

NEUROLOGICAL AND COGNITIVE DECLINE IN ADOLESCENCE

Rob J Forsyth

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The evaluation of progressive neurological and/or cognitive decline poses one of the greatest challenges to the paediatric neurologist. While the potential causes are individually quite rare, collectively neurodegenerative disorders are quite common with an incidence of approximately 0.5/1000 live births.¹ Faced with an individual child, it is easy to feel daunted by textbooks^{2,3} that tend to be organised according to pathology, rather than presentation, and which emphasise that many of these conditions have “variants” that can present at widely differing ages. Confusing terminologies, and non-specific presentations, tend to add to a sense of despair at ever getting to grips with the field.

Confining the scope of this paper to conditions presenting in adolescence limits the number of conditions under discussion, simplifying matters considerably. However, considerations pertinent to the evaluation of progressive disease across the paediatric age range still arise.

PROGRESSION OR EVOLUTION?

In young children, the interplay of physiological developmental progress (even at a reduced rate) and a neurodegenerative condition can result in surprising difficulty in establishing whether signs and symptoms are truly progressive. The progressive nature of a new onset disease in a previously healthy adolescent will clearly be much more obvious, but such clear cut situations are quite rare. Quite frequently, new concerns are raised about an adolescent child with pre-existing neurological signs and symptoms, especially the child with longstanding “learning difficulties” or “cerebral palsy” (CP). Jean-Pierre Lin and Chris Rittey discuss the differential diagnoses of these entities elsewhere (see pages i23 and i30). Such labels may have been assigned after only a limited aetiological work up and mask a slowly progressive primary diagnosis. A diagnosis of severe *quadriplegic* or *dyskinetic* CP ideally requires an unambiguous history of severe hypoxic ischaemic encephalopathy (HIE) in a term infant. A diagnosis of *diplegic* CP is most secure in a child born prematurely with demonstration by computed tomography (CT) or magnetic resonance imaging (MRI) of relatively symmetrical periventricular white matter loss in the occipital horns and ischaemic signal change. Normal MRI appearances in brain and cord in a child with “diplegic CP” would raise the possibility of a slowly progressive hereditary spastic paraplegia or even dopa responsive dystonia.

Diagnosis of this condition—whose importance, as is often the case in paediatric neurology, lies not in its prevalence but its potential treatability—in a child previously labelled as having “severe CP” is a truly momentous event. Diagnosis of “dyskinetic” and particularly “ataxic” cerebral palsy diagnoses must only be made after adequate evaluation, and promptly revisited if any progression of symptoms or signs is observed (table 1). Characteristically, dyskinetic CP caused by severe term HIE gives rise to hyperintensity in the putamen and/or thalamus on T2 weighted MRI. Other signal abnormalities, or atrophy, of the putamen, or involvement of the globus pallidus or caudate, should raise suspicion of missed metabolic disease.⁴

While *progression* of signs is inconsistent with a diagnosis of CP, *evolution* is not, and this again can pose diagnostic challenges. The manifestations of a non-progressive insult evolve with the changing developmental stage of the central nervous system around it. One well described and important example is the evolution of dystonic and/or choreic features in the upper limbs during the second decade of life of a child with previously purely spastic diplegic CP. Measures of functional performance of children with CP (such as walking distance or speed) may also deteriorate in adolescence for more prosaic reasons such as increasing weight and height, or preventable complications such as the development of contractures. In these circumstances, detailed examination will confirm that formal neurological signs have not altered (assuming these have been previously well documented).

PSEUDO-REGRESSION

While there is a tendency to equate progressive neurological and/or cognitive decline with primary neurodegenerative diseases, it is vital to consider causes of reversible, “pseudo-” regression. Cognitive decline in adolescence is most likely to manifest as underachievement or failure at school.

