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Mini Review

Approach to Neurodegenerative Disease in Children: A Short Review

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Abstract

Neurodegenerative disorders of childhood are complicated diseases with wide range of systematic involvement. These diseases often pose great challenge 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. Many inherited metabolic disorders present with neural regression. The clinical approach depends upon the age of presentation, site of involvement in brain. Sound clinical knowledge and better approach leads to early diagnosis, better management and above all genetic counselling. As the medical science is in the track of rapid progression several treatment modalities are in the pipeline for neurodegenerative syndromes, early diagnosis and referral to higher centres can bring a better future to the child.

Keywords: Neurodegenerative Diseases; Hepatomegaly; White Matter; Grey Matter

Introduction

Neurodegenerative disorders of childhood include large, heterogeneous group of diseases that result from specific genetic and biochemical defects, chronic viral infections, and varied unknown causes. The hallmark of a neurodegenerative disease is regression and progressive deterioration of neurologic function with loss of speech, vision, hearing, or locomotion, often associated with seizures, feeding difficulties, and impairment of intellect [1]. The acquisition of new developmental milestones does not exclude the existence of a degenerative disorder. Most degenerative CNS disorders can be divided clinically into three groups: gray-matter diseases, white-matter diseases, and system diseases [1,2].

Classification

Approach to child with marked regression:

Table 1: Area of brain involvement.

Areas of brain involvement [3]	Structural changes	Clinical features	Disease/syndrome
Gray-matter	-lobar gray matter -the basal Ganglia and cerebellar nuclei -ganglion cells of the retina	early onset dementia, progressive loss of Cognitive abilities, myoclonic seizures -extrapyramidal And cerebellar signs, such as ataxia -pigmentary degeneration Of the retina	GM1 gangliosidosis Sandhoffs' disease (GM2 gangliosidosis) NiemannePick C and related disorders Sialidosis Mucopolysaccharidosis (MPS) Gaucher type III
White matter	Abnormal myelin that breaks down rapidly. These "dysmyelinating" disorders are called Leukodystrophies	-the earliest sign spasticity. -Dementia and seizures Can occur, but later -Extrapyramidal signs Rare, but ataxia due to cerebellar pathway involvement -optic atrophy is the most characteristic ocular change - cortical blindness	Metachromatic Leukodystrophy (MLD) Adrenoleukodystrophy (ALD) Krabbe disease Alexander disease Canavan disease Mitochondrial disorders

System	Own signs and symptoms, Depending on the particular neural Pathways involved	Seizures, stereotypic behaviour, irritability, And insomnia, gross delay in milestones	Rett syndrome

a) History: In a patient with developmental regression the history is very vital. Clues for diagnosis lie in the history. 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? Did the child attained milestones before losing it? Which milestones the child lost? In autism and other pervasive developmental disorders regression of language skills is noted first followed by loss of social skills (Tables 1-5).

Table 2: Approach according to age of presentation [4].

Age group	Disease	Hard clinical features
<2 yr with hepatomegaly	Fructose intolerance	Vomiting, hypoglycemia, poor feeding, failure to thrive (when given fructose)
	Galactosemia	Lethargy, hypotonia, icterus, cataract, hypoglycemia (when given lactose)
	Glycogenosis (glycogen storage disease)	Hypoglycemia, cardiomegaly
	Mucopolysaccharidosis types I and II	Coarse facies, stiff joints
	Tay-Sachs disease	Seizures, cherry-red macula, edema, coarse facies
	Gaucher disease (neuronopathic form)	Extensor posturing, irritability
	Carbohydrate-deficient glycoprotein syndromes	Dysmyelination, cerebellar hypoplasia
	Zellweger syndrome	Hypotonia, high forehead, flat facies
<2 yr without hepatomegaly	Krabbe disease	Irritability, extensor posturing, optic atrophy, and blindness
	Rett syndrome	Girls with deceleration of head growth, loss of hand skills, hand wringing, impaired language skills, gait apraxia
	Maple syrup urine disease	Poor feeding, tremors, myoclonus, opisthotonos
	Phenylketonuria	Light pigmentation, eczema, seizures
	Menkes kinky hair disease	Hypertonia, irritability, seizures, abnormal hair
	Subacute necrotizing encephalopathy of Leigh disease	White matter disease
	Canavan disease	White matter disease, macrocephaly
	Neurodegeneration with brain iron accumulation disease	White matter disease, movement disorder
2-5 yrs	Niemann Pick disease types III and IV	Hepatosplenomegaly, gait difficulty
	Wilson disease Liver disease	Kayser-Fleischer ring; deterioration of cognition is late
	Gangliosidosis type II	Gray matter disease
	Neuronal ceroid lipofuscinosis	Gray matter disease
	Mitochondrial encephalopathies	myoclonic epilepsy with ragged red fibers [MERRF])
	Ataxia telengactasia	Basal ganglia disease
	Huntington disease (chorea)	Basal ganglia disease
	Neurodegeneration with brain iron accumulation syndrome	Basal ganglia disease
	Adrenoleukodystrophy	White matter disease, behavior problems, deteriorating school performance, quadriparesis
	Metachromatic leukodystrophy	White matter disease

