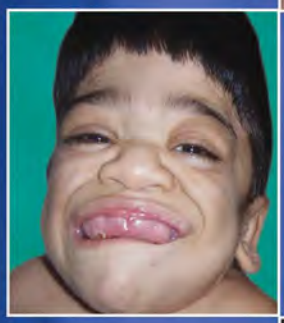
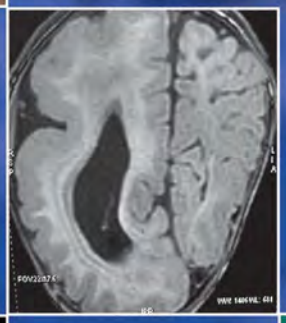
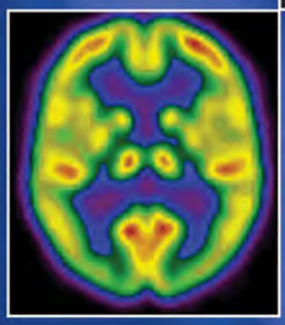
Frontiers in PEDIATRIC NEUROLOGY







Editor-in-Chief
TM Ananda Kesavan

Foreword
MKC Nair

JAYPEE

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CHAPTER 4

Approach to Neurodegenerative Disorders

PA Mohammed Kunju

INTRODUCTION

Most genetic causes of neurodegenerative disorders in childhood are due to neurometabolic disease. There are over 200 disorders including amino acidopathies, creatine disorders, mitochondrial cytopathies, peroxisomal disorders and lysosomal storage disorders.[1] However, diagnosis can pose a challenge to the clinician when patients present with non-specific problems such as epilepsy, developmental delay, autism, dystonia and ataxia.

Usually, neurodegenerative disorders are suspected when there is a decline in the neurological function or there is a regression of developmental milestones.[2]

However, a static (cerebral palsy like) presentation with atypical neurological features and systemic manifestations also must be a situation for directed investigation for neurometabolic disorder.[3]

Presentation will depend on the area of neuraxis involvement **(Table 4.1)**.

Dementia like presentation (psychomotor retardation) seen when there is diffuse affection and restricted affection produces progressive neurological deficit like progressive ataxic syndrome (e.g. spinocerebellar ataxia), paraplegia (e.g. hereditary spastic paraplegia), or peripheral neuropathy (e.g. hereditary motor sensory neuropathy).

CLINICAL CLUES OF NEURODEGENERATIVE DISORDERS

Following are some of the clinical clues:[4,5]

- Gradually progressive
- Symmetrical affection
- No signs of increased intracranial pressure
- No inflammatory response (no fever)
- Positive family history or consanguinity
- Recurrent coma and vomiting
- Recurrent ataxia or spasticity
- Mental retardation without congenital anomalies
- Associated somatic manifestations.

So after a thorough clinical examination specific neuroimaging and biochemical/molecular tests can be utilized for the diagnosis of neurodegenerative disorders.

Even though inherited metabolic disorders are rare causes of neurologic disease, they should always be considered because many are treatable currently.[6-8]

The characteristics of treatable metabolic disorders are:

- Abrupt onset, episodic relapses and nonspecific clinical/physical features.
- Many are identified through newborn screening programs and thus paves the way for preventive/therapeutic strategies.

Table 4.1 Clinical differentiation of neurodegenerative disorders

Acute encephalopathy (Due to accumulation of small molecules)
- *Symptoms*
  - Recurrent vomiting, poor feeding, lethargy, dehydration
  - Seizures, coma
- Rapidly progressive course or episodic
- No other specific signs; so investigations only differentiate them

Chronic encephalopathy (Due to accumulation of large molecules)
- Late infancy, children, adolescents
- *Symptoms*: Depends on gray matter (GM) or white matter (WM) involvement
  - *Gray matter symptoms:*
    - *Cortical gray matter:*
      a. Dementia
      b. Seizures
      c. Fundus showing cherry red spot or retinitis pigmentosa
      d. Affection of other organ systems
    - *Deep gray matter:*
      a. Dystonia
      b. Choreoathetosis
  - *White matter symptoms:*
    - Spasticity
    - Ataxia
    - Fundus showing optic atrophy
- Gradually progressive
- Specific symptoms and signs may help in clinical differentiation
- Treatable conditions are less

INHERITANCE

Generally, neuromuscular diseases (NMDs) are inherited in an *autosomal recessive* manner. Knowing just the exceptions will help one in remembering the inheritance pattern.

- Exceptions of carbohydrate metabolism—with X-linked recessive (XLR) inheritance—Liver phosphorylase kinase deficiency, Phosphoglycerate kinase deficiency
- Exceptions of lipidoses—XLR; Fabry's disease
- Exceptions of protein metabolic disorders—XLR; Lesch-Nyhan syndrome
- Exceptions of mucopolysaccharidoses (MPS)—XLR; Hunter's syndrome
- Exceptions of urea cycle disorder—XLR; OTC deficiency (ornithine transcarbamylase deficiency).

Autosomal dominant: For example, acute intermittent porphyria, familial hypercholesterolemia.

Progressive neurological manifestation can occur as complications of neurocutaneous syndromes which are *autosomal dominantly* inherited. Exceptions to that general rule are incontinentia pigmentii (X-linked dominant) and Sturge-Weber syndrome (sporadic occurrence).

