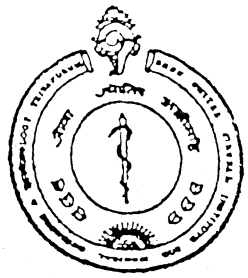
39
DM NOO



SREE CHITRA TIRUNAL INSTITUTE FOR MEDICAL SCIENCES & TECHNOLOGY

THIRUVANANTHAPURAM - 695 011

PROJECT REPORT

NAME : **DR. N.V. AHSAN MOOSA**

PROGRAMME : **D.M. NEUROLOGY**

MONTH AND YEAR OF SUBMISSION : **NOVEMBER 2000**

SREE CHITRA TIRUNAL INSTITUTE FOR
MEDICAL SCIENCES & TECHNOLOGY

A DESCRIPTIVE STUDY OF PROGRESSIVE CEREBRAL DEGENERATION IN CHILDHOOD

N.V. AHSAN MOOSA

CERTIFICATE

I, **Dr. N.V. Ahsan Moosa**, hereby declare that I have actually performed all the procedures listed/carried out the project under report.

Signature.....

Place: Trivandrum

Date: 13/11/2000

Name: **N.V. Ahsan Moosa**

Forwarded. He has carried out the project under report.

Signature
Head of the Department

SREE CHITRA TIRUNAL INSTITUTE FOR MEDICAL SCIENCES AND TECHNOLOGY TRIVANDRUM 695011	Name	
	Page	of
	Date	

PROJECT REPORT

A DESCRIPTIVE STUDY OF PROGRESSIVE CEREBRAL DEGENERATION IN CHILDHOOD

NAME	: **DR. N.V. AHSAN MOOSA**
PROGRAMME	: **D.M. NEUROLOGY**
MONTH AND YEAR OF SUBMISSION	: **NOVEMBER 2000**

SREE CHITRA TIRUNAL INSTITUTE FOR MEDICAL SCIENCES AND TECHNOLOGY TRIVANDRUM 695011

Name		
Page	of	
Date		

ACKNOWLEDGEMENT

I sincerely thank **Dr. Muralidharan Nair**, Additional Professor, department of Neurology, for his invaluable guidance and help throughout the study.

I am grateful to **Dr. K.Radhakrishnan**, Professor and Head, Department of Neurology, for permitting me to carryout this study and for his support.

I thank **Mr. Thampi, Ms. Prameela, Mr. Christu Das** of the Medical Records Depatment for their help and co-operation in collecting the data.

Last but not the least, I immensely thank **Mr. Kumar C.** whose obsession for perfection has helped a lot in giving a good final shape to this project report.

Dr.N.V.Ahsan moosa

CONTENTS

ABBREVIATIONS

- ADEM - Acute disseminated encephalomyelitis.
- ALD - Adrenoleukodystrophy.
- COREN - Corencephalopathy.
- IEM - Inborn errors of metabolism.
- HD - Huntington's disease.
- LD - Leukodystrophy.
- LKS - Landau-Kleffner syndrome.
- MLD - Metachromatic leukodystrophy.
- MPS - Mucopolysacharidoses
- MERRF - Myoclonic epilepsy, ragged red fibres.
- NCL - Neuronal ceroid lipofuscinoses.
- NDD - Neurodegenerative disorders.
- PDD - Pervasive developmental disorders.
- PMD - Pelizaeus-Merzbacher disease.
- PME - Progressive myoclonic epilepsy.
- SSPE - Subacute sclerosing panencephalitis.
- TORCH - Toxoplasmosis, Rubella, Cytomegalovirus, Herpes and Others.

