Clinical approach to children with suspected neurodegenerative disorders

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ABSTRACT

Inherited neurodegenerative disorders are common in the Kingdom of Saudi Arabia as a result of the high rate of consanguinity. This is a complex field with a multitude of different disorders characterized by a variety of clinical manifestations, complex molecular biology, and a long list of potential investigations. As a result, this is often a confusing and difficult area for non-specialists, resulting in delays in reaching the diagnosis. Reaching a specific diagnosis is of clear importance for providing appropriate therapy, prognosis, and genetic counseling. This paper is intended to provide a simplified practical approach to guide residents and generalists in the initial diagnostic evaluation of children with suspected neurodegenerative disorders. Emphasis is placed on useful clinical signs, diagnostic tips, potential pitfalls, and recent advances in therapy.

Keywords: Nervous system, degenerative, diagnosis, child, inherited, evaluation.

Neurosciences 2002; Vol. 7 (1): 2-6

Inherited neurological disorders are common in the Kingdom of Saudi Arabia as a result of the high rate of consanguineous marriages, which is a common traditional practice followed within certain sectors of the community.[1,2] This practice led to the high prevalence of many neurodegenerative disorders (NDD), which may become more common in the future.[1] The evaluation of children with suspected NDD requires good background knowledge, accurate assessment, and formulation of a list of differential diagnoses. The initial clinical assessment would guide the physician in requesting the required laboratory investigations in order to reach a specific diagnosis. Reaching a specific diagnosis is of clear importance for providing appropriate therapy, prognosis, and genetic counseling.

Many students, residents, and fellows consider neurologic disorders, particularly NDD, difficult to master. Studies have documented that generalists are less confident in handling neurological patients than patients with other medical conditions.[3,4] More than 50% of general pediatricians referred most of their patients with neurologic complaints to neurologists.[4] These findings reflect the diversity and complexity of various neurological disorders. Neurodegenerative disorders are discussed to variable extent in most pediatric textbooks, and in more detail in every pediatric neurology textbook. In fact, there are certain books designated only for inherited NDD in children.[5] However, a concise and simple outline with practical tips to facilitate the diagnosis of various NDD is lacking. Different classification systems exist making these disorders confusing to most physicians. In this paper we will present a practical diagnostic approach based on the medical literature and the author's personal experience. Important diagnostic tips and possible pitfalls will be discussed, as well as updates in terms of the diagnostic and therapeutic interventions.

The initial evaluation of children with suspected neurodegenerative disorders. The evaluation of children with suspected NDD starts with a comprehensive history taking followed by detailed physical examination. Diagnostic labels should not

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be taken for granted, as misdiagnosis is not uncommon. This is particularly true for cerebral palsy, a term loosely applied to children with various chronic neurological disorders.[6] We frequently encounter children diagnosed with cerebral palsy who end up having a progressive central nervous system (CNS) disorder. After taking the history and examining the child, formulation of a list of differential diagnoses is an essential first step in formulating a diagnostic hypothesis that directs further laboratory investigations.

A list of important NDD and their inheritance patterns is shown in **Tables 1 & 2.** These disorders may have predominant white matter involvement (central, peripheral demylination, or both) or gray matter involvement (neuronal loss or dysfunction). Important differentiating features between the 2 groups are summarized in **Table 3.** Although clinically useful, this distinction is somewhat arbitrary as many NDD have mixed white and gray matter involvement particularly in the later stages of the disease, such as secondary demylination following progressive neuronal loss and secondary neuronal loss following progressive demylination. As well, classification schemes are changing with the recent advances at the molecular and cellular levels. Most NDD are now regrouped under specific disease categories according to the defected cellular component. Examples include Peroxisomal disorders (Adrenoleukodystrophy, Zellweger syndrome, Refsum disease), Lysosomal disorders (Krabbe leukodystrophy, Metachromatic leukodystrophy), and Mitochondial disorders (MELAS, Kearns-Sayre syndrome). However, the distinction between predominantly gray and white matter NDD remain clinically useful in narrowing the differential diagnosis list, examining for associated and complicating features, and guiding the initial laboratory investigations **(Table 3).**

