An approach to developmental regression

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Abstract

Neurodevelopmental regression is often challenging to clinicians in terms of diagnosis and management. The purpose of this article is to outline a systematic approach to a child presenting with suspected neurodevelopmental regression.

Inherited metabolic disorders account for significant proportion of developmental regression in childhood. Onset of regression and the associated symptoms provide clues to the underlying diagnosis. A systematic approach will aid in diagnosing treatable disorders and early treatment. Therapeutic options in most cases are limited and management is essentially symptomatic. Palliative care and family counselling play an invaluable role in the multidisciplinary management.

Future treatment is on the horizon in the form of gene therapy, enzyme replacement therapy and stem cell therapy leading hopefully to improved quality of life and longevity of these life limiting conditions.

Keywords developmental regression; gene therapy; neurodegenerative disorders; regression

Practice points

- Sudden onset regression in a child could be caused by raised intracranial pressure secondary to CNS tumour, hydrocephalus or meningitis
- Vitamin B12 deficiency could cause developmental regression, hypotonia and cerebral atrophy in infants
- Rett and Landau–Kleffner syndrome exhibit regression as seen in autism
- Children with stagnation or loss of developmental milestones should be referred to a Paediatric Neurologist or a developmental Paediatrician for further assessment

Text

The clinical management of children with developmental regression remains a challenge. Diagnosis can be difficult, and treatment is limited. Neurodevelopmental regression, which characterizes neurodegenerative conditions, is defined as a sudden or gradual loss of previously acquired developmental milestones.

Recognition and diagnosis is important as in certain conditions early intervention could lessen the impairment. Even if the disorder is not amenable to treatment diagnosis could still be beneficial in implementing preventive strategies for future pregnancies.

Important for clinician looking after these children is to adopt a systematic approach to understand what causes regression.

Aetiology

The conditions causing developmental regression are a vast group of heterogeneous disorders which occur as a result of genetic, metabolic, structural and infective/inflammatory causes.

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Although inherited causes predominate it's important to bear in mind that raised intracranial pressure caused by brain tumour, hydrocephalus, meningitis or encephalitis could cause sudden onset regression. Other treatable causes of regression are vitamin B12 deficiency, chronic lead poisoning and hypothyroidism and hence should be looked for.

Developmental regression is a common phenomenon in autism. Epilepsy with autistic regression is usually idiopathic but can be seen in some genetic disorders e.g. Rett syndrome, with epileptic encephalopathy e.g. Landau–Kleffner syndrome and certain inherited metabolic disorders.

In this review we will focus on inherited metabolic disorders. There are an increasing number of disorders described; many do not have a specific treatment. Ideally one would classify these neurometabolic disorders based on the causative factors. One simplified approach would be to classify them into two broad categories – grey matter diseases and white matter diseases. The other approach is based on the age of onset of regression and the presence of visceromegaly. The third approach would be to consider treatable conditions first. Table 1 delineates these approaches.

An approach to regression in hospital setting

Case history: let us consider a case history and discuss the approach. GB first presented to ophthalmology at the age of 7 years with an isolated visual impairment. She then represented 4 years later with generalized tonic clonic convulsions. Subsequently she developed cognitive regression. From the age of 13 years she developed progressive worsening motor difficulties (bradykinesia) and anxiety. She had an uneventful past medical history. Birth history, development and schooling history were unremarkable prior to the onset of regression. There was no history of consanguinity.

An accurate history should hopefully enable us to decide whether we are dealing with structural or genetic/metabolic or an inflammatory cause accounting for regression.

