

Regression in Children and Young People



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Adult neurologists practising outside tertiary units can expect to see young people presenting with concerns about regression. Furthermore, they often care for young adults who may be living with a disease of childhood onset, causing progressive intellectual and neurological deterioration. It is of great importance that these young people are assessed in an appropriate way, and that their condition is placed within the context of their overall developmental level. This series of articles has covered some of these issues already, and this article will focus on elements of the diagnostic process in regression. The focus will be on those disorders likely to present in children and young people over the age of five; younger than this, and diagnosis is very likely to be the domain of paediatric neurologists.

Regression is classically associated with neurodegeneration. These illnesses are progressive, so the clinician will expect to uncover a loss of previously acquired skills. Underpinning such diseases are abnormalities of structural or enzyme proteins – but the exact metabolic error or genetic defect may not yet have been isolated. This can make it tricky to prove the diagnosis with a single test, so there is ongoing emphasis on careful history taking, family investigation and neurological examination, followed by special tests. The tests most often needed are biochemical, neuroimag-

ing, neurophysiology, and expert review by ophthalmology.

The take home message of this article is, however, that most referrals about regression are evaluated to be due to non-neurodegenerative disease.

“Seeming to regress” – non-neurological causes

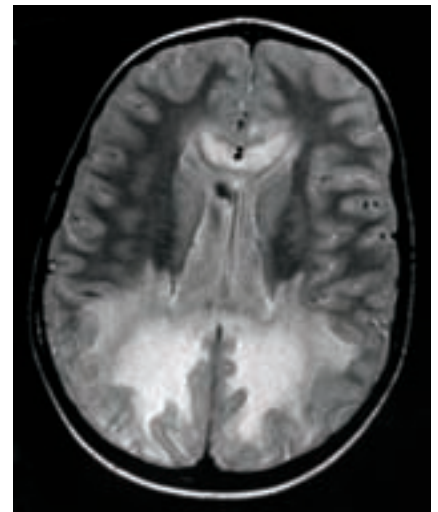
Most children and young people who present to paediatric or adult neurologists with concerns about school performance do not have a neurodegenerative disease. Worsening grades may derive from bullying or stress, from school absence (which may itself derive from a medical cause), or from previously unidentified developmental disorders such as dyslexia or autism. As children go through school, what we expect of them in academic and social terms increases and this may uncover a long standing problem that had previously gone unrecognised – thus an apparent regression or loss of skills is actually a static problem revealed by a change in environment. Sadly, adolescents are the archetype for factitious illness; for this reason, an in-depth social history should be taken, including any recent bereavement, moving house, parental separation and so on. This is an opportunity to be justifiably nosy. More rarely, autoimmune disease, vasculitis and endocrine disorders may present with failure in school.

TABLE: Disorders producing changes in density or signal on MRI brain imaging

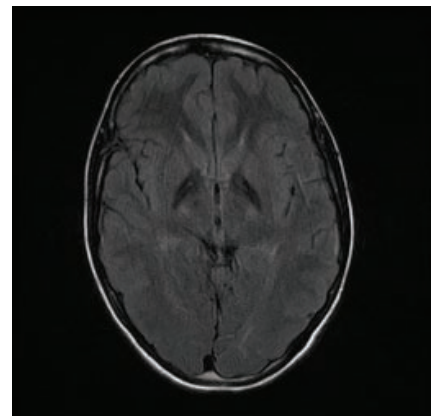
White Matter	Grey Matter
Genetic	
Leukodystrophies	Alpers
Mitochondrial Encephalopathies	Gangliosidosis GM1, GM2
Refsum	Mucopolisidoses
L-hydroxyglutaric aciduria	Fucosidosis
Phenylketonuria	Wilson
Maple Syrup Urine Disease	Lafora Body Disease
Mucopolysaccharidoses	Niemann-Pick A,C
Giant Axonal Neuropathy	Mucopolysaccharidoses
Congenital Muscular dystrophies	Gaucher
Farber	Mitochondrial
Trichothiodystrophies	Menkes
Acquired	Huntington
Diffuse post-anoxic encephalopathy	
Periventricular leukomalacia	
Toxic leukoencephalopathy (methotrexate, radiotherapy, immunosuppression)	
Viral infections eg HSV encephalitis, SSPE	

TABLE – Possible tests in neurodegeneration

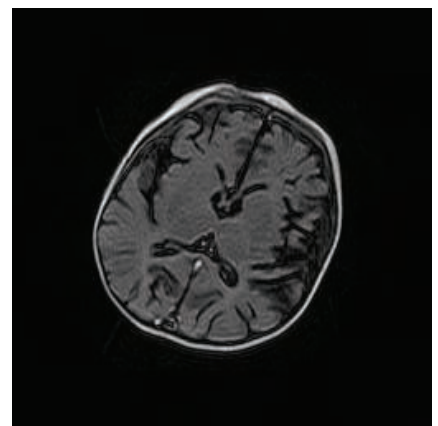
Condition	Test
Mitochondrial	Muscle biopsy. Respiratory chain enzymes
NCL – juvenile	White cell enzymes. Electron microscopy of skin: 'fingerprint' inclusions in neurones
NBIA/PKAN	MRI – iron deposition in the basal ganglia followed by the 'tiger eyes' sign as necrosis develops. Genetics
Refsum	Phytanic acid
HIV dementia	Viral load, CD4 estimation
Niemann-Pick C	Cholesterol transport/storage in cultured fibroblasts
Unverricht-Lundborg	EPMI mutation
Friedreich ataxia	Frataxin mutation
vCJD	MRI – bilateral pulvinar high signal
Wilson	Caeruloplasmin, Urine copper excretion, penicillamine challenge
SSPE	CSF measles PCR
Lafora Body disease	Biopsy axilla – Lafora bodies in sweat glands
Huntington	Genetics
Cerebrotendinous Xanthomatosis	Cholesterol levels



Adrenoleucodystrophy age two.