Correspondence to:
Dr R J Forsyth, Children's
Outpatients, Newcastle
General Hospital, Newcastle
upon Tyne NE4 6BE, UK;
r.j.forsyth@newcastle.ac.uk

Table 1 Diagnostic possibilities in children with longstanding diagnoses of “ataxic” or “dyskinetic” cerebral palsy (CP) showing slow progression in second decade of life

▶ “Ataxic CP”	Slowly growing posterior fossa lesions Ataxia telangiectasia Metachromatic leukodystrophy G _{M2} gangliosidosis Salla disease
▶ “Dystonic CP” (unusual for other potential differential diagnoses not to have declared in the first decade of life)	Sandifer syndrome (dystonic movements of head and neck related to gastro-oesophageal reflux) Late variants of Leigh disease

Although some neurodegenerative diseases can have predominantly cognitive or psychiatric initial presentations, this is rare, and a number of much more likely considerations apply to the situation where new academic concerns arise *in the absence of neurological signs*. Over the last two decades the conventional wisdom that depression was not common in adolescence has been overturned; this is now rightly recognised as

an important differential in the evaluation of school failure. Comparable, reversible “regression” of cognitive skills can be seen in children with learning difficulties who endure a period of emotional deprivation—for example, arising from prolonged hospitalisation.

A more subtle situation concerns the child with pre-existing, static, cognitive impairments who begins to fail as academic demands increase through adolescence. The adolescent survivor of traumatic brain injury (TBI) earlier in childhood is an excellent example. Children often make remarkably good *motor* recoveries after TBI at a young age, but are left with largely cognitive deficits. These can initially be accommodated in the highly structured primary school setting and are thus effectively “latent”. Upon transition to the much more demanding environment of secondary education these children’s executive, problem solving, attentional, and learning speed difficulties become apparent. Unfortunately failure to understand the notion of latent deficits may result in failure to ascribe the newly manifesting problems to the past TBI.

Exacerbation of a severe seizure disorder is another important cause of pseudo-regression requiring EEG evaluation for the possibility of non-convulsive (“subclinical”) status epilepticus. It would be unusual for such acquired cognitive

Table 2 Useful findings to consider in light of specific clinical findings

	Useful clinical findings for this presenting syndrome	Useful investigations for this presenting syndrome
▶ Paraparesis/pyramidal signs	Peripheral neuropathy? Eye findings? Rate of progression? Family history?	MRI, NCV, CSF protein, VLCFA, WCE
▶ Ataxia	Areflexia? Dorsal column involvement? Seizures? Extrapyramidal? Eye movements? Head tremor? Conjunctivae? FHx?	Cardiac function, NCV, CSF protein, lactate, cholesterol, lipoproteins, vitamin E, acanthocytes, MRI, WCE
▶ Myoclonus, seizures	Age onset, rate of progression; eye movements; hearing; seizures	EEG, ERG, BAEP, MRI, CSF lactate, skin/muscle biopsy
▶ Extrapyramidal	Dysarthria? Learning difficulties? Slit lamp exam? Consider trial levodopa	MRI, ERG, copper studies, acanthocytes
▶ Peripheral polyneuropathy	Retinae? FHx?	NCV, CSF protein, phytanic acid
▶ Visual loss/symptoms	Fundi; FHx “mitochondrial” symptoms*	MRI, ERG, CSF lactate, muscle biopsy
▶ Fundoscopic abnormalities	FHx “mitochondrial” symptoms	
▶ Eye movement abnormalities	FHx “mitochondrial” symptoms? Paternal FHx of “neurological disease”? Tremor? Organomegaly?	MRI, CSF lactate
▶ Stroke-like episodes	Fundi; FHx “mitochondrial” symptoms	MRI, ERG, CSF lactate, muscle biopsy
▶ Episodic encephalopathy	Fundi; FHx “mitochondrial” symptoms	MRI, ERG, CSF lactate, muscle biopsy
▶ Personality/behavioural/dementia	Eye findings? Pre-existing “epilepsy”? Paternal FHx? Tendon xanthoma?	Copper studies, slit lamp, MRI, EEG†

*FHx “mitochondrial” symptoms refers to family histories of deafness, diabetes, epilepsy or neurological disease.

†If variant CJD is suspected full infection control measures must accompany EEG, lumbar puncture, and intubation/general anaesthesia for any procedure such as MRI. Seek local advice.

BAEP, brainstem auditory evoked potential; CSF, cerebrospinal fluid; EEG, electroencephalogram; ERG, electroretinogram; MRI, magnetic resonance imaging; NCV, nerve conduction velocity; VLCFA, very long chain fatty acids; WCE, “white cell” (lysosomal) enzyme screen.