First step would be to ascertain the age of onset of regression and the acquisition of various milestones prior to that. Was the child completely normal before regression or was there a concern regarding development even prior to regression? The sequential loss of various skills should be explored. In autism and other pervasive developmental disorders regression of language skills is

Classification of neuroregressive conditions

(a) Grey and white matter conditions

Grey matter conditions	White matter conditions
With visceromegaly	Metachromatic Leukodystrophy (MLD)
GM1 gangliosidosis	Adrenoleukodystrophy (ALD)
Sandhoffs' disease (GM2 gangliosidosis)	Krabbe disease
Niemann—Pick C and related disorders	Alexander disease
Sialidosis	Canavan disease
Mucopolysaccharidosis (MPS)	Mitochondrial disorders
Gaucher type III	
Without visceromegaly	
Mitochondrial e.g. Alpers' syndrome	
Tay—Sachs disease (GM2 gangliosidosis)	
Menkes disease	
Neuronal Ceroid Lipofuscinosis (NCL)	
Neuronal axonal dystrophy	

(b) Neuroregressive conditions according to age

Age at onset	Condition
<2 years with hepatomegaly	Fructose intolerance
	Galactosaemia
	Glycogen storage disorder types 1—4
	Mucopolysaccharidosis types 1 and 2
	Niemann—Pick disease
	Tay—Sachs disease
	Zellweger Syndrome
	Gaucher disease
<2 years without hepatomegaly	Krabbe disease
	Maple syrup urine disease
	Phenylketonuria
	Menkes disease
	Mitochondrial disease
	Canavan disease
2—5 years	Niemann—Pick disease
	Wilson disease
	Mitochondrial e.g. Myoclonic epilepsy ragged red fibers and Alpers
	Metachromatic leukodystrophy
	Adrenoleukodystrophy (ALD)
	MPS III/SanFilippo disease
5—15 years	Peroxisomal e.g. ALD and Refsum disease
	Neuronal ceroid lipofuscinosis
	Mitochondrial disorders
	MLD and Krabbe
	Niemann—Pick C
	Wilson Disease
	Cerebrotendinous xanthomatosis
	Huntington's disease

(c) Treatable disorders

Biotinidase deficiency
Wilson disease
Niemann—Pick C
Neurotransmitter disorder e.g. Segawa, tyrosine hydroxylase deficiency
Cerebral folate disorder
Glucose transporter disorder
Biotin responsive basal ganglia disease
Pyruvate dehydrogenase deficiency
Creatine disorders

Table 1

noted first followed by loss of social skills. Table 2 elaborates important points in history of a child with regression of milestones.

Symptoms of raised intracranial pressure like headache, projectile vomiting and recent change in personality could explain sudden onset regression.

Epilepsy is a presenting symptom in a number of neurodegenerative conditions which could be considered based on the age at presentation (Table 3).

In a neonate, non-ketotic hyperglycinaemia usually presents with very early seizures and burst suppression picture on EEG. Molybdenum Cofactor Deficiency (MOCD) and sulphite oxidase deficiency should be considered too, especially as there is now some treatment for MOCD. Lack of significant asphyxia insult would help us differentiate this condition from hypoxic ischaemic encephalopathy. Disorders like Biotinidase deficiency and Menkes disease presenting in the first year of life could be suspected by skin (dry) and hair (alopecia in Biotinidase deficiency, coarse kinky hair in Menkes disease).

Late infantile neuronal ceroid lipofuscinosis (Batten's disease) presents with initial seizures in the second year of life with a subtle developmental plateau and visual impairment (retinopathy).

Wilson disease should be considered in a child who presents with movement disorder and behavioural change especially if there is a history of liver disease. Non-epileptic drop attacks in association with extrapyramidal features (ataxia) may suggest Niemann–Pick C disease.

Alpers' syndrome is a rare, but well recognized autosomal recessive disorder, characterized by a clinical triad of psychomotor regression, epilepsy and liver disease. Liver disease in these children is often due to Sodium Valproate.

Important points in history

Present history
Seizures
Cognitive impairment & deterioration in school performance
Gait disturbances: spasticity, ataxia, bradykinesia, dystonia
Personality and behavioural change
Headache and projectile vomiting
Exaggerated startle response
Faltering growth
Feeding difficulties

Birth history
Prematurity
Very low birth weight
Birth asphyxia

Postnatal
Meningitis
Encephalitis
Trauma

Developmental history

Family history
Consanguinity
Early onset deaths
Previous affected siblings

Table 2

Examination: a detailed neurological examination should be done in addition to a general physical and systemic examination as outlined below.