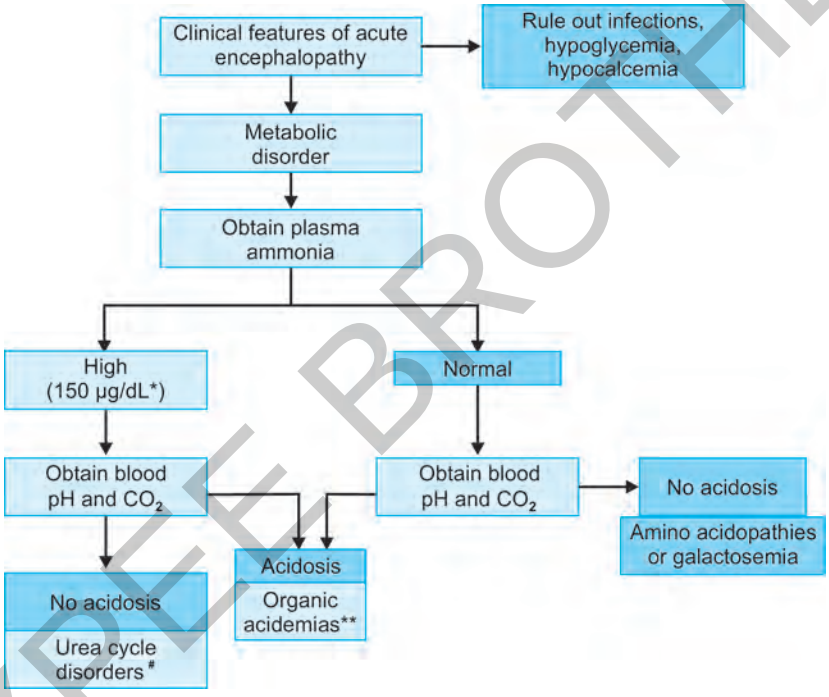
Approach to a child with acute encephalopathy (small molecule disorders):

- The small molecule disorders are caused by defects in pathways of intermediary metabolism either due to an enzyme deficiency or a cofactor defect (compared to the organelle disorders exemplified by lysosomal storage diseases or peroxisomal disorders). Mainly they are due to defects in amino acid metabolism: organic acidemias (OAs), aminoacidopathies, and urea cycle defects.
- A neonate affected with an OA is usually well at birth and for the first few days of life. The usual clinical presentation is that of toxic encephalopathy and includes vomiting, poor feeding, neurologic symptoms such as seizures and abnormal tone, and lethargy progressing to coma. Outcome is enhanced by diagnosis and treatment in the first ten days of life. In the older child or adolescent, variant forms of the OAs can present as loss of intellectual function, ataxia or other focal neurologic signs, Reye syndrome, recurrent ketoacidosis, or psychiatric symptoms.
- In the setting of an acute encephalopathy, intractable seizures or seizures occurring in sibships, consider an NMD in parallel with more common disorders, especially if fever is not a major symptom.
- Serum and urine metabolic screening **(Table 4.2)** will detect many small molecule disorders. This includes serum ammonia and blood gas analysis for acidosis as the first step. Other associated findings, such as respiratory alkalosis or hypoglycemia with or without ketosis, can narrow the diagnostic possibilities further. Specific diagnosis is possible by doing serum aminogram (for aminoacidopathies) and plasma acyl carnitine and urine organic acids (for organic acidurias).

Table 4.2 Screening tests in acute encephalopathy and the usefulness

Urine/serum	*Conditions identified*
Serum ammonia	Urea cycle disorders (UCDs)[9]
Ammonia and arterial blood gas	Organic aciduria
Serum aminogram	Aminoaciduria, urea cycle disorders, organic aciduria
Urine organic acids	Organic aciduria, aminoacidurias
Plasma acylcarnitine	Organic acidurias

Flow chart 4.1 Stepwise approach for a baby with acute encephalopthy (small molecule disorders)



* 150 µg/dL in neonates, 70 µg/dL in infants to age one month, 35–50 µg/dL in older children and adults
**Organic acidemias can be differentiated by looking for presence of ketosis
See text for steps

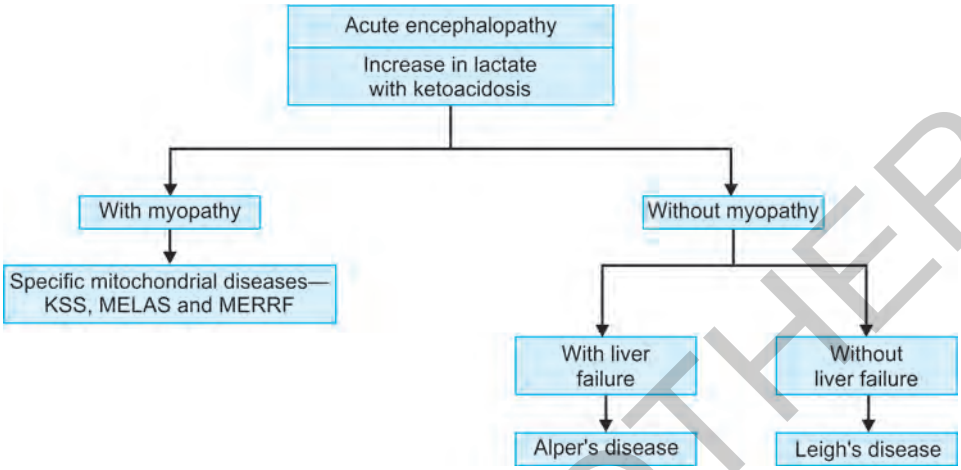
- If *ketosis is present* with abnormal urine odor consider maple syrup urine disease (MSUD) and without urine odor—methyl malonic acidemia and propionic acidemia (with *neutropenia*)
- With ketosis and skin manifestations like alopecia—multiple carboxylase deficiency
- If *ketosis is not present* with sweaty feet odor—Isovaleric acidemia.
- Organic acidemias without ketosis are glutaric acidemia and Acyl-CoA dehydrogenase deficiency

Following is a step wise approach for a baby presenting with *acute encephalopathy* **(Flow charts 4.1 and 4.2)**.

Urea cycle disorders (UCDs) can be differentiated by serum amino acid estimation:

- *Increased arginine* level means arginase deficiency which can be confirmed by red cell enzyme assay
- *Increased citrulline* level means ASS or ASL (elevated arginosuccinate level) deficiency

Flow chart 4.2 Stepwise approach for a baby with acute encephalopathy (when lactic acidosis is detected)



Abbreviations: KSS, Kearns-Sayre syndrome; MELAS, mitochondrial encephalomyopathy, lactic acidosis, and stroke-like episodes; and MERRF, myoclonic epilepsy with ragged-red fibers

which can be confirmed by fibroblast enzyme assay.
  - In ASL deficiency elevated arginosuccinate level is seen
- *Low citrulline or arginine* level seen in ornithine transcarbamylase (OTC) or CPS I deficiency; which can be differentiated by urinary orotic aciduria.
  - Orotic aciduria is seen in OTC deficiency
- Final confirmation of acute encephalopathy is possible by
  - Detection of organic acid, aminoacid, and sulfites in urine
  - Detection of specific enzyme deficiency or DNA analysis in WBC and fibroblasts
  - *Clinical distinction* between various diseases coming under each category is not possible
  - Histologic evaluation of affected tissues such as skin, liver, brain, heart, kidney, and skeletal muscle may help but not foolproof.