5-15yrs	Multiple sclerosis	White matter disease
	Neuronal ceroid lipofuscinosis, juvenile and adult (Spielmeyer-Vogt and Kufs disease)	Gray matter disease
	Schilder disease	White matter disease, focal neurologic symptoms
	Refsum disease	Peripheral neuropathy, ataxia, retinitis pigmentosa
	Sialidosis II, juvenile form	Cherry-red macula, myoclonus, ataxia, coarse facies
	Subacute sclerosing panencephalitis	Diffuse encephalopathy, myoclonus; may occur years after measles

Table 3: Treatable conditions with neural regression [5] loss of social skills.

Biotinidase deficiency
Wilson disease
NiemannePick 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 4: Specific pointers in history.

History	Points to be asked
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	Decrease intrauterine movements
	Prematurity
	Very low birth weight
	Birth asphyxia
	Neonatal jaundice
	Birth trauma
	Neonatal hypoglycaemia
	Neonatal seizures
Developmental history	
Family history	Consanguinity
	Early onset deaths
	Previous affected siblings

Table 5: Individual disease and clues for diagnosis.

Disease	Clinical clue	Investigation	Treatment
Fructose intolerance [6]	Vomiting, Hypotonia, FTT Neuropathy, Hepatomegaly More symptoms with fructose diet	a fructose tolerance test gene sequencing	Exclusion of fructose from diet
Galactosemia [7]	Lethargy, hypoglycemia hypotonia, jaundice, cataract, seizure, ataxia, hepatomegaly, FTT	Beutler's test and the Hill test NBS, CVS	eliminating lactose and galactose from the diet.
Glycogenosis (glycogen storage disease) [8]	Hypoglycemia, cardiomegaly FTT, muscle disease hepatomegaly	Liver biopsy Genetic testing	Enzyme replacement therapy for GSD-II Symptomatic management
Mucopolysaccharidosis types I and II [9,10]	Hurler (type-I): coarse facies, vertebral anomaly, cloudy cornea Hunter (type-II): coarse facies, clear cornea, bone changes	Clinical features Enzyme assay	Enzyme replacement Bone marrow transplant
Tay-Sachs disease [11]	cognitive and motor skill deterioration, dysarthria, dysphagia, ataxia, and spasticity	enzyme assay of hexoaminidase	symptomatic
Gaucher disease (neuronopathic form) [12]	Hepatosplenomegaly Pancytopenia, bone pain, seizure, osteoporosis	Enzyme testing for glucocerebrosidase	Enzyme replacement therapy
Zellweger syndrome [13]	Syndromic facies, hypotonia, seizure, apnea, cartilage disease	elevated very long chain fatty acids	LCT, Lorenzo oil, diet restriction, fat soluble vitamins
Krabbe disease [14]	irritability, fevers, limb stiffness, seizures, feeding difficulties, vomiting, slowing of mental and motor development	multinucleated globoid cells, nerve demyelination and degeneration	Bone marrow transplantation, symptomatic treatment
Rett syndrome [15,16]	Cognitive skill loss, seizure, muscle weakness, autistic behaviour	Clinical features MECP2 mutation	Symptomatic treatment
Maple syrup urine disease [17]	sweet-smelling urine, hallucinations, anorexia, weight loss, anemia, diarrhea, vomiting, dehydration	plasma amino acid measurement,	Symptomatic, diet control
Phenylketonuria [18]	Hypopigmentation, intellectual disability, microcephaly, seizures, musty mousy order of skin	New born screening test Tendem mass spectrometry	PKU Diet, symptomatic treatment