- **General physical examination**: the height, weight, head circumference should be measured and plotted. Faltering growth could be seen in regression secondary to genetic or metabolic causes.

Occipitofrontal circumference: is again a vital parameter. Macrocephaly is seen in Alexander and Canavan disease. An obvious increase in the head circumference compared to the previous centiles would indicate raised intracranial pressure explaining sudden onset regression. Grey matter diseases often cause microcephaly due to brain atrophy.

- **Skin and hair**: dry skin and alopecia are seen in Biotinidase deficiency and abnormal kinky coarse hair in Menkes disease.
- **Dysmorphism:** children with mucopolysaccharidosis have coarse facial features. Those with Zellweger syndrome have a typical craniofacial dysmorphism including a high forehead, a large anterior fontanelle, hypoplastic supraorbital ridges, broad nasal bridge, micrognathia, deformed ear lobes, and redundant nuchal skin folds.
- **Neurological examination:** cognitive impairment is usually quite severe and early in conditions affecting the grey matter. Cerebellar signs and spasticity are noted early in conditions affecting the white matter.
- **Ophthalmic examination:** Fundal examination might show optic atrophy in white matter disease and retinal degeneration in grey matter disease. Cherry red spot on fundus examination is a typical feature of Tay–Sachs. Children with Menkes disease might have ptosis and optic disc pallor. Strabismus may be the presenting symptom of

Neurodegenerative conditions that may present with epilepsy

Infancy	1–5 years	>5 years
Non-ketotic Hyperglycinaemia	Mitochondrial disorders e.g. MERRF, Alpers' syndrome	Niemann–Pick type C
Molybdenum Cofactor Deficiency (MOCD) and isolated sulphite oxidase deficiency	Homocystinuria	Progressive myoclonus epilepsy: MERRF
D-Glyceric aciduria	Late infantile NCL	Lafora body disease
Biotinidase deficiency	Gauchers type III	Unverricht–Lundborg disease Juvenile NCL
Infantile NCL		Sialidoses
Menkes disease		
Krabbe disease		
Tay–Sachs		
Peroxisomal disorders		
Hyperammonaemia		
Organic aciduria		

NCL-neuronal ceroid lipofuscinosis, MERRF-myoclonic epilepsy with ragged red fibres.

Table 3

Infantile Neuronal Axonal Dystrophy. Ptosis and external ophthalmoplegia are seen in children with mitochondrial disorders.

- **Abdominal:** hepatosplenomegaly and signs of liver disease should be looked for.

Examination findings in our case

At the age of seven, her examination showed macular pigmentary changes in both eyes but otherwise normal neurological examination. At the age of 13 years she had paucity of facial expressions, shuffling gait and cogwheel rigidity. She was alert, well oriented and had normal speech. Vision deteriorated gradually along with gait abnormalities. Cognition was normal earlier on with impairment noted since the age of 11years.

Investigations should be tailored according to: history and examination. Deciding which investigation to consider may be a difficult task. Below is a list of investigations, which is not exhaustive, in view of the many metabolic disorders causing regression (Table 4). Some are highly specific and invasive and therefore a high index of clinical suspicion is required to request them.

Genetic tests (microarray, karyotype) may be diagnostic in children with a more static encephalopathy. Tests for Congenital Disorder of Glycosylation (transferrin isoelectric focusing), glucose transporter disorders (CSF glucose) and creatine disorders (MRS and urine) should be considered in this group of children too.

Investigations to consider in a child with developmental regression

MRI brain +/− spine + MRS (lactate/creatine)
Blood
Ammonia
Lactate
Plasma amino acids
VLCFA — Very Long Chain Fatty Acids
Carnitine, acylcarnitine
Copper and ceruloplasmin
Biotinidase
White cell enzymes for GM1/2, Krabbe, MLD etc
Sulphocysteine and uric acid
Urine
Organic acids
Amino acids
Glycosaminoglycan and oligosaccharides
CSF
Lactate, pyruvate
Amino acids with glycine
Glucose
Neurotransmitters and folate
Visual evoked potentials and electroretinogram
Skin/muscle biopsy
Liver biopsy

Table 4

Management in our case

Electrodiagnostic tests showed rod/cone dystrophy.