Effects of Bayes' theorem on the interpretation of the results of tests with imperfect sensitivity and specificity

- ▶ This sort of discussion tends to bring some people out in a rash. Unfortunately it is of fundamental importance in an area of medicine where we are looking for rare diseases with tests of imperfect sensitivity and specificity.
- ▶ A test's sensitivity is the probability that the test will be positive when the disease is there—that is, imagining the test being administered to a group of people all of whom actually have the disease, how likely the test is to “pick it up”. A test's specificity is the probability that the test will be negative when the disease is indeed not there—that is, imagining the test being administered to a group of people *none* of whom actually have the disease, how likely the test is *not* to mistakenly show up positive. (The fact that specificity is a probability of *not* misleading can cause some confusion: it is expressed that way so that both sensitivity and specificity are desirable things. If they are both 100% the test will never miss a true case and never mislead you into thinking a case is there when it is not.)
- ▶ The positive predictive value is the probability of the disease truly being present if the test is positive. While this may sound very much like sensitivity, it is not. It is “turned round”: the probability, given that an animal is a cat, of it having four legs is greater than the probability, given that an animal has four legs, of it being a cat. Think of positive predictive value as answering the question “just how useful/meaningful *is* a positive test result?”
- ▶ The vital factor to grasp about positive (and negative) predictive values is that *they depend on the prevalence of the condition in the population*—that is, how likely it was that the disease was present even *before* you applied the test. This is also known as the “prior odds”. If you apply a test with a less-than-perfect sensitivity indiscriminately to look for a condition that is unlikely in the clinical context (low prior odds), then false positives are quite likely and in extreme situations could *even outnumber true positives*, making the usefulness of a positive test result (the positive predictive value) low. If investigations are tailored so that, on the basis of clinical assessment, your *prior expectation* of a positive diagnosis is reasonable, then the chances of being misled by a false positive result are much lower.

problems to predate the recognition of a seizure disorder very long, although this can happen in absence epilepsies (some of which present in adolescence). Landau-Kleffner syndrome (LKS) is an acquired receptive aphasia (“auditory agnosia”—the child behaves “as if deaf”) with seizures. Although presentation is usually in the first decade of life, a related syndrome, confusingly laboured under two interchangeable acronyms—ESES (electrical status epilepticus in sleep) and CSWS (continuous spike wave discharges in slow wave sleep)—can present later. Its nosological relation to LKS is controversial: LKS is probably best regarded as a subtype of CSWS/ESES with language specific cognitive effects. The cognitive effects of ESES/CSWS are much less specific. There is active controversy regarding the suggestion that these can include autistic features, raising the possibility of ESES as a probably rare, but potentially reversible, cause of such a picture. The important feature to be aware is the restriction of severe EEG abnormalities to slow wave sleep, necessitating full sleep EEG studies if this condition is suspected, with the consequent logistical challenges.

It is not uncommon to be faced with the challenge of distinguishing an intrinsic epileptic encephalopathy causing

temporary academic difficulty from the less likely possibility that the regression and epilepsy are both symptoms of the same primary neurodegenerative process. It is important to revisit this issue periodically in “intractable” epilepsy, particularly with myoclonus (see below).

CLINICAL EVALUATION

From the above it will be seen that detailed history taking is probably the single most important component of a successful diagnostic conclusion. What is the objective evidence for progression of symptoms or signs? Were there pre-existing concerns? If so, is this progression, or evolution?

From now on we will confine ourselves to the relatively uncommon situation of unambiguously progressive neurological signs and symptoms in a previously neurologically normal adolescent. Progressive disease with manifestations confined to the peripheral nervous system (for example, primary hereditary neuropathies and acute intermittent porphyria) and structural brain disease (for example, cerebrovascular disease and hydrocephalus) will also not be considered further.