ORGANIC ACID DISORDERS

The "organic acidemia" or "organic aciduria" (OA) are disorders characterized by the urinary excretion of non-amino organic acids in urine. The majority are caused by abnormal amino acid catabolism of branched-chain amino acids or lysine.

They include:
- Maple syrup urine disease (MSUD)
- Propionic acidemia
- Methylmalonic acidemia (MMA)
- Methylmalonic aciduria-homocystinuria
- Isovaleric acidemia
- Biotin-unresponsive 3-methylcrotonyl-CoA carboxylase deficiency
- 3-hydroxy-3-methylglutaryl-CoA (HMG-CoA) lyase deficiency
- Ketothiolase deficiency
- Glutaric acidemia type I (GA I).

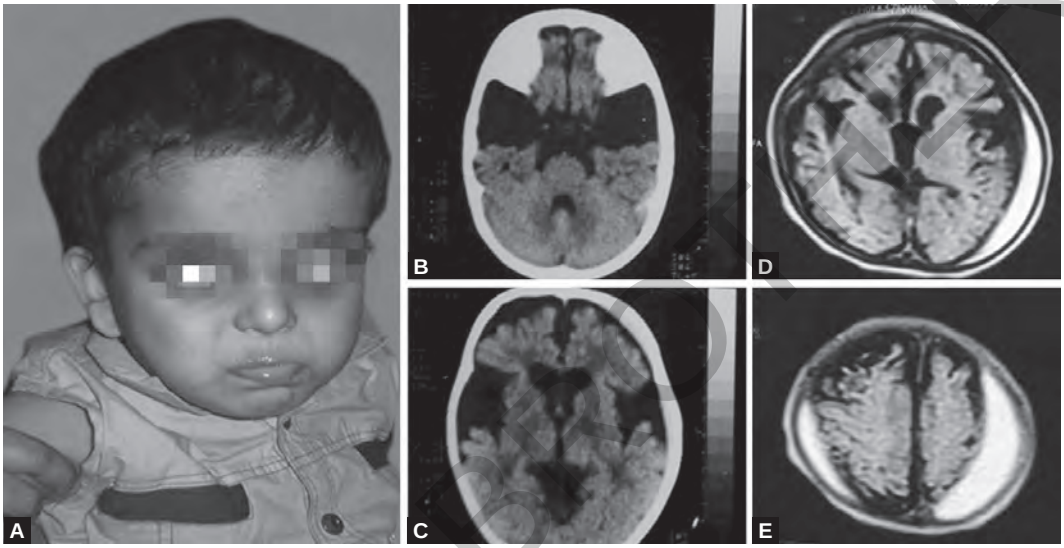
Outcome is enhanced by diagnosis and treatment in the first ten days of life. In the older child or adolescent, OAs can present as loss of intellectual function, ataxia, Reye syndrome, recurrent ketoacidosis, or psychiatric symptoms.

Organic acidurias (OAs) is diagnosed first by urine organic acid analysis using gas chromatography with mass spectrometry (GC/MS). Depending on the specific disorder, plasma amino acid analysis using a quantitative method such as column chromatography, high-performance liquid chromatography (HPLC), or GC/MS can also be helpful. A plasma or serum acylcarnitine profile can also provide a rapid clue to the diagnosis. Finally confirmatory testing involves assay of the activity of the deficient enzyme in lymphocytes or

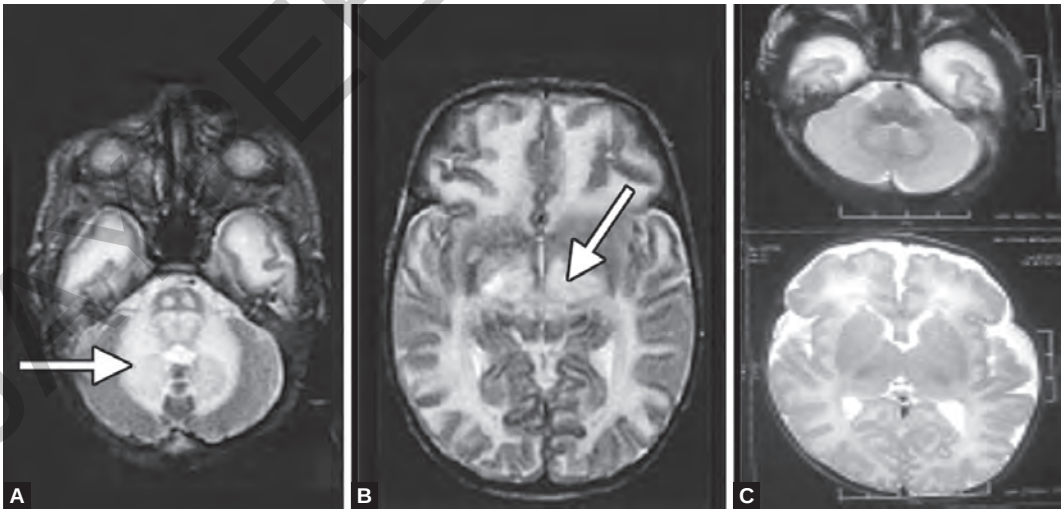
cultured fibroblasts and/or molecular genetic testing.

MRI findings in the Organic Acidurias:

- Distinctive basal ganglia lesions with macrocephaly in glutaric acidemia type I (GA I), Also has wide Sylvian fissure (bat-wing appearance) and nontraumatic subdural hematoma **(Figs 4.1A to E)**
- White matter changes in Maple syrup urine disease **(Figs 4.2A to C)**
- Abnormalities of the globus pallidus in methylmalonic acidemia **(Fig. 4.3)**.