History taking. Findings supporting the diagnosis of NDD include an uneventful pregnancy and delivery of a normal full term infant. Postnatal complications such as kernicterus, meningitis, and head trauma should be excluded. Family history of neurological disorders and early or unexplained deaths may indicate an undiagnosed inherited NDD. The nature of the neurological manifestations should be clarified. Detailed developmental history is needed. The distinction between static (non-progressive) and progressive clinical course is very important. Classically, loss of previously acquired milestones (regression) marks the onset of most NDD with subsequent progressive neurological deterioration. However, some NDD or metabolic disorders have a slow rate of progression and can be misdiagnosed as cerebral palsy.[6] Therefore, clear developmental regression may not be evident, particularly in the early stages of the disease or at a younger age of onset. Beware that the neurological consequences of fixed congenital lesions or insults may be delayed for several months because of the immaturity of the nervous system.[7]

Developmental regression does not occur solely in children with genuine NDD. Behavioral syndromes such as attention deficit hyperactivity disorder (ADHD), autism, and pervasive developmental disorders may result in developmental regression, simulating NDD.[5] Other neuropsychiatric disorders such as depression and child neglect may also result in developmental regression.[5] Finally, visual

Table 1 - Groups of neurodegenerative disorders and their inheritance patterns.

Neurodegenerative disorders	Inheritance patterns
Disorders predominantly involving the white matter	
Canavan disease	Autosomal recessive
Alexander disease	Sporadic
Krabbe Leukodystrophy	Autosomal recessive
Metachromatic Leukodystrophy	Autosomal recessive
Pelizaeus Merzbacher disease	X linked recessive
Adrenoleukodrystrophy	X linked recessive
Multiple Sclerosis	Sporadic
Disorders predominantly involving the gray matter	
Menkes kinky hair syndrome	X linked recessive
Symptomatic progressive myoclonic epilepsies (such as Unverricht-Lundborg disease, lafora disease)	Autosomal recessive
Progressive infantile poliodystrophy	Autosomal recessive
Sialidosis (Type I)	Autosomal recessive
Neuronal ceroid lipofuscinosis	Autosomal recessive
Mitochondrial encephalopathies	Variable

Table 2 - Neurodegenerative disorders with preferential central nervous system involvement.

Neurodegenerative disorders	Inheritance patterns
Disorders predominantly involving the basal ganglia	
Juvenile Huntington disease	Autosomal dominant
Dystonia musculorum deformans	Autosomal dominant
Hallervorden Spatz disease	Autosomal recessive
Wilson disease	Autosomal recessive
Spinocerebellar degeneration and related conditions	
Friedreich Ataxia	Autosomal recessive
Spinocerebellar ataxia	Autosomal dominant
Olivopontocerebellar atrophy	Autosomal dominant
Roussy Levy disease	Autosomal recessive
Spastic paraplegia	
Familial Spastic paraplegia	Autosomal dominant
Peripheral neuropathy	
Spinal muscular atrophy	Autosomal recessive
Infantile neruoaxonal dystrophy	Autosomal recessive
Charcot Marie Tooth Disease	Autosomal dominant
Refsum Disease	Austosomal recessive

impairment, hearing loss, and intractable epilepsy may interfere with the ability of the child to perceive and utilize the multitude of environmental inputs necessary for normal development, resulting in failure of developmental progression and achievement of milestones (such as speech, motor, and cognitive arrest). Therefore, a thorough history is very important for the proper assessment of any child with developmental regression and exclusion of other disorders that may simulate NDD. It is needless to say that the approach, management, and prognosis of these disorders are completely different.