Having a clear age at onset in the second decade of life is an extremely useful “handle” in approaching the potential differential diagnostic list and has been used here to limit the number of disorders discussed. In starting to synthesise findings, general questions should be asked about sites of general system involvement. Evidence of manifestations outside the central nervous system—such as (hepato-) splenomegaly, bone marrow, skin, muscle or connective tissue involvement—is of great diagnostic value, although rare in this age group. On the basis of history and examination findings attempts should also be made to decide between predominant involvement of either grey or white matter (reflected by predominance of seizures or cognitive features versus pyramidal tract signs respectively), and if white matter disease is present, whether this includes a peripheral neuropathy.⁵ In practice many adolescent onset neurodegenerative processes show multi-system involvement. The presence of one or more clinical features as listed in table 2 in conjunction with the age at onset begins to narrow the differential.

INVESTIGATION

Consideration of tables 2 and 3 will start to suggest a number of possible differential diagnoses and investigations to consider. Searching for very rare conditions with tests of imperfect specificity and sensitivity throws one up against the very real phenomenon of Bayes' theorem and the dangers of blindly performing batteries of tests looking on the off-chance for conditions that are improbable in the clinical context (see box). Investigation must be tailored and based on reasonable prior expectations of the disease's presence in light of the clinical findings. It is vital to try to form an impression of prior likelihoods of conditions based on what is known of population prevalences, bearing in mind that rare or variant presentations of common diseases may be more common than common presentations of rare diseases. Some of the conditions in table 3 are orders of magnitude more prevalent than others: some represent a handful of known cases *worldwide*. On-line diagnostic support systems (for example, Simulconsult: www.simulconsult.com) are available to guide investigation selection based on Bayesian principles. Such projects are,

Table 3 Features of some causes of progressive neurological and/or cognitive disease in adolescence

Estimated prevalence and condition	OMIM number	Paraparesis/pyramidal signs	Ataxia	Myoclonus, seizures	Extra-pyramidal	Peripheral poly-neuropathy	Visual loss/symptoms	Fundoscopic abnormalities	Eye movement abnormalities	Stroke-like episodes	Episodic encephalopathy	Personality/behavioural/dementia	Other comments	Specific diagnostic tests
HIGH														
Friedreich ataxia	22930	**	**			**							Scoliosis, late cardiac involvement, absent peripheral tendon reflexes, upgoing plantars	Frataxin mutations
Leigh syndrome late variants	Various (220111, 161700, 266150, 308930, 516060, 185620, 220110)		**	**	**	*			**	*	*		Characteristic symmetrical brainstem, basal ganglia changes on MRI	CSF lactate, respiratory chain assays
Primary torsion dystonia	236200				***								Initial focal dystonia (typically foot) later progressing ± tremor	DYT1 mutation
MODERATE														
Homocystinuria	236200							***		***		**	Learning difficulties may be static and longstanding with little to suggest regression. Lens dislocation highly suggestive. Marfanoid habitus. Should be considered in all young ischaemic strokes	Homocystinuria, plasma amino acids (raised homocysteine and methionine)
Juvenile Huntington disease	143100				**				*			***	Paternal FHx, failure of horizontal saccades. Caudate atrophy late	Huntingtin mutation analysis after appropriate pre-test genetic counselling
Juvenile neuronal ceroid lipofuscinosis (Batten; CLN3)	204200			***	*		***	**				***	Retinal pigmentation. Visual loss (typically between 5–8 years of age) may predate onset of other signs by several years	Extinguished ERG. Skin biopsy, CLN3 mutation
Kearns-Sayre and variants	530000		**					**	***		**	**	Cardiac conduction defects, high CSF protein, lactate. Ragged red fibres on muscle histology	CSF lactate, mtDNA studies
Niemann-Pick with vertical ophthalmoplegia	257220		**	*					***				(First presentation in adolescence would be unusual.) Intention tremor, dysarthria. Supranuclear vertical gaze palsy. Modest organomegaly	Sea blue histiocytes on bone marrow; cholesterol studies in cultured fibroblasts
LOW														
Abetalipoproteinemia	200100	*	**			*		*					"Coeliac"-like like malabsorption syndrome in infancy. Head tremor a specific feature (cf Friedreich)	Acanthocytes on blood film. Characteristic cholesterol and plasma lipid profiles

