy has presented as the initial feature of a progressive neurodegenerative disease in a child is often a diagnostic dilemma in those with more challenging cryptogenic epilepsy. Epilepsy as a sole presenting feature is rare, but recognised in a certain number of disorders (see below). More specifically, in a child presenting with cognitive decline, the question may remain as to whether this is secondary/related to the epilepsy or whether there is associated intrinsic pathology.

Cognitive or developmental plateau or regression is well recognised at the onset of certain of the more severe early epilepsy syndromes. The underlying pathophysiology to this remains uncertain, however, and appears to be related in part to the early onset of frequent seizures. The term 'epileptic encephalopathy' is now recognised as part of the ILAE classification of the epilepsies[1], described as disturbances of cognition, behaviour, and motor control that occur with epileptic seizures and are attributed to epileptiform activity, which may be subclinical. Many individuals show periods of apparent improved developmental progress in association with improved seizure control. In some children it is relatively easy to determine the relationship of epilepsy to the cognitive problems and the need to investigate such. Although aggressive treatment of overt seizures is appropriate, it is more difficult to define the criteria to treat subclinical discharges, in the absence of overt non-convulsive status epilepticus.

Is it real?

The initial phase of the evaluation is to determine whether the cognitive decline is 'real' as opposed to 'apparent'. Children may experience developmental plateau in association with the presentation of severe epilepsy. There is usually an accurate documentation by the parents of previous developmental milestones, and the history may give detail of lack of progress with, rather than loss of, milestones. It is more difficult to determine the answer to the question 'Why is he going backwards?' In children with long-standing symptomatic epilepsy lack of progress becomes evident. In these children, learning does not progress with age, which means the gap between the child and their peers widens – with a consequent drop in IQ. This is not a loss of skills but rather a failure to progress, and becomes particularly apparent around the age of seven years when abilities such as practical reasoning and abstract thought start to develop in normal children.

Key points in the history are age at onset, the relationship or not to frequency of seizures, and the pattern of regression. A pattern of fluctuating abilities as opposed to steady decline is likely to suggest an epileptiform basis, although some neurodegenerative conditions may show a stepwise progression. Periods of apparent encephalopathy should also alert the doctor to the need for investigation. The history may distinguish whether this is likely to be part of

a metabolic disorder or periods of non-convulsive status, but investigation at the time of acute deterioration may be the only way to differentiate between these.

The emergence of neurological signs in a child with epilepsy, in association with possible cognitive decline, signals the need for investigation, particularly if signs are progressive. These include a motor disorder with pyramidal or extrapyramidal signs and abnormalities of eye movement. There remains the possibility that this is still epileptiform in origin; motor disorders such as monoparesis or ataxia may revert with aggressive antiepileptic drug (AED) treatment. However this does not preclude the need for exclusion of other causes, as the EEG itself may be inconclusive. It is also unusual for epilepsy alone to present with hard neurological findings on examination unless a known deficit has been previously established.

Epileptiform or non-epileptiform?

The mechanisms of cognitive/neurodevelopmental plateau or regression in certain epileptic encephalopathies remain unclear. This is particularly true of the early onset epilepsy syndromes, both those that are focal and those that are generalised in onset. Generalised syndromes that are almost always associated with this include the early myoclonic encephalopathies, West syndrome, Dravet syndrome and the Lennox-Gastaut syndrome.

West syndrome pertains to the triad of infantile spasms, hypsarrhythmia on the EEG, and developmental plateau. The latter involves a regression in communication skills with poor eye-to-eye interaction. Infantile spasms may occur in association with a variety of pathologies, although the EEG and developmental pattern may be similar. Prognosis with regard to initial seizure control is relatively good with vigabatrin or steroids, however it remains poor with regard to developmental outcome, and the later development of further seizures. Developmental outcome appears better in some infants who are treated early after presentation and in whom there is a rapid resolution of seizures and EEG abnormality, suggesting that the epileptic activity plays a major part in subsequent cognitive development. However the underlying pathology is a strong indicator of future developmental outcome.

Focal seizure syndromes can also feature a similar clinical picture of neurodevelopmental regression at presentation. Sturge-Weber syndrome is characterised by a facial capillary haemangioma (port wine stain) involving the periorbital area, forehead or scalp, a venous angioma of the leptomeninges and, in a proportion of cases, a choroidal angioma. Epilepsy is reported in approximately 80% cases. However, these figures are derived from selected groups of individuals with Sturge-Weber syndrome, and may therefore not be fully representative of all cases. Seizures start in the first year of life in the majority. One study found that the onset of epilepsy was within the first two years of life in 86%, and 95% by five years of age. Early-onset, poorly controlled seizures tend to be associated with progressive hemiparesis and developmental slowing; in such cases early resective surgery should be considered. The underlying pathophysiology of the 'encephalopathy' is unclear, but may be related to ischaemia secondary to venous hypertension within the angioma.

Landau-Kleffner syndrome is an age-related syndrome with a probable focal aetiology leading to a more widespread encephalopathy. Typically, children have a period of normal language development, followed by a period of language regression with auditory agnosia. There is a marked associated behaviour disorder. Seizures may be infrequent, but a profound abnormality is seen on the EEG, usually over the temporal regions. Some may demonstrate very little in the waking state, however, but show almost continuous spike-wave activity in sleep (electrical status epilepticus in slow sleep/continuous spike-wave in slow sleep). Although conventional AEDs may have some benefit, there appears to be a particular role for steroids early in the treatment of this disorder, in an attempt to reverse the language disorder.