Figures 4.1A to E *Glutaric acidemia type I*: (A) Macrocephaly; (B and C) Dilated Sylvian fissure (Bat-wing appearance); (D and E) Nontraumatic subdural hematoma *(For color version, see Plate 2)*



Figures 4.2A to C MRI in MSUD; T2 prolongation seen in already myelinated brain areas: (A) Hyperintensity in posterior brainstem tracts and the central cerebellar white matter; (B) Basal ganglia and ventrolateral thalamic nuclei; (C) Normal T2 images to show normal MRI of same age

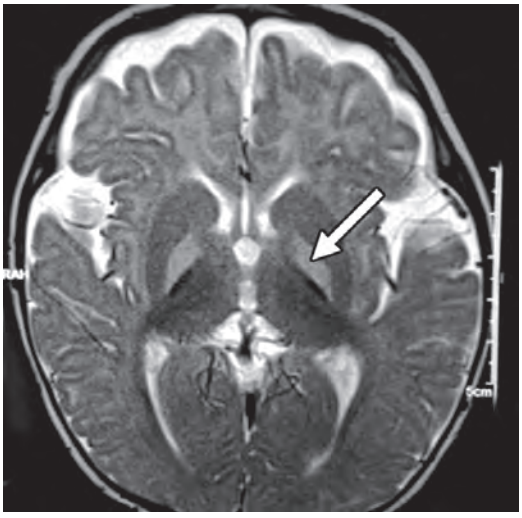


Figure 4.3 Bilateral pallidal hyperintensity in methylmalonic aciduria (arrow)

UREA CYCLE DEFECTS[10]

Severe deficiency of any of the first four enzymes (CPS1, OTC, ASL, ASS-carbamoyl phosphate synthetase I, ornithine transcarbamylase, arginosuccinate lyase; arginosuccinate synthetase) in the urea cycle or the cofactor producer (NAGS—N-acetyl glutamate synthetase) results in the accumulation of ammonia and other precursor metabolites during the first few days of life. Infants are normal at birth but rapidly develop cerebral edema manifested by lethargy, anorexia, hyper- or hypoventilation, hypothermia, seizures, abnormal posturing, and coma. In milder (or partial) deficiencies of the above enzymes and in arginase (ARG) deficiency, symptoms may be triggered by illness or stress at almost any time of life. In these hyperammonia and clinical symptoms are often subtle and the first recognized clinical episode may not occur for months or decades. In ARG deficiency progressive spastic quadriplegia and mental retardation may even mimic cerebral palsy.[11,12]

Traditionally the outcome of newborns with UCDs was considered poor. However, with institution of early treatment with recent protocols, recent data from the NIH-sponsored longitudinal study show IQ measures within a less severe range.

Approach to a Child with Chronic Encephalopathy

Developmental neurological history supplemented with family history will definitely give the diagnostic clues. There will be a decline in the neurological function and the disease keeps worsening as time goes on. But the single most important clue is regression of developmental milestones.

Stepwise Approach to Neurodegenerative Disorders

Step I: Is it a progressive or static disorder?

- *Clues to suspect static encephalopathy:*
  - *History*: High-risk factors, e.g. prematurity, asphyxia, birth trauma
  - *Constellation of signs*: Group of congenital stigmata
    - Suggest malformation of brain
  - *Degenerative diseases mistakenly diagnosed as static encephalopathy*
  - Degenerative diseases with slow evolution may mimic static encephalopathy in infancy
    - For example, progressive disorder that may mimic a "diplegic cerebral palsy"—Arginase deficiency and metachromatic leukodystrophy
    - Dystonia/choreoathetotic cerebral palsy like presentation—Glutaric aciduria type 1 and Lesch-Nyhan syndrome
    - Mixed pyramidal and extrapyramidal cerebral palsy—Pelizaeus-Merzbacher disease
- *Clues to suspect progressive disorder*
  - Positive family history
  - Parental consanguinity
  - Affection of CNS with PNS
  - Presence of neurocutaneous stigmata
  - Dysmorphic features
  - Unusual smell to urine and skin
  - Skeletal abnormalities
- *Somatic involvement (Hepatosplenomegaly and dysostosis multiplex)*:
  - Pitfalls in diagnosing degenerative diseases:
    - Child with hypertonia may turn over early with subsequent delay in milestones
    - Extrapyramidal movements like dystonia may appear late in static encephalopathy.

Step II: Find out site/sites of affection:

- The involvement can be either central or peripheral or a combination of central and peripheral nervous system
- By noting selectivity of regression site can be identified.
  - Global deterioration (Regression of motor, social, adaptive and language, milestones) or cognitive regression (dementia dominant) is suggestive of a central disorder
  - Regression only in motor function can be either due to a UMN or LMN lesion
    - *UMN lesion (hyper- or hypotonia with hyper-reflexia)*—Spinal cord lesion (e.g. hereditary spastic paraplegia)
    - *LMN* lesion (Hypotonia with absent reflexes), e.g. Anterior horn cell disease (e.g. SMA); Muscle disease (e.g. Pompe disease); Polyneuropathy (+/– Sensory, e.g. Hereditary motor sensory neuropathy)
  - In both pure central and peripheral disorders, try to find out gray or white matter involvement.

Step III: Always rule out treatable conditions:

- Inflammatory conditions—presence of fever
- Tumors—associated with increased intracranial pressure
- Vascular—lesion has an arterial territory involvement
- Endocrinological conditions, e.g. Hypothyroidism developing myopathy
- Recurrent seizures—progressive encephalopathy

General Examination

It is an important prerequisite for a better diagnosis as external systemic findings will give away the diagnosis. Following are some of the examples:

- Skin/neurocutaneous lesions **(Figs 4.4 and 4.5)**
- Dysmorphic features **(Fig. 4.6)**
- Hair abnormalities
- Micro- or macrocephaly
- Examination of eye
- Hepatosplenomegaly
- Skeletal change (dysostosis multiplex **Figs 4.7A to C**).