Table 3—continued

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Adrenoleukodystrophy/adrenomyeloneuropathy	300100	**				**	**					***	X linked recessive; female carriers may be symptomatic. Evidence of adrenal insufficiency (usually asymptomatic). The "myelopathy only" of AMN variant more common in adults than adolescents. See also comments on SSPE	Raised VLCFA
Alexander disease	203450	**										**	Very late onset variant (neonatal onset much more common). Dementia may be very slowly progressive. Progressive macrocephally, leukodystrophic MRI	Histology on brain biopsy; GFAP gene mutation analysis
Cerebro-tendinous xanthomatosis ("cholestanolosis")	213700	*	***				*	*				***	Insidious onset dementia, behaviour. Characteristic tendon xanthomas and cataracts. Palatal myoclonus	Low plasma cholesterol; cholesterol abnormalities in urine, bile, CSF
Dopa responsive dystonia	605407				***								Onset usually before adolescence. Clinical distinction sufficiently imprecise to warrant low threshold levodopa trial	Therapeutic challenge with levodopa
DRPLA	125370		***	***								**	Variable symptomatology	DRPLA mutation
Fabry disease	301500					***		*		*			X linked (males only, occasional affected female heterozygote). Corneal changes early (slit lamp only). Severe pain and oedema of extremities. Late focal signs from ischaemic strokes	α Galactosidase activity
Hallervorden-Spatz	234200	*			***			*				**	Possible retinal pigmentation	Pathognomonic MRI appearances of globus pallidus; recent mutations identified in pantothenate kinase genes may allow future genetic confirmation
Hereditary spastic paraplegias (simple)	182600, 182601 and others	**						*					Very slow; usually dominant Fhx; ± retinal pigmentation	DNA mutation analysis for some
Hereditary spastic paraplegias (complicated)	Many	**				?	?					?	Various forms: AD, XLR, AR	

Table 3—continued

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Lafora disease	254780			***			*					***	Visual hallucinations. Fairly rapid cognitive decline (cf Unverricht-Lundborg)	Axillary skin biopsy: PAS-positive inclusion in apocrine glands and/ or eccrine ducts. EPM2 mutation analysis
Late variant GM1 gangliosidosis	230650	*			**								Dysarthria and dystonia may be prominent. Very non-specific presentations possible	β Galactosidase
Late variant GM2 gangliosidosis	230700	***	***	*	*	**	*					***	Pure motor neuropathy with denervation and prominent amyotrophy, or a Friedreich-like syndrome. Visual loss can occur late: misdiagnosis as Batten possible?	Hexosaminidase A deficiency (some variants)
MELAS	540000			**			*		*	***	**		High CSF protein, lactate. Ragged red fibres on muscle histology	Mitochondrial DNA analysis
MERRF	545000		**	***								**	Short; deaf; mixed cerebellar and sensory ataxia	Mitochondrial DNA analysis
Metachromatic leukodystrophy (late onset)	250100, 249900	**	*			**						**	(Presentation far more commonly in pre-school period with death in first decade.) CSF protein up; leukodystrophy on MRI	Arylsulfatase A activity (rare variants with normal activity); sulfatiduria
Neuroacanthocytosis	200150				***							**	Striatal changes on MRI	Acanthocytes on film
Refsum disease	266500		**			***		***					Retinal pigmentation, cataracts, cardiomyopathy, rash, deafness; high CSF protein. Episodic deteriorations. Dietary treatment ± plasmapheresis stabilises neurology	Raised plasma phytanic acid
SCA 7	164500		***		*		**	**	*			*	SCA7 in practice the only dominant spinocerebellar ataxia that presents in the paediatric age range. Pigmentary retinopathy/maculopathy and visual failure are cardinal features. Late supranuclear ophthalmoplegias, dementia, and extrapyramidal signs	SCA 7 mutation analysis
Sialidosis type 1	256550			***			**	**					Macular cherry red spot	Urinary sialyloligosaccharides; α neuraminidase in fibroblasts