Menkes kinky hair disease [19]	Developmental delay, irritability, fragile hypopigmented hair, FTT, Seizure, osteoporosis	copper and ceruloplasmin levels, skin biopsy, and optical microscopic examination of the hair Urine homovanillic acid/ vanillylmandelic acid ratio	Copper supplement Symptomatic treatment
Subacute necrotizing encephalopathy of Leigh disease [20]	Hypotonia, ataxia, diarrhea, vomiting, opthalmoparesis, nystagmus, peripheral neuropathy	Serum lactate raised, genetic testing	Succinic acid, thiamine, sodium citrate, bicarbonate Symptomatic treatment
Canavan disease [21]	intellectual disability, feeding difficulties, abnormal muscle tone, poor head control, and megalocephaly. Paralysis, blindness, seizures	high concentration of N-acetylaspartic acid (NAA) in the urine, molecular genetic testing	Treatment is symptomatic
Neurodegeneration with brain iron accumulation disease [22]	Pyramidal, extrapyramidal features, cognitive decline, optic atrophy, retinal degeneration, seizures	MRI of brain	Symptomatic treatment
Niemann Pick type C [23]	Hepatosplenomegaly, dysarthria, ataxia, dystonia, seizures	Clinical features genetic study	Symptomatic In NPC-Miglustat [24]
Wilson disease Liver disease [25]	neuropsychiatric features, dystonia, KF Ring,	Serum ceruloplasmin, urinary copper	Zinc, penicillamine, symptomatic treatment
Gangliosidosis type II [26]	skeletal abnormalities, seizures, profound intellectual disability, vision loss, distinctive facial features	Genetic testing	Symptomatic treatment

Neuronal ceroid lipofuscinosis [27]	vision loss due to retinal dystrophy, with seizures, psychological degeneration	Eye test, enzyme assay, skin tissue sampling	Gene therapy, stem cell therapy, flupirtine [28], cystagon [29]
Ataxia telengactasia [30]	Ataxia, occulomotor apraxia, telengiectasia, repeated infections, multiple malignancy	Raised AFP, low level IgA, IgE, Chromosomal assay, MRI	Symptomatic treatment
Huntington disease [31] (chorea)	poor academic performance, or evident regression in cognitive and language skills, chorea, behavioural anomaly, seizure	Genetic testing for CAG repeats	symptomatic
Adrenoleukodystrophy [32]	Musclestiffness, paraparesis, dementia, progressive neuropathy, autonomic features, addisons disease	New born screening, plasma VLCFA	gene therapy dietary therapy, symptomatic management
Metachromatic leukodystrophy [33]	muscle wasting and weakness, muscle rigidity, developmental delays, progressive loss of vision leading to blindness, convulsions, impaired swallowing, paralysis, and dementia. late infantile form, which is the most common form of MLD	An ARSA-A enzyme level blood test with a confirming urinary sulfatide test is the best biochemical test for MLD	Symptomatic treatment
Subacute sclerosing panencephalitis (SSPE) [33]	primary measles infection followed by several asymptomatic years (6-15 on average), and then gradual, progressive psychoneurological deterioration, consisting of personality change, seizures, myoclonus, ataxia, photosensitivity, ocular abnormalities, spasticity, and coma.	periodic activity (Rademecker complex) in EEG elevated anti-measles antibody (IgG) in the serum and cerebrospinal fluid, and typical histologic findings in brain biopsy	oral isoprinosine) combined with intrathecal or intraventricular interferon alpha [34,35]

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