Developmental history and assessment for delay or regression, detailed neurological

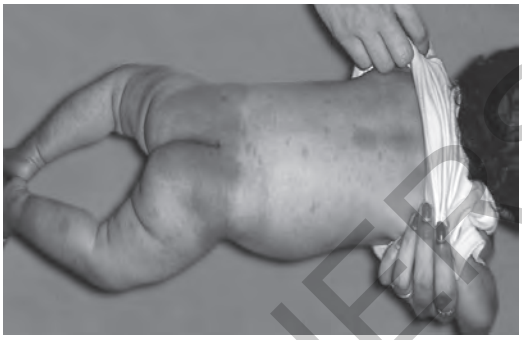


Figure 4.4 Extensive and persistent Mongolian blue spots may be an indicator of gray matter disorders like GM1 gangliosidosis or mucopolysaccharidosis *(For color version, see Plate 2)*

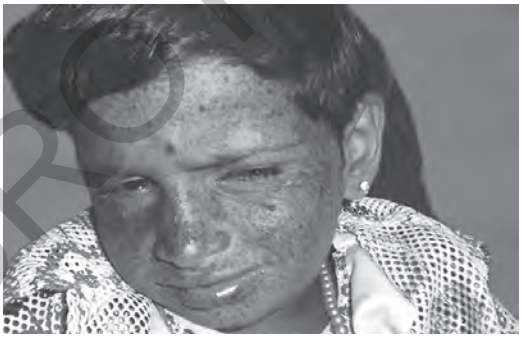


Figure 4.5 A subtle skin change to severe photodermatitis can be seen in xeroderma pigmentosa. This child had severe mental retardation (*DeSanctis-Cacchione syndrome) (For color version, see Plate 2)*

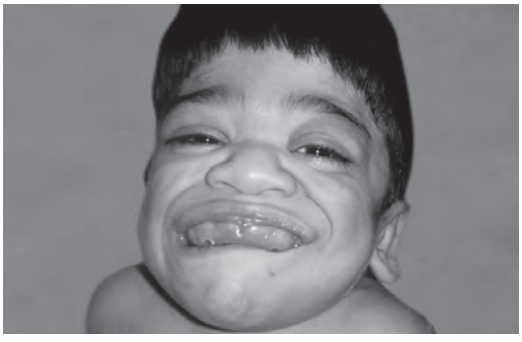
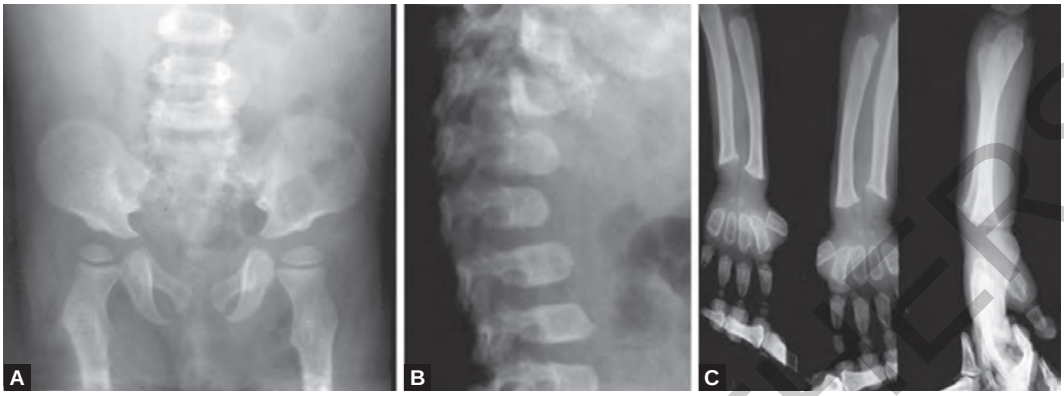


Figure 4.6 Role of facies

- High forehead, puffy eyelids, epicanthal folds
- Flat nasal bridge, anteverted nares, long philtrum
- Gingival hypertrophy, macroglossia—diagnostic of mucolipidosis type 1 (sialidosis I)

(For color version, see Plate 3)



Figures 4.7A to C Disostosis multiplex in gray matter disorders and mucopolysaccharidosis: (A) Round iliac wing, inferiorly tapered ilia; (B) Beaked vertebra; (C) Bullet-shaped phalanges

examination including the motor system and looking for unusual posturing or involuntary movements will further categorize these disorders.

Formulating the Diagnosis

Nonprogressive Central Motor Disorder (Cerebral Palsy)

Features are in history. Positive risk factors in antenatal, natal, postnatal and behavioral soft signs that include colicky behavior, feeding problems and irregular sleep patterns. Physical examination may not yield specific findings. So look for associated findings that may help in rehabilitation.

Neurodevelopmental examination shows delayed milestones or disordered sequence of motor milestones and abnormalities of tone (either hypotonia or poor control of head or a stiffness and rigidity).

In reflex behavior, a combination of delay in disappearance of primitive reflexes and delay in appearance of postural reflexes or incomplete expression is also a powerful predictor of cerebral palsy. Diagnosis of specific type of CP can be done by 1–2 years.

Progressive Central Disorder

When there is delay or regression in development, the pregnancy and birth history is normal with positive family history and consanguinity, progressive central disorder must be thought of.

Progressive disorders can be clinically grouped as gray or white matter disease.

Approach to these disorders are given in the **Flow charts 4.3 to 4.7**.

Among them, a progressive lipidosis may be considered when there are positive eye grounds and hepatosplenomegaly. A Hurler phenotype should be considered in a situation where dysmorphic features combined with dysostosis multiplex are seen.

Nonspecific progressive disorders or gray or white matter should be considered where the history is normally in association with marked subsequent developmental delay. Pelizaeus-Merzbacher disease may masquerade as cerebral palsy. The give away clue is peculiar rhythmic eye movements.