Table 3—continued

Estimated prevalence and condition	OMIM number	Paraparesis/pyramidal signs	Ataxia	Myoclonus, seizures	Extra-pyramidal	Peripheral poly-neuropathy	Visual loss/symptoms	Fundoscopic abnormalities	Eye movement abnormalities	Stroke-like episodes	Episodic encephalopathy	Personality/behavioural/dementia	Other comments	Specific diagnostic tests
SSPE	n/a			**								***	School failure and subtle cognitive difficulties can look very much like ALD, until the myoclonic epilepsy supervenes	Measles IgM in blood and IgG in CSF. Characteristic late EEG
Tangier disease	205400					***							Pain and temperature insensitivity; tonsillar appearances; organomegaly	High density lipoprotein very low
Unverricht-Lundborg disease	254800			***								*	Synonymous with "Baltic myoclonus". Myoclonus giving "jerky" quality to speech. Cognitive decline slow. Often notable benefit from valproate	EPM1 mutation
Variant Creutzfeldt-Jakob disease	n/a		**	**	*				*			***	May present initially with psychiatric and cognitive symptoms. Reported in children as young as 12	High T2 signal in pulvinar on MRI highly suggestive in appropriate clinical context
Wilson disease	277900			**	**							***	Consider in all unexplained neurological regression	Copper studies; slit lamp
Wolfram syndrome (DIDMOAD)	222300			*			**	**	*			**	Juvenile onset insulin dependent diabetes mellitus and optic atrophy cardinal. DI and variable cognitive/psychiatric features reported. Autosomal recessive	

Conditions are grouped into indicative bands of relative prevalence, reflecting our experience in the north east of the UK (serving a population of approximately three million) although of course these may reflect local gene pool and other random effects. "HIGH" is intended to convey several active cases in a regional paediatric neurology centre; "MODERATE", one or two at any one time, and "LOW", none currently. The one, two or three star rating for findings in each condition are again intended as very approximate reflections of frequency/importance.

however, unable to circumvent the fact that the data informing the underlying estimates of disease prevalences, test specificities, etc, are of necessity sometimes very imprecise.

SPECIFIC CONDITIONS AND PICTURES

Some of the conditions listed in table 3 (such as Friedreich ataxia, Wilson disease, primary torsion dystonia, and the mitochondrial cytopathies) will be familiar from adult neurological practice and will not be discussed in detail. Additionally, the OMIM reference numbers for the known and presumed single gene conditions in table 3 are given. These will link to current information and further reading in the Online Mendelian Inheritance in Man database at <http://www3.ncbi.nlm.nih.gov/Omim>.

A UK national surveillance programme for progressive intellectual and neurological deterioration (PIND) in childhood was instituted in May 1997, primarily to monitor possible paediatric variations in the presentation of variant Creutzfeldt-Jakob disease (vCJD) (see below). Some of the conditions in table 3 such as Friedreich ataxia do not meet entry criteria of intellectual and neurological decline and thus do not appear in these figures. In the five years to date approximately 40 UK cases of new onset PIND in adolescence have been reported with the following "top 10" diagnoses (in alphabetical order): DIDMOAD, G_{M1} gangliosidosis, juvenile Huntington disease, metachromatic leukodystrophy, mitochondrial cytopathies (combined), juvenile neuronal ceroid lipofuscinosis (CLN3, Batten disease), Niemann-Pick type C, SSPE and vCJD (Verity C, personal communication). Because of possible biases in reporting it is not possible to rank these or extrapolate to estimated prevalence rates, but again some of the diagnoses even in this large series are represented by one or two cases only, and again some are considerably more important in a UK setting than others. I have endeavoured to group conditions in table 3 into approximate prevalence bands based on personal experience and reading.

Batten disease (CLN3, juvenile neuronal ceroid lipofuscinosis)

This is usually a straightforward diagnosis once the condition is considered. Presentation is often *sequential*: typically visual failure predates educational difficulties that in turn predate seizures each by a few years, although the precise order may vary. The initial visual loss is severe, typically beginning between 5–10 years of age, although sometimes later. I know of more than one occasion where the diagnosis was suggested by teachers in specialist schools for children with severe visual loss. Extinction of the ERG and pronounced retinal pigmentation are strongly supportive.