INTRODUCTION

Degeneration is defined as a change from a higher to a lower level of function; neurodegeneration refers to progressive loss of neurological function due to structural or functional abnormalities in the central or peripheral nervous system. A large group of diverse diseases exist in infancy and childhood, characterised by progressive loss of central neurological function, termed the neurodegenerative disorders. Collectively, these conditions represent one of the most common clinical problems in the practise of pediatric neurology. [1]

Many of the neurodegenartive disorders are to be due to biochemical defects, although many of these defects are unknown or poorly understood. Some of the conditions may be caused by persistent viral infection or disturbances in the host-immune functions. Chronic environmental insults, long standing nutritional alterations, iatrogenic factors, and refractory seizures in infancy may be important causes. Yet, a large proportion of the disorders are of uncertain or unknown cause [2], emphasizing a need for focused attention on the group.

Considering the fact that many of these disorders are not treatable, it is important to make a firm diagnosis based on laboratory evidence and also aim at excluding treatable causes. Apart from treatment, a definite diagnosis has important implications for genetic counseling that aids in the antenatal diagnosis in many conditions, which may be the only way to tackle these frustrating disorders. Moreover a firm diagnosis made on biochemical grounds will probably halt the cycle of doctor shopping which many of the parents are forced to do to put an end to the diagnostic uncertainity. As the majority of the disorders are metabolic in nature, it requires sophisticated biochemical tests and

genetic studies to confirm the diagnosis, which many times are not freely available in many of the centres. As a result, many are diagnosed as probable neurodegenerative disorders of unknown etiology, which has got serious implications in the ultimate outcome of the child.

This study was aimed to estimate the relative frequency of this group of disorders affecting the central nervous system as a whole and of selected individual diseases, over a five year period and to find out the group of disorders in which a specific diagnosis could not be made and the reasons for it.

REVIEW OF LITERATURE:

Inborn errors of metabolism are inherited diseases that cause abnormalities in the production, synthesis or catabolism of the cell's metabolic substrates, proteins, or structural constituents. [3] Most inborn errors of metabolism are inherited as autosomal recessive or X-linked recessive traits and are the result of an enzymatic defect. Some autosomal dominant and X-linked disorders are caused by enzyme deficiencies; others are caused by a change in structural proteins. Many of these disorders affect the nervous system resulting in progressive neurological impairment.

Truly speaking most degenerative diseases are metabolic. Those diseases where we have been able to identify a metabolic basis have been classified as neurometabolic. In many so-called idiopathic degenerative disorders, we are yet to find out the underlying metabolic defect. In the years to come many of these degenerative disorders will come under the rubric of metabolic diseases. For example, Hallervorden Spatz disease, which was once thought to be a degenerative disease of unknown nature, is now found to be due to a deficiency of Cysteine deoxygenase[4]. Apart from the metabolic causes, other conditions like Subacute sclerosing panencephalitis, progressive rubella panencephalitis, HIV encephalopathty, congenital syphilis, some chronic fungal meningitis, hydrocephalus, battered baby syndrome can present with features suggestive of neurodegenarative disease, yet not metabolic.[2,5] However majority fall under the metabolic banner.

Although individual metabolic diseases are relatively rare, collectively their prevalence is such that most physicians encounter affected patients. Most of the diseases are diagnosed by relatively simple diagnostic tests even in the neonatal period.

Knowledge of theses diseases and an accurate diagnosis are essential for the genetic counseling, heterozygote detection and prenatal diagnosis. Many of the diseases are treatable (Table-1) .

Table-1. Some treatable causes for neurodegeneration

Disease	**Therapy**
Hypothyroidism	Throxine
Galoctossemia	Withdraw lactose
Wilson's disease	Chelation therapy
Biotinidase deficiency	Biotin
Aminoacidurias	Dietary restriction
Sjogren Larsen syndrome	MCT diet.
Cerebrotendinous Xantomatosis	Chenodeoxy cholic acid
HIV	Anto-retro viral therapy

The inborn errors of metabolism affecting the nervous system can be divided into (1) metabolic encephalopathy that impairs neuronal function because of excessive production of toxic intermediary metabolites, (2) lysosomal storage diseases that cause cell injury because of excessive accumulation of the toxic material within the cells, (3) diseases of mitochondrial and oxidative metabolism, (4) peroxisomal disorders.[6] The later three can be considered together as chronic progressive encephalopathies. The syndrome of acute metabolic encephalopathies needs a different clinical and biochemical approach.