Abnormal lymphoblasts raised the suspicion of Neuronal Ceroid Lipofuscinosis type 3, which was confirmed on genetic studies.

She had been reviewed regularly in the neurometabolic clinic. She received ongoing care and input from physiotherapy, psychology and special education. At the age of 17years she was referred to adult neurology services.

Management

Developmental regression is a worrying signal. It is almost always pathological and should alert the clinician to an underlying neurodegenerative condition that is often not curable. Goals of management are to provide symptomatic treatment and involve palliative care and family counselling services at an early stage.

Treatment of dystonia, epilepsy, swallowing problems and other comorbidities often necessitate multidisciplinary input from various professionals. Formulating a care plan for the child and communicating this to all professionals involved is of immense benefit to the child and the family. Most hospitals in the UK have passport systems or open access documents in place for such patients. These delineate instructions to ambulance personnel and admitting doctors regarding the treatment required and advance care or end of life wishes.

Ethical and cultural factors play a tremendous role in decision making and parents need to be well supported throughout. Genetic counselling is an invaluable preventive strategy that could define the risk to future pregnancies and offer presymptomatic testing of siblings when necessary.

As emphasized earlier, treatable conditions should be meticulously tested for as early intervention could halt the neurodegenerative process and produce a favourable outcome.

Prognosis

Neurodegenerative disorders are associated with significant morbidity and mortality. Prognosis is guarded and survival rates vary according to the underlying condition. Studies report improvement in survival rates with interventions like gastrostomy.

Future

Advances in research may revolutionize the management of these conditions in the future with the introduction of various therapies like gene therapy, enzyme therapy and stem cell therapy. Enzyme therapy has already its role in the management of non-CNS symptoms of inherited metabolic conditions. Gene therapy involving targeted delivery of therapeutic genes to the neural tissues could possibly modulate and restore neuronal function. Although these therapies are still nascent and pose unique challenges, clinical trials are on the horizon and will advocate their use in managing children with neurodegenerative conditions. ◆

FURTHER READING

1 Michelson DJ, Shevell MO, Sherr EH, et al. Evidence report: genetic and metabolic testing on children with global developmental delay: report

of the Quality Standards Subcommittee of the American Academy of Neurology and the Practice Committee of the Child Neurology Society. *Neurology* 2011; **77:** 1629.

2 Wendy AG, Osann K, Pauline A, et al. Language and other regression: assessment and timing. *J Autism Dev Disord* 2003; **33:** 607—16.

3 Boorstein HC. Regressive and early onset autism spectrum disorders: a comparison of developmental trajectories, autistic behaviors, and medical histories. Dissertations collection for University of Connecticut, 2001, Paper AAI3475517.

4 Poling JS, Fyre RE, Shoffner J, Zimmerman AW. Regression and mitochondrial dysfunction in a child with autism. *J Child Neurol* 2006; **21:** 170—2.

5 Carter J, Scuchman E. Gene therapy for neurodegenerative diseases: fact or fiction. *Br J Psychiatry* 2001; **178:** 392—4.

6 Nanou A, Azzouz M. Gene therapy for neurodegenerative diseases based on lentiviral vectors. *Prog Brain Res* 2009; **175:** 187—200.

7 McMenamin MM, Wood MJA. Progress and prospects: immunobiology of gene therapy for neurodegenerative disease: prospects and risks. *Gene Ther* 2010; **17:** 448—58.

8 Davidovitch M, Glik L, Holtzmann L, Tirosh E, Safir M. Developmental regression in autism: maternal perception. *J Autism Dev Disord* 2000; **30:** 113—9.

9 Johnston M. Neurodegenerative disorders of childhood. In: Behrman RE, Kliegman RM, Jenson HB, eds. Nelson textbook of pediatrics. 17th edn. Saunders, 2004; 2029—33.

Practice points

- Always consider and rule out treatable disorders in any child with regression of milestones
- Developmental regression should prompt an assessment of autism in a child
- Genetic/metabolic causes account for significant proportion of regression in childhood