It is becoming increasingly evident that a progressive epileptic encephalopathy may be seen in association with certain chromosomal abnormalities, most notably ring chromosome 20. These children present with an early onset apparent focal (frontal) epilepsy. Onset is usually before six years of age. Seizures are often bizarre in semiology, although suggestive of frontal origin; they may include seizures with fear, often with visual symptoms, hallucinations and illusions, generalised tonic, clonic or tonic-clonic seizures, nocturnal tonic seizures or arousals and recurrent non-convulsive status epilepticus. Cognitive outcome is variable although a plateau in skills not inevitable.

To what degree is autism related to epileptic regression?

The cognitive plateau and regression seen in association with some of the early epileptic encephalopathies may show a particular pattern, particularly involving communication skills, with similarities to children presenting with autism. This is seen in children with infantile spasms, and also in children with early presentation of seizures associated with right temporal lobe lesions, especially boys. Conversely, a number of children with classical presentation of autism have epileptiform abnormalities on EEG (30%) and about 20% suffer from epilepsy. The question arises as to how much of the epileptiform activity seen on EEG, particularly in sleep, is related to the autistic regression, and how much this warrants aggressive AED treatment. To date, there are no studies demonstrating the relationship of epileptiform abnormalities on EEG to classical autism, or the merits of treatment. Most children showing a response are those who present with a history of some seizures, and therefore warrant investigation and treatment from this standpoint. The potential role of AEDs in others needs further investigation.

Epilepsy as the presentation of a neurodegenerative disorder

A few conditions have epilepsy as a presenting feature (Table 1). The range of disorders that need to be considered will depend on the age at presentation. In the neonate, metabolic disorders, particularly non-ketotic hyperglycinaemia, may present with a clinical/electrophysiological picture suggestive of hypoxic ischaemic encephalopathy, with very early seizures and a burst-suppression picture on EEG. One may be alerted by the apparent lack of history of a significant hypoxic insult. Later in the first year, Menkes disease and biotinidase deficiency may be suggested by the condition of the hair.

Alpers' disease (also known as progressive neuronal degeneration of childhood – PNDC) is a rare but well recognised disorder in which progressive epilepsy is seen in association with liver dysfunction. The condition usually presents in the first two years of life, though may present at any time during childhood and even into early adult life. It is an autosomal recessive disease caused by mutation in the gene for the mitochondrial DNA polymerase POLG. It is likely that many of the reported valproate-associated hepatic failures occurred in individuals with Alpers' disease.

Late infantile neuronal ceroid lipofuscinosis (Batten's disease) presents with initial seizures in the second year of life, usually including myoclonus with a subtle developmental plateau that may only later become apparent as regression. Electrical visual studies may lead to suspicion (with enhanced visual evoked response), and confirmation with white cell enzyme analysis and genetic studies.

In older children, conditions that may still need to be considered include subacute sclerosing panencephalitis (SSPE). Progressive behaviour change in association with periodic jerks will give a clue to this. Wilson's disease may have associated movement disorder and behaviour

change, with Kayser Fleischer rings on the iris. Extrapyramidal features, in particular in association with non-epileptic drop attacks (cataplexy) may suggest Niemann Pick type C.

The progressive myoclonic epilepsies are again likely to present with infrequent seizures, with a later increase in frequency and associated cognitive concerns. A high index of suspicion is required to investigate these early.

Table 1. Neurodegenerative conditions that may present with epilepsy as a symptom.

Infancy	1–5 years	5–10 years	Adolescence and adulthood
Metabolic • Non-ketotic hyperglycinaemia • D-glyceric aciduria • Hyperammonaemia Biotinidase deficiency Late infantile NCL Menkes syndrome Krabbe disease Tay Sachs disease Peroxisomal disorders Alpers' disease	Mitochondrial cytopathy Homocysteinuria Rett syndrome Late infantile NCL Gaucher's type III Alpers' disease	SSPE HIV Alpers' disease Wilson's disease Niemann Pick type C	Progressive myoclonic epilepsy • Lafora body • Unverricht-Lundberg Sialidoses Alpers' disease

NCL: neuronal ceroid lipofuscinosis; SSPE: subacute sclerosing panencephalitis; HIV: human immuno-deficiency virus; PNDC: progressive neuronal degeneration of childhood

Table 2. Investigations to consider with 'true' neurological deterioration in association with epilepsy.

EEG (including sleep)
ERG/VEP
MRI
Blood
• FBC, LFT, NH$_3$, amino acids, lysosomal enzymes,VLCFA,
bile salts, vacuolated lymphocytes/buffy coat, Cu/Caeruloplasmin, biotinidase, lactate
Genetic studies for specific conditions
• Discuss with paediatric neurologist and geneticist
Urine
• Amino acids, organic acids
CSF
• Lactate, amino acids, virology
Biopsy
• Skin, liver, muscle

EEG: electroencephalogram; ERG: electroretinogram; VEP: visual evoked potential; FBC: full blood counts; LFT: liver function tests; VLCFA: very long chain fatty acids

What investigation when?

Recognising the need for investigation and deciding which investigations to consider is often the most difficult task. Investigations that may be considered are outlined in Table 2. Obviously, some are highly specific and more invasive, and a high index of clinical suspicion is therefore required to direct the investigation required. Recognising that intrinsic pathology is present may be difficult in the early stages of presentation of many disorders, and constant re-evaluation of the individual may be necessary.

Reference

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Further reading

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