METABOLIC ENCEPHALOPATHIES

A metabolic encephalopathy is caused by an enzymatic deficiency that blocks a metabolic pathway. The result is (1) an impairment of subsequent substrate production, (2) excessive production of the intermediary metabolites proximal to the metabolic blockage, and (3) excessive production of metabolites of alternate pathways.[6] The injury to the nervous system is caused by the direct toxic effects of these metabolites; by the deficiency of the essential metabolites or by the disturbance of the internal milieu due to severe acidosis, hyperammonemia, hypoglycemia, or other metabolic derangement. These secondary metabolic disorders are valuable clues for the rapid detection of many metabolic diseases.[1, 6]

The clinical presentation is often is that of an acute a neonatal encephalopathy with altered consciousness and seizures. Typically, the clinical signs begin after dietary exposure to an unmetabolised substrate. Unlike infants with syndromes associated with chromosomal abnormalities, these infants do not have distinctive dysmorphic features. Another common presentation is episodic encephalopathy with vomiting, altered consciousness, or ataxia. A chronic progressive or chronic static course can also be encountered [7]. These disorders differ from the storage diseases in that there are often no specific neurological or physical features that are distinctive enough to be helpful for a clinical diagnosis. One feature is an unusual odor that some patients have with metabolic encephalopathies (Table-2).[1, 6]

Table-2. Unusual odors of metabolic diseases

Odor	Disease or enzyme deficiency
Sweaty feet	Glutaric academia III, Isovaleric academia
Tomcat urine	Multiple carboxylase deficiency
Maple syrup	MSUD
Musty	Phenylketonuria
Rotten cabbage	Tyrosinemia, Methionine malabsorption
Rotten fish	Trimethylaminuria
Fermented	Oasthouse

A diagnosis of metabolic encephalopathy due to an inborn error of metabolism requires high index of suspicion. Initial screening tests include arterial blood gases, lactate, glucose, and electrolytes for calibration of the anionic gap (Table-3). These studies offer clues to the underlying metabolic defect [1,6,8,9]. And direct subsequent diagnostic evaluation such as quantitative plasma amino acid analysis, urine organic acid and sugar analysis, and enzyme assays (*Fig.1*). More important, these screening tests allow for refinement of the therapy for severe metabolic disturbances. One cannot over emphasise the importance of an early diagnosis because rapid initiation of appropriate therapy can avert poor neurological outcome and death.