Clinical examination. The neurological examination may be normal in the early stages of some NDD. Behavioral symptoms (such as ADHD) may be the initial manifestation of certain NDD, specifically metachromatic leukodystrophy, juvenile adrenoleukodystrophy, and subacute sclerosing panencephalitis, but will all eventually manifest clinical signs with careful follow-up. Careful neurological examination should be performed in any child with behavioral problems to detect early neurological signs. The main differentiating features of predominantly white or gray matter NDD are summarized in **Table 3.** The head circumference should be measured and plotted on age appropriate percentile charts. Megalencephaly is an important feature of certain white matter disorders (such as Canavan and Alexander disease). Microcephaly is a usual feature of many gray matter disorders due to progressive neuronal loss. Examination of the skin and hair can be of diagnostic value in certain metabolic disorders such as Hartnup disease (pellagra-like skin rash) and Menkes disease (kinky hair or pili torti under the microscope). The skin and nervous system have the same embryological origin (ectoderm). Therefore, developmental CNS disorders may have associated skin signs such as neurocutaneous disorders.[8] Some of these disorders may result in progressive loss of CNS function (such as Sturge Weber syndrome). Examination of the spine for deformities, particularly scoliosis, is important to exclude these commonly associated complications. Examination for dysmorphic features is needed, as some NDD may have associated facial dysmorphism (such as Zellweger syndrome, Neonatal Adrenoleukodystrophy).[9] Gargoyle-like facial features are characteristic of mucopolysaccharidosis and oligosaccharidosis. Careful and full neurological examination is needed in all children with suspected NDD. Examination of eyes (the window of the brain) may give important diagnostic information as shown in **Table 4.** In general, white matter disorders may result in optic atrophy (demylination) while gray matter disorders may result in retinal degeneration, as retinal receptors are in fact neuronal cells. Other system examination may provide important clues to the diagnosis. Hepatomegaly, splenomegaly, or both are evident in the neurovisceral sphingolipidosis, mucopolysaccharidosis, peroxisomal, and mitochondrial disorders.[10] Cardiopathy occurs in

Table 3 - Differentiation between predominantly white and gray matter neurodegenerative disorders.

Differentiating features	White matter disorders	Gray matter disorders
Age of onset	Usually late (childhood)	Usually early (infancy)
Head size	May have megalencephaly	Usually microcephaly
Seizures	Late, rare	Early, severe
Cognitive functions	Initially normal	Progressive dementia
Peripheral neuropathy	Early demyelination	Late, axonal loss
Spasticity	Early, severe	Later, progressive
Reflexes	Absent (neuropathy) or exaggerated (long tracts)	Normal or exaggerated
Cerebellar signs	Early, prominent	Late
Fundal examination	May show optic atrophy	Retinal degeneration
EEG	Diffuse delta slowing	Epileptiform discharges
EMG	Slowed nerve conduction velocity	Usually normal
Evoked potentials (VEP, ABR)	Prolonged or absent	Usually normal
ERG	Normal	Abnormal

EEG=electroencephalogram, EMG=electomyography, VEP=visual evoked potential, ABR= auditory brain stem response, ERG=electroretinogram

Table 4 - Specific ocular abnormalites in different neurodegenerative disorders.

Disorder or groups of disorders	Ocular abnormalities
Peroxisomal disorders	Optic atrophy
GM1, GM2, Niemann-Pick disease	Cherry red spot
Leukodystrophies	Optic atrophy
Mitochondrial disorders	Pigmentary retinal degeneration
Mucopolysaccaridosis	Corneal clouding
Mucoplipidosis	Corneal clouding
Ataxia-telengiectasia	Conjunctival telangiectasia
Cockayne syndrome	Lenticular opacities (cataracts)
Wilson disease	Kayser-Fleisher corneal ring
Niemann-Pick disease (type C, D)	Vertical gaze palsy
Kearns-Sayre syndrome	Progressive external ophthalmoplegia
Pelizaeus-Merzabacher disease	Pendular nystagmus

GM1, GM2 - Gangliosidoses 1 & 2

mitochondrial disorders, friedreich ataxia, and mucopolysaccharidosis. Features of progressive renal failure are evident in fabry disease, sialidosis II, and Lowe syndrome.