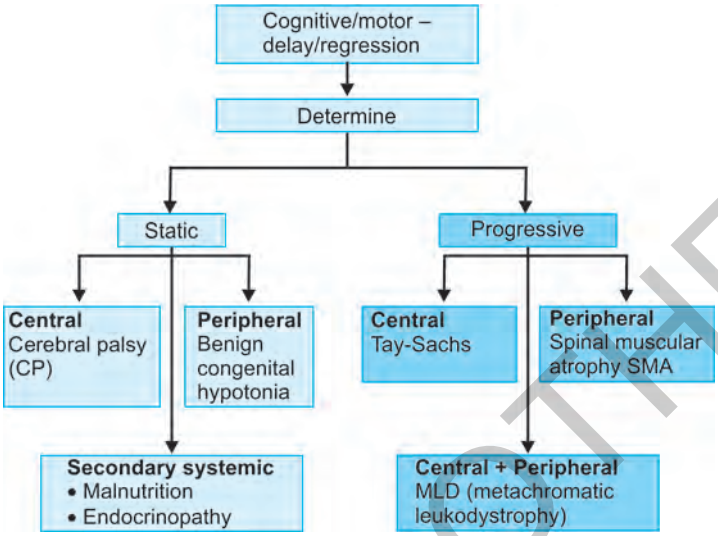
White matter disorders can be differentiated by the imaging finding **(Figs 4.8 and 4.9)**.[13]

Since the demonstration of the DOPA sensitive dystonia (Segawa syndrome), L-dopa has been tried in some of the cases of congenital cerebral palsy where choreoathetotic rigidity is seen. A marked improvement suggests the possibility of Dopa responsive dystonia.[14]

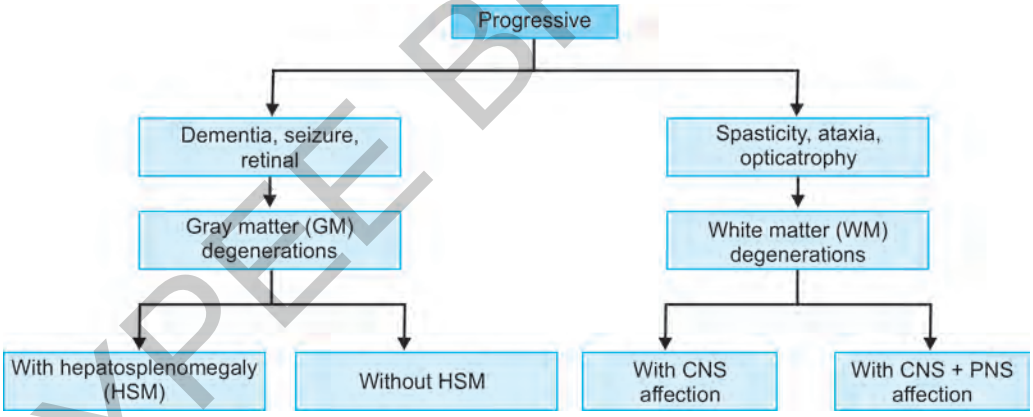
Peripheral Progressive Disorder

Myasthenia gravis and congenital myasthenia, muscular dystrophy and a spectrum of intrinsic muscle disease along with spinal muscular atrophy are considered in this group. Congenital myotonic dystrophy is to be considered in children thought

Flow chart 4.3 Chronic encephalopathy—general approach



Flow chart 4.4 Chronic encephalopathy—an approach to progressive disorders



to be having cerebral palsy. A maternal myotonia and myopathic facies with history of fetal wastage are the diagnostic clues.

Pure neuromuscular disease in this group are Pompes' disease, Refsum disease, etc.

Other Presentations

Psychomotor retardation with connective tissue involvement homocystinuria.

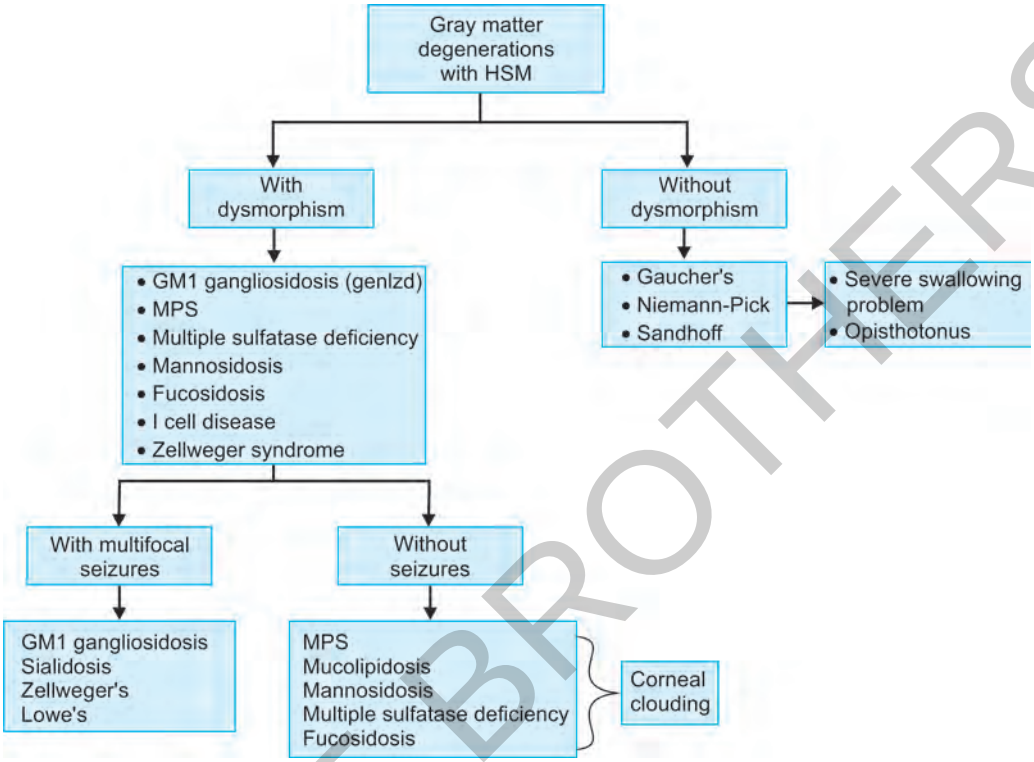
Investigations

A careful history and physical examination can help more than all the investigations put together.[15,16]

Exercise prudence in the investigations. Some children need little or no testing as part of evaluation for motor delay; others may require an extensive search.