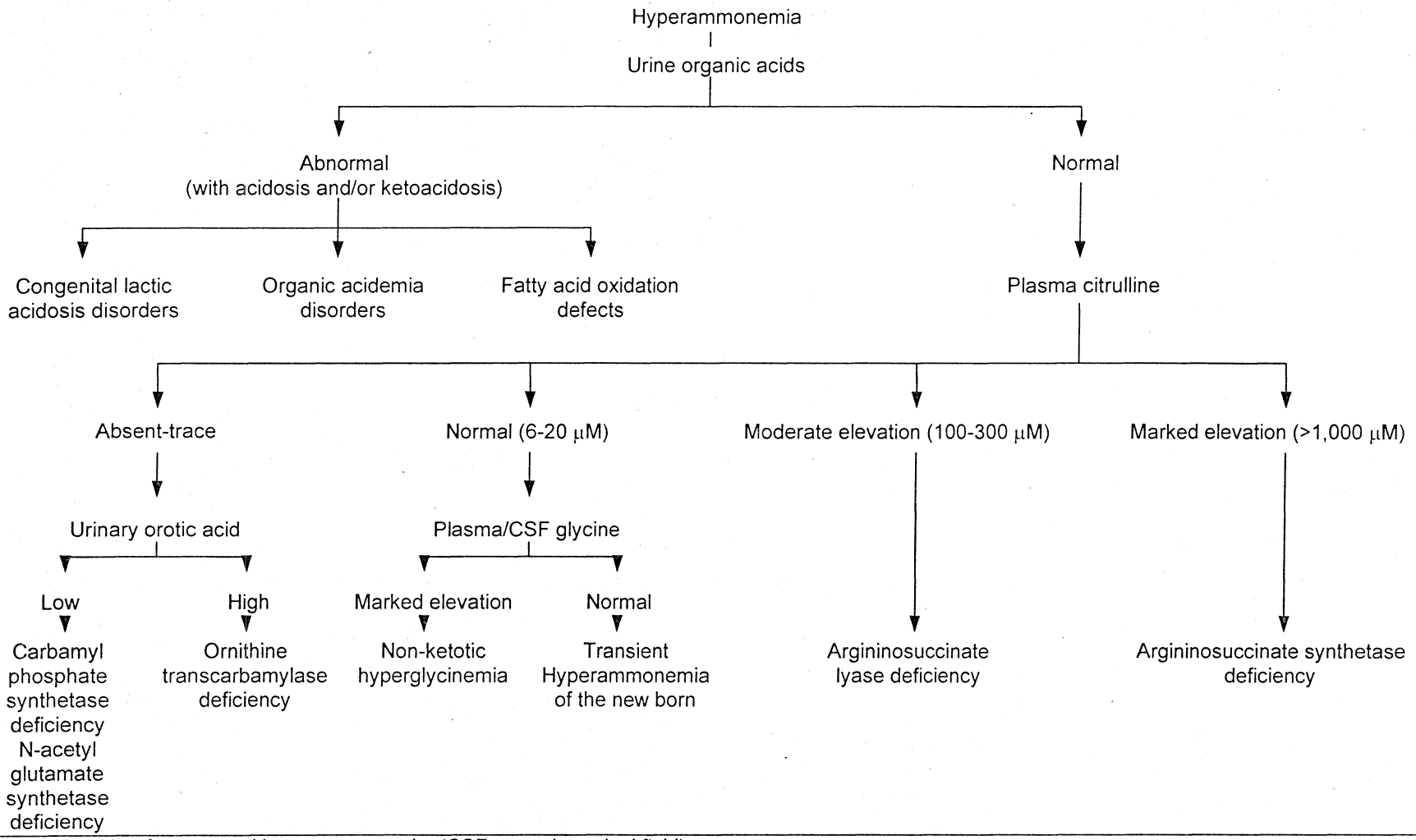


Fig. 1 - Algorithm for neonatal hyperammonemia. (CSF = cerebrospinal fluid)

Table-3. Common laboratory abnormalities of the IEM

Disorder of enzyme deficiency	Hypoglycemia	Hyperammonemia	Met. Acidosis	RTA	Ketosis
Amino acids					
PKU	-	-	-	-	-
Tyrosinemia	+	+	-	+	-
MSUD	+	-	+	-	+
Lysine intolerance	-	+	-	-	-
Organic acidosis					
BCKA disorders	±	±	+	-	+
Glutaric academia	-	-	+	-	-
5-Oxoprolinemia	-	-	+	-	-
Propionic academia	±	+	+	-	+
Methylmalonic academia	+	+	+	-	+
Multiple carboxylase	+	+	+	-	+
Carnitine deficiency	+	+	+	-	-
Pyruvate metabolism					
PDH deficiency	-	-	+	-	-
PC deficiency	+	+	+	+	+
Mitochondrial disorders	±	-	+	±	-
Sugar metabolism					
Galactosemia	+	-	-	+	-
Fructose intolerance	+	-	+	+	-
Fructose 1,6 - bisphosphatase	+	-	+	-	-
Glycogen storage disease I, III	+	-	+	-	-