Investigations. Investigations of children with NDD are directed towards identifying the underlying diagnosis and examining associated complications (such as seizures) as shown in **Tables 3 & 5.** The findings on history and physical examination will guide the physician in selecting the required laboratory investigations. Basic blood works may prove useful in certain disorders. Complete blood count may reveal pancytopenia in certain organic acidopathies (such as isovaleric, proprionic, and methylmalonic acidemias). Blood film may show vacuolated lymphocytes in neuronal ceroid lipofuscinosis, fucosidosis, and sialidosis. Acanthocytosis are characteristic of choreoacanthocytosis, abetalipoproteinemia, and hallervorden-spatz disease. Blood gas analysis will detect metabolic acidosis in many metabolic disorders such as organic acidopathies, urea cycle disorders, and mitochondrial encephalopathies. Serum electrolyte abnormalities may result from adrenal insufficiency in adrenoleukodystrophy. Liver function tests are disturbed in neurovisceral sphingolipidosis and certain gray matter NDD (such as progressive infantile poliodystrophy). Renal function tests and urinalysis may reveal tubular dysfunction (Lowe syndrome, Wilson disease), nephrotic syndrome (storage diseases), or renal failure (fabry disease, sialidosis II, and Lowe syndrome). Chest x-ray may reveal cardiomegaly in early mitochondrial disorders, friedreich ataxia, and mucopolysaccharidosis. Electrocardiogram could identify conduction abnormalities that may complicate some of these disorders (such as refsum disease). Skeletal survey may reveal specific bony abnormalities such as dysostosis multiplex in mucopolysaccharidosis. Neuroimaging, particularly brain magnetic resonance imaging (MRI), is critical in all children with suspected NDD. Characteristic MRI features are noted in several white and gray matter NDD including; Alexander disease, Leigh disease, and Hallervorden-Spatz disease. Neuroimaging would exclude slow growing brain tumors, which may result in developmental regression simulating NDD. Magnetic resonance imaging would also identify developmental abnormalities and malformations. Patients with peroxisomal disorders (Zellweger disease) have associated cortical neuronal migration abnormalities and agenesis of corpus callosum. Serum ammonia, lactate, pyruvate, amino acids, and urine for amino acids and organic acids would screen for most amino acid disorders, organic acidopathies, and urea cycle abnormalities. Frequently, specific diagnostic tests and enzyme assays are needed to reach a definitive diagnosis. These specialized tests are summarized in **Table 5.** The physician should be selective and never

Table 5 - Specific diagnostic tests of some important neurodegenerative disorders.

Neurodegenerative disorders	Diagnostic test
Canavan disease	N-acetylaspartic acid (urine)
Alexander disease	β-crystallin (CSF)
Krabbe leukodystrophy	β-galactosidase (leukocytes/fibroblasts)
Metachromatic leukodystrophy	Arylsultatase A (leukocytes/fibroblasts)
Adrenoleukodystrophy	Very long chain fatty acids (VLCFA)
Mucopolysaccaridosis	Mucopolysaccarides (urine)
Mucolipidosis	Oligosaccharides (urine)
Menkes kinky hair syndrome	Serum copper and ceruloplasmin
Lafora disease	Skin biopsy (intracytoplasmic lafora bodies)
Sialidosis (Type 1)	α-neuraminidase (leukocytes/ fibroblasts)
Neuronal ceroid lipofuscinosis	Skin, conjunctival, or rectal biopsy
Mitochondrial encephalopthies	Lactate (CSF/blood), muscle biopsy
Wilson disease	Urine copper, serum copper and ceruloplasmin
Friedreich ataxia	DNA studies (blood)
Spinal muscular atrophy	Muscle biopsy, DNA studies (blood)
Infantile neuroaxonal dystrophy	Nerve biopsy
Charcot Marie Tooth disease	Nerve biopsy, DNA studies (blood)
Refsum disease	Phytanic acid (blood)
Lesch-Nyhan disease	Hyperuricuria and hyperuricemia

DNA=deoxyribonucleic acid, CSF=cerebro spinal fluid, VLCFA=very long chain fatty acid

Table 6 - Specific treatment of some important neurodegenerative disorders.