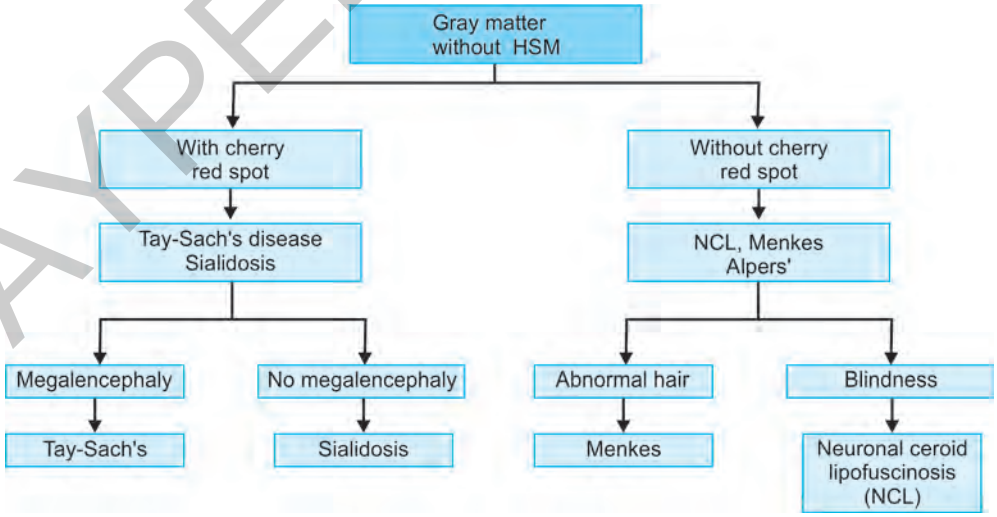
Karyotyping, electroencephalogram, brain electrical activity mapping, brain imaging studies

Flow chart 4.5 Chronic encephalopathy—approach to gray matter disorders-I



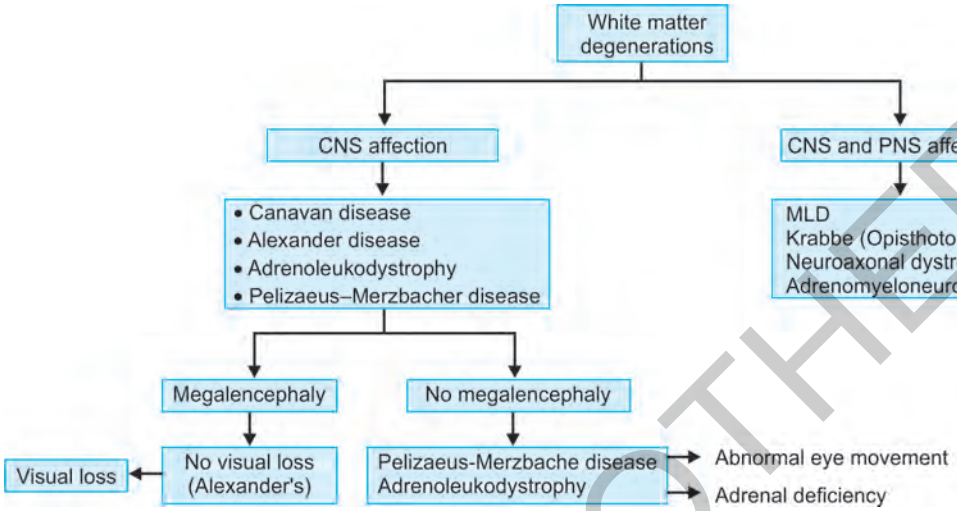
Abbreviations: MPS, mucopolysaccharidosis, HSM, hepatosplenomegaly

Flow chart 4.6 Chronic encephalopathy—approach to gray matter disorders-II



Abbreviations: HSM, hepatosplenomegaly; NCL, neuronal ceroid lipofuscinosis

Flow chart 4.7 Chronic encephalopathy—approach to white matter disorders



(computed tomography, magnetic resonance imaging and positron emission tomography) and metabolic screening may be utilized in appropriate situations.

Following are some points in deciding on the investigations:

- Although brain imaging may not be required routinely, in the following situations it will be of help: an unexpected change in behavior, head circumference, motor status, cognitive abilities, neurologic examination, or seizure frequency.
- Based on the extremely low prevalence of inborn errors, metabolic screening does not need to be a routine part of an evaluation. If there is a history if intermittent episodes of vomiting and lethargy, failure to thrive, progressive loss of skilled or a plateau in milestone acquisition, an unusual body odor, or a suggestive family history, metabolic screening studies should be performed.
- In peripheral (motor unit) disorders, muscle enzyme studies, electromyography and nerve conduction studies and muscle or nerve biopsy will help in differentiating muscle, nerve, anterior horn cell and for myoneural junction disease neostigmine test.