CHRONIC PROGRESSIVE ENCEPHALOPATHY

Well over 600 disorders and their variants fall under the rubric of neurodegenerative disorders of infancy and childhood [10]. A review on this subject in 1983 has listed more than 300 disorders on an alphabetical order. Such an extensive and diverse listing of disorders necessitates the establishment of a workable classification for

clearer understanding. Since the cause of many disorders is not known, and etiological classification in not possible at present. Dyken and Krawiecki [10] have proposed a classification based mainly on the anatomical grounds, which has significant correlation with the clinical features, is as follows:

Polioencephalopathies

Leukoencephalopathies

Corencephalopathies

Spinocerebellopathies

Diffuse encephalopathies

The *polioencephalopathies* are a group of disorders in which the major clinical or anatomical effect is on the cerebral cortex. Disorders listed in this category are either genetically predisposed or show no known or an inconsistent genetic effect.

The *leukoencephalopathies* are those disorders in which the brunt of the clinical or pathological effect is on the subcortical white matter. Some of these are genetically predisposed (the 'leukodystrophies'); others are non genetic.

The term *corencephalopathies* refer to those disorders in which the core features occur in the deep telelencephalic, diencephalic and/or mesencephalic structures, including both gray and white matter. The anatomical areas affected are usually those of the extra pyramidal system and other deep gray and white matter but excluding the subcortical white matter and the structures of the brain stem.

The *spinocerebellopathies* include disorders involving the pons, medulla, cerebellum and spinal cord.

The *diffuse encephalopathies* are characterized by symptomatology or pathological effect suggesting diffuse anatomical involvement or are diseases of unclear or uncertain clinical and anatomical localization.

The first problem is to find out that the disease in question is really degenerative or not?

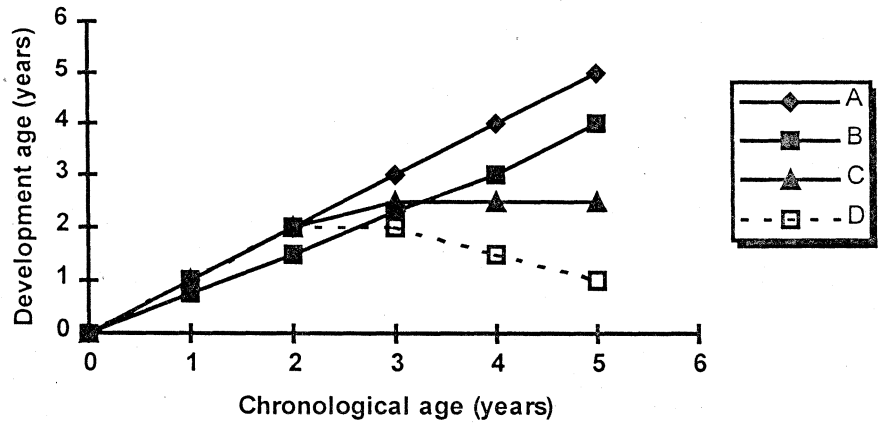
A thorough knowledge about the normal developmental milestones in different sectors of development is essential for arriving at this conclusion. A Denver's developmental screening is a reliable, reproducible and an objective for assessing the development .

Problems such as "delay" and "deviance" should be looked for and need appropriate attention. A degenerative process is suspected when an individual sustains a loss of developmental skills, or a decreased velocity of acquiring development. *Fig-2* shows four curves depicting different patterns of development.[11]

Patient A maintains a normal developmental profile and the milestones are achieved at the appropriate chronological age. Patient B suffers from a static encephalopathy where milestones are met at twice the expected chronological age, yet the rate at which the patient acquires skills is constant. This is not a degenerative process. However one should be aware of the pitfalls in or missing a neurodegenerative disease in this context. When the tempo of evolution of the degenerative disease is slow, it may present initially only as delayed developmental milestones and the evidence of regression may be obvious only later. In the same context, some of the patients with static encephalopathy may develop additional symptoms later in the course as it occurs in

dyskinetic cerebral palsy, which may lead to erroneous diagnosis of a degenerative disorder.