Neurodegenerative disorders	Specific treatment modality
Krabbe leukodystrophy	Bone marrow transplantation
Metachromatic leukodystrophy	Bone marrow transplantation
Adrenoleukodystrophy	Glyceryl trioleate and trierucate, steroids for adrenal insufficiency, diet low in VLCFA, bone marrow transplantation
Mucopolysaccaridosis	Bone marrow transplantion, recombinant human α-L-iduronidase
Menkes kinky hair syndrome	Copper sulfate
Mitochondrial encephalopathies	Nicotinamide, riboflavin, dichloroacetate, L-carnitine, CoQ10
Wilson disease	D-penicillamine, trietine, zinc acetate, liver transplantation
Refsum disease	Reduction of phytanic acid intake
Lesch-Nyhan disease	Allopurinol
Fabry's Disease	Recombinant human α galactosidase A

VLCFA=very long chain fatty acid, CoQ10=Coenzyme Q 10

use routine or screening tests, as most of these tests are quite expensive. They will frequently involve skin fibroblast culture, CSF examination, DNA studies, nerve, or muscle biopsy. Reaching a specific diagnosis is very important for providing appropriate therapy, prognosis, and genetic counseling. When possible, prenatal diagnosis can be offered in subsequent pregnancies. Specific enzyme levels can be measured in cultures of chorionic villus or amniocytes, but may not be entirely reliable. The use of molecular analysis and specific DNA mutations could improve the accuracy of prenatal diagnosis.

Treatment. Treatment of children with NDD is directed towards the underlying disorder, other associated features, and complications. The treatable complications include; epilepsy, sleep disorder, behavioral symptoms, feeding difficulties, gastro-esophageal reflux, spasticity, drooling, skeletal deformities, and recurrent chest infections. These children require a multidisciplinary team approach with the involvement of several specialties including pediatrics, neurology, genetics, orthopedics, physiotherapy, and occupational therapy. Many newer antiepileptic drugs are now available to treat intractable epilepsy.[11] Melatonin, 3mg at bedtime, has been documented to regulate the sleep-wake cycle, particularly in those with visual impairment.[12] Lioresal or diazepam may relieve spasticity, improve motility of the limbs, and combat pain. Specific treatments to counteract the offending metabolite, replace the dysfunctional enzyme, or vitamin therapy are summarized in **Table 6.** Significant advances have been made in regards to specific treatment of NDD. Allogeneic bone marrow transplantation could provide an exogenous source of normal enzymes in several lysosomal storage diseases **(Table 6).** Recombinant human α-L-iduronidase has been recently shown to be effective in ameliorating some clinical manifestation of mucopolysaccharidosis.[13] Counseling the families and educating the public about these potentially preventable disorders is very important in the management of these children. Consanguinity needs to be strongly discouraged in order to prevent most NDD in our region.

In conclusion, we presented a practical diagnostic approach to children with suspected neurodegenerative disorders. Important diagnostic tips and possible pitfalls were discussed. Updates in terms of diagnostic and therapeutic interventions were also presented. Although many students, residents, and generalists will continue to have difficulties in mastering various NDD, we hope that this concise and simple outline with the aid of their ongoing experience will facilitate in better handling and less delays in reaching the diagnosis of children with various NDD. Reaching a specific diagnosis is of paramount importance for providing accurate therapy, prognosis, and genetic counseling.

Counseling the families and educating the public about these potentially preventable disorders is very important. A national campaign to increase the public awareness about these devastating disorders and discourage consanguineous marriages is urgently needed in our region.

Acknowledgments. The author gratefully acknowledges the helpful comments made on a draft of the manuscript by Dr. Timothy J. Watson, BSc, MD, FRCPC.

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