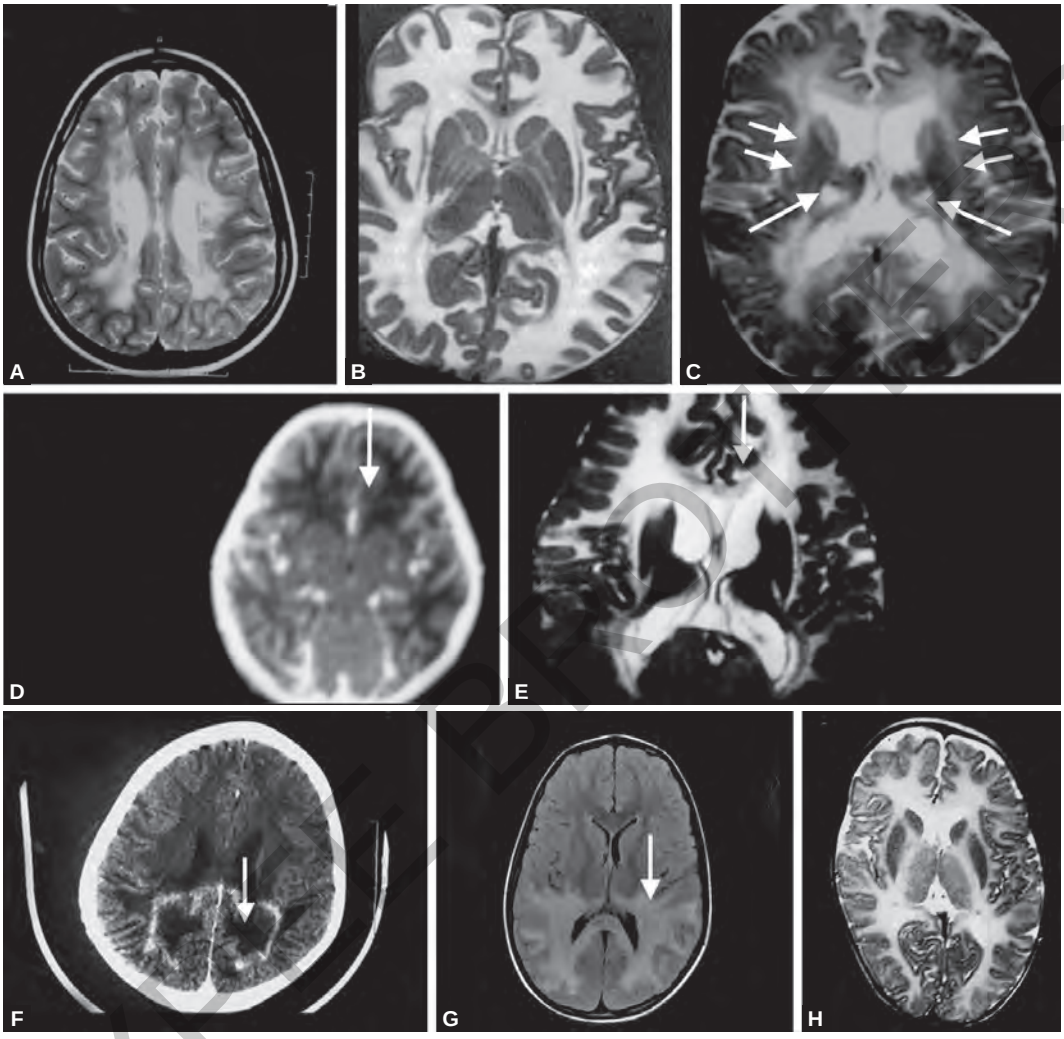
Diagnostic (molecular) testing: When a pattern of disease and its tissue localization are identified other laboratory testing can be employed to make a specific diagnosis, and direct treatment.

Tissue characterization test are:

- Muscle biopsy
- *Histochemistry*: Diagnosis by specific morpholgic features
  Mitochondrial disease
- *Immunohistochemistry*: Absent or reduced staining for specific protein
  Emery-Dreifuss muscular dystrophy
  Duchenne muscular dystrophy
- *Biochemistry*: Absent or reduced enzyme function
  Myophosphorylase deficiency
- Nerve biopsy
  Vasculitis metachromatic leukodystrophy
- *Antibodies in serum or CSF*: It may define specific immune neuromuscular disorders.

Genetic testing: Defines specific hereditary disorders.

- Usually with symmetric weakness if facilities are available
- Hexosaminidase A (multisystem disorder)
- Spinal muscular atrophy [survival motor neuron (SMN)] deletion
- Bulbo-spinal muscular atrophy (Androgen receptor triplet repeat)
- The age of onset of symptoms is often a helpful guide in deciding which progressive degenerative disorders should be considered.



Figures 4.8A to H Imaging in white matter disorders: (A) MLD-symmetric demyelination that spares the subcortical U fibers; (B) Canavan disease—Symmetric demyelination that involves subcortical U fibers; (C) Krabbe disease white matter dysmyelination with high-density basal ganglia; (D and E) Alexander disease; (D) CT scan-frontal hypodensity; (E) MRI—Frontal white matter most involved; (F and G) Adrenoleukodystrophy; Occipital white matter most involved (also callosal splenium) (F) CT scan—Garlanding appearance; (G) MRI hyperintensity posterior brain region; (H) Pelizaeus-Merzbacher disease—extensive dysmyelination including white matter of basal ganglia and thalami showing tigroid appearance

Frontiers in
Pediatric Neurology

Salient Features

- Provides a proper perspective to the pediatricians, postgraduates in pediatrics and neurology, practicing pediatricians and teaching faculty to understand the important neurological diseases that they may come across in their practice
- Discusses many topics which may not be available in recently published pediatric neurology books
- Includes topics ranging from the problems arising from clinical examinations, congenital malformations and developmental defects, infectious diseases, autoimmune problems, various aspects of epilepsy, and electrolyte imbalance to brain death
- Gives much importance to relevant clinical examinations, particularly in chapters such as pitfalls in neurological examination, ataxia and muscle disorder
- Useful as a reference book for all doctors dealing with neurological problems of the children.

TM Ananda Kesavan MD DNB MNAMS FIAP FIAMS PGDDN is currently working as Additional Professor, Department of Pediatrics, Government Medical College (GMC), Thrissur, Kerala, India. His area of interest is pediatric neurology. He is a Fellow, Indian Academy of Pediatrics (IAP) and IMA Academy of Medical Sciences. He holds a postgraduate diploma in developmental neurology (PGDDN).

He is the Nodal Officer, Institutional Research Committee, Government Medical College, Thrissur; and the Chairman, Institutional Ethics Committee, GMC, Palakkad. He has a teaching experience of 18 years to undergraduate and postgraduate students; and, is a Member, International Forum of Teachers (UNESCO Chair in Bioethics).

He has been elected as the National President, IAP Pediatric Neurology Chapter for the year 2017 and National Executive Board Member of IAP. He occupied various organizational posts in IAP such as the National Executive Board Member (4 times), Secretary and President of IAP Kerala, and National Secretary of IAP Pediatric Neurology Chapter. He is the Editor-in-Chief of *IAP Textbook of Pediatric Radiology*.

He has many publications to his credit and also contributed chapters in many pediatric textbooks.

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