Fig. 2 - Comparison of developmental milestones in neurodegenerative disorders (C + D) with normal control (A) and cerebral palsy (B)



In contrast, Patient C demonstrates a decrease in developmental velocity, eventually leading to a plateau in acquisition of skills. This is a degenerative disease. Patient D also suffers from a degenerative process. In this case the milestones are lost following a decrease in developmental velocity [11].

Once the diagnosis of a degenerative disease is considered based on the patient's developmental history, attention should be directed to the associated evaluation of signs and symptoms (Table-4). Degenerative processes are divided into those affecting primarily the gray matter (neurons), versus those affecting white matter (oligodendrocytes and myelin). [11]

Table-4. Evaluation of signs and symptoms.

Grey matter	White matter
Early	
Cognitive deterioration Seizures Retinal pathology Ataxia	Spasticity Babinski''s signs Peripheral neuropathy Optic atrophy Ataxia
Late	
Spasticity Babinski''s signs	Cognitive deterioration Seizures

The distinction between grey and white matter degenerative disorders is often helpful in formulating the patient's differential diagnosis. However, the clinician must rely on the patient's early symptoms and signs, since grey matter and white matter are clinically indistinguishable at late stages.

Finaily the family can facilitate the process of differential diagnosis. It is important to document all members of the kindred with neurological impairment, in that the mode of inheritance can be established. It is important to remember that several degenerative disorders may present with phenotypic variability within the family members of different ages as in Adrenoleukodystrophy .[12]

PHYSICAL EXAMINATION

A thorough neurological examination is imperative when evaluating the degenerative patient. Equally important, however, is the patient's general physical examination. Features that require special attention and their relevance are given as follows:

Head Circumference.

Microcephaly is defined as the head circumference below minus 2 SD for the age. Many of the NDD have microcephaly as a prominent feature. Hence it has little to do in narrowing the differential diagnosis. It is an important criteria for the diagnosis, only in few conditions such as Rett's syndrome, Lesch-Nyhan syndrome, etc.

On the other hand, "*macrocephaly*", which is defined as head circumference more than 2 SD for the age has got definite diagnostic significance as there are only very few conditions that result in macrocephaly. Notable important causes are [13]

Leukoencephalopathies:

Alexander's disease

Canavan's disease

Polioencephalpathies:

Tay-Sach's disease

Sandhoff's disease

Others:

Hydrocephalus

Chronic subdural effusions

Osteopetrosis, haemolytic anaemias

Familial macrocephaly

In many cases of autism, a relatively large head not qualifying to be called as macrocepphaly is seen.

Skin and Hair findings [1,8,11,]

1. Ash-leaf macules, Shagreen patches, sub ungual fibromas- Tuberous sclerosis
2. Angiokeratomas - Fabry's disease
3. Alopecia - Coackyaner syndrome, boitinidase deficiency.
4. Kinky hair - Menkes's kinky hair disease
5. Photosensitivity, rash - Cockayane syndrome
6. Hyper pigmentation - Adrenoleukodystrophy
7. Xanthomas - cerebro tendinous xanthomatosis
8. Skin findings suggestive of hypothyroidism
9. Icthyosis - Refsum's disease, Sjogren- Larsen syndrome
10. Hypomelanosis of Ito.
11. Axial lipomas - mitochondrial disorders.
12. Self mutilation marks - Lesh-Nyhan syndrome, neuroacanthocytosis
13. Telangiectasia -Ataxia telangiectasia.
14. Petechial rash - Congenital Intrauterine infection
15. Dysmorphic facies -MPS, Mannosidosis

Peripheral neuropathy

One of the important diagnostic clues in these disorders is the finding of peripheral neuropathy. It helps to narrow down the differential diagnosis to a great extent.