Tiger-eye sign in PANK (Hallervorden Spatz) age four.



Menkes atrophy age one.

Seeming to regress – non-degenerative neurological conditions

Not all neurological causes of apparent regression are neurodegenerative.

Other causes to consider include:

- **Drugs** – Centrally acting drugs, such as anti-epileptic medications or recreational drugs (including alcohol), may be implicated.
- **Sensory impairment** – The young person may be losing visual acuity or becoming deaf.
- **Raised intracranial pressure** – this is classically associated with change in behaviour and deterioration at school.
- **Psychiatric disorder** – Psychosis and depression may cause difficulty accessing the educational curriculum.
- **Epilepsy** – disorders such as Landau-Kleffner can cause apparent regression. Landau-Kleffner may have an insidious (or rarely abrupt) onset, and is characterised by language deficit – loss of verbal comprehension, followed by loss of oral expression. There may be auditory agnosia, but crucially there may be few (or no) classical seizures.
- **Autism** – Regression is common in autism, occurring in 30% of cases but usually under the age of three. Incidental EEG abnormalities are common (21-68% have an 'epileptiform sleep EEG'), but they are independent of regression, suggesting no evidence of causality. There is no evidence that treatment with anti-epileptic medication improves core deficits in autism. The National Autism Plan for Children 2003 (UK) proposed that an EEG should only be considered in autistic children where there were clinical epileptic features, or where there is
 - A fluctuating clinical course
 - Coming and going of Skills
 - A fluctuating movement disorder or unusual behaviour

- Possible regression in the second year. If features of non-neurodegenerative disorders predominate and there are no neurological signs, then the focus should be on addressing the root cause. Thereafter, the role of the health professional lies in communicating with education regarding appropriate assessment in school – which would usually involve an educational psychologist.

Neurodegenerative disease

Psychomotor regression may be difficult to objectively demonstrate in clinic in the early stages. Tests of parietal, temporal and frontal lobe function will be familiar to adult neurologists, and adolescents will be able to participate in tests for astereognosis, sensory inattention and so on.

It must be emphasised that investigation in suspected neurodegenerative disease should be targeted. This is guided by information from the history, examination and investigations. Perhaps one exception to this rule of targeting is the near-ubiquitous use of MRI brain scanning in these patients. This is largely because this investigation has the single greatest diagnostic yield, and provides useful hints as to the 'next step'.

The British Paediatric Surveillance Unit has been collecting data on the clinical presentation of progressive intellectual and neurological deterioration for eleven years. All individual causes of neurodegeneration are rare, but for adolescents presenting with true regression, the most common cause has been variant Creutzfeldt-Jakob disease.

In all things – first comes the history.

- Is there myoclonus? Subacute sclerosing panencephalitis, Lafora-body disease, Unverricht-Lundborg and variant Creutzfeldt-Jakob disease (vCJD) may all present with this.
- If the predominant school complaint is deterioration in behaviour, then juvenile neuronal ceroid lipofuscinosis (NCL),

Wilson disease and juvenile Huntington should be considered.

- A vary rapid rate of regression may suggest neurodegeneration with brain iron accumulation (NBIA, formerly known as Hallervorden-Spatz).

Examination may be fruitful, particularly in terms of looking at the co-ordination of movement.

- Extra-pyramidal signs may suggest juvenile Huntington, NBIA, Wilson and vCJD.
- Ataxia may point to Niemann-Pick Type C, vCJD, Refsum, cerebrotendinous xanthomatosis (CTX), or Friedreich ataxia (FA).

- The loss of deep tendon reflexes promotes Refsum or FA. A large liver suggests Wilson or Refsum.

Clues from the MRI brain scan are invaluable in the evaluation of infants and younger patients with regression, but are still of considerable value in older children.

- NBIA may demonstrate the tiger eye sign – a symmetrical bilateral hypointense signal on T2 in the globus pallidus, surrounding a hyperintense signal anteriorly.
- A hint to vCJD may be found in bilateral intensities in the posterior thalamus.

It is hard to overstate the importance of an experienced neuroradiologist in the interpretation of these images. If you don't have local access to such an opinion, it is often well worth going the extra mile to get the scans reported at another institution.

Ophthalmological assessment may be a valuable screening tool.

- Early optic atrophy points towards juvenile NCL, and this may be supported by attenuation of the ERG. Optic atrophy may also be found in SSPE.
- Retinitis pigmentosa may be found in NBIA or Refsum.
- A cherry red spot is found in many childhood causes of regression, but in this age group Niemann Pick type C is promoted (a vertical gaze palsy is nearly always present).
- Cataracts may be found in CTX.
- Progressive central visual loss has been associated with SCA 7 mutation.

- Kayser-Fleischer rings are as important in paediatric practice as they are for 'grown-up' neurologists!

Summary

Patients presenting for the first time with apparent loss of skills must be carefully evaluated. The first step is defining the problem. Is this true neurodegenerative disease, with progressive loss of skills and the development of neurological signs? Or is this a pseudo-regression, where the problems derive from non-degenerative causes (including neurological, social, psychiatric and 'other')?

Where neurodegenerative disease is suspected – focus investigation on those conditions suggested by your initial assessment, the MRI findings, and the ophthalmology review. ♦

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