Abbreviations

ALD: adrenoleukodystrophy
CP: cerebral palsy
CT: computed tomography
CSWS: continuous spike wave discharges in slow wave sleep
DIDMOAD: diabetes insipidus, diabetes mellitus, optic atrophy, and deafness
ERG: electroretinogram
ESES: electrical status epilepticus in sleep
HIE: hypoxic ischaemic encephalopathy
LKS: Landau-Kleffner syndrome
MERRF: myoclonic epilepsy with ragged red fibres
MRI: magnetic resonance imaging
OMIM: Online Mendelian Inheritance in Man
PIND: progressive intellectual and neurological deterioration
SSPE: subacute sclerosing panencephalitis
TBI: traumatic brain injury
vCJD: variant Creutzfeldt-Jakob disease
VLCFA: very long chain fatty acids

Adrenoleukodystrophy

An X linked recessive condition, adrenoleukodystrophy (ALD) has two distinct presentations: a *cerebral* presentation with cognitive features; and a *myelopathic* form with slowly progressive spastic paraparesis and dorsal column sensory disturbance. The latter (comprising 25% of all presentations) is seen more frequently in adult onset ALD. The more common cerebral form comprises a relatively rapid onset of cognitive disturbance (slowed thinking, lack of interest, hyperactivity) with central sensory disturbances (visual field cuts and hearing loss) and possible hemiparesis. Adrenal insufficiency is biochemically demonstrable in nearly all, but is rarely the presenting feature. About 10% of female heterozygotes will demonstrate features of the myelopathy. MRI appearances are very characteristic with widespread increased T2 signal particularly in the occipital white matter, often involving the splenium of the corpus callosum, with involvement of the descending corticospinal tracts also often evident. Diagnosis is

confirmed by measurement of high levels of saturated very long chain fatty acids (VLCFA).

Progressive myoclonic epilepsy

As mentioned above, the regressing child with epilepsy poses a particular diagnostic challenge. The large majority of these children have primary epilepsy with pseudo-regression, but underlying causes of progressive epilepsy should be considered, particularly when regression is accompanied by *myoclonic* seizures. The main causes in the adolescent age group are Unverricht-Lundborg disease (where the cognitive involvement is modest and slowly progressive), Lafora body disease (rapid dementia), and myoclonic epilepsy with ragged red fibres (MERRF). Batten disease certainly is accompanied by a progressive myoclonic epilepsy but this is predated by other features (see above).

Sialidosis type 1 has the more helpfully memorable synonym "Cherry red spot myoclonus syndrome"; the characteristic fundal changes can be late, however. Other lysosomal storage disorders (for example, juvenile G_{M2} gangliosidosis) are rare causes.

Variant Creutzfeldt-Jakob disease (vCJD)

This has been the subject of several recent reviews.^{6,7} First presentation of vCJD has been noted at as young as 12 years of age.⁸ The current (2002) diagnostic criteria are given in table 4. There is no evidence to date that the presentation of vCJD in adolescents differs significantly from that seen in young adults.

CONCLUSION

Neurological and/or cognitive decline in adolescence is an alarming presentation. In many cases the regression is apparent rather than real, and reassurance can be given. A number of relatively common conditions account for many of those with true adolescent onset regression. Prompt diagnosis helps families come to terms with what is often devastating news by connecting them with condition specific support groups. Occasionally, even at this age, diagnosis will permit families to make informed decisions about future pregnancies. Ultimately diagnoses are not reached in a significant proportion of children with neurodegenerative disease.

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Table 4 Current (2002) diagnostic criteria for variant Creutzfeldt-Jakob disease (vCJD)

Group 1 features	(a) Progressive neuropsychiatric disorder (depression, anxiety, withdrawal, delusions) (b) Duration of illness > 6 months (c) Routine investigations do not suggest an alternative diagnosis (d) No history of potential iatrogenic exposure
Group 2 features	(a) Early psychiatric symptoms (depression, anxiety, apathy, withdrawal, delusions) (b) Persistent painful sensory symptoms (includes frank pain and/or unpleasant dysaesthesia) (c) Ataxia (d) Myoclonus or chorea or dystonia (e) Dementia
Group 3	(a) EEG does not show the typical appearance of sporadic CJD (or no EEG performed) (b) Bilateral pulvinar high signal on MRI scan
Group 4	(a) Positive tonsil biopsy

Definite: 1A (progressive neuropsychiatric disorder) and neuropathological confirmation of vCJD.
 Probable: All group 1 items and four or five from group 2 and 3a and 3b (or all group 1 items and group 4a).