Further, it is often helpful to group these entities based on whether the neuropathy is of axonal or demyelinating type [14]

Those with axonal neuropathy may include:

1. Abetalipoproteinemia
2. Vitamin-E deficiency
3. Chediak-Higashi syndrome
4. Ataxia telangiectasia
5. Giant axonal neuropathy
6. Neuroaxonal dystrophy
7. ALD can have axonopathy as well [15]

Those with demyelinating neuropathy may include

1. MLD
2. ALD
3. Krabbe's leukodystrophy

Abdominal examination:

To carefully look for visceromegaly.

Hepatosplenomegaly - MPS, Galactosemia, GM 1 gangliosidosis, Sandhoff's disease etc.

Renomegaly- Glycogen storage disease type-I (Von-Geirk's disease).

DIAGNOSTIC EVALUATION

Once the child's history and physical examination are completed, formulation of differential diagnosis and further work-up are initiated.

The following flow sheet is recommended for further evaluation: *(Appendix-II)*

AIM

To review our experience with progressive cerebral degeneration in childhood, in a tertiary neurological referral center.

OBJECTIVES

1. To estimate the frequency of progressive cerebral degenerative disorders of childhood as a whole and selected individual diseases.
2. To identify the problems and pitfalls in diagnostic work up of these cases.
3. To describe an algorithmic approach to this diagnostic problem.

METHODS

This descriptive retrospective study was conducted at Sri Chitra Tirunal Institute for Medical Sciences and Technology, Trivandrum, Kerala, India.

Cases were identified, by reviewing the admission registry of the patients admitted in the Pediatric ward between the period Jan 1996 and June 2000. Case files of patients less than twelve years with a discharge diagnosis of a specific neurodegenerative disease and also children with various diagnostic labels like leukodystrophy, poliodystrophy, developmental delay, mental retardation, cerebral palsy, neurometabolic disease, etc were screened.

Inclusion Criteria:

Children less than 12 yrs with clinical features suggestive of a neurodegenerative disease at the time of discharge from the hospital, as evident by

1. A progressive decline in the cognitive or motor function from the previous status *OR*

2. A stage of plateau in acquisition of mile stones with a normal previous developmental profile *OR*

3. Delayed development without regression, but a definite cause found as evidence for a neurodegenerative process

Any of the above three, in the absence of any acute neurological illness, systemic illnesses preceding the illness and diseases of peripheral nervous system significant enough to account for the features.

Excluded were:

Children with Epileptic encephalopathy, viz- West's syndrome and Lennox-Gastaut syndrome.

The medical records of all the files screened during this period were reviewed. A specific diagnosis was recorded based upon clinical history and examination, neuroimaging results, laboratory and other special ancillary investigations like genetic studies. An effort was then made to classify each patient into an appropriate diagnostic category as proposed by Dyken and Krawiecki [10] Also the degree of certainty of the diagnosis was assesed based on the evidence available for the diagnosis made. Accordingly, cases were categorized as "confirmed" cases if they had the classical clinical picture with a laboratory evidence wherever appropriate, "possible" if the diagnosis appeared likely without laboratory evidence and "undiagnosed" if the diagnosis was uncertain. The data collected were entered in a pro-forma. (*Appendix-I*)

RESULTS

More than 230 files were screened and 69 cases satisfying the inclusion criteria were included in the study. There were 52 boys and 17 girls. Mean age of the patients was 6.3 yrs. (range 6 months to 12 yrs).

MAJOR CATEGORIES

Cases were categorized into five groups, as proposed by Dyken and Krawiecki [10] (Table-6).

Table-6. Frequency of diseases in the five major groups

Group	No of cases no (%)
Polioencephalopathy-	21 (30%)
Leukoencephalopathy	35 (51%)
Corencephalopathy	7 (10%)
Diffuse encephalopathy	4 (6%)
Non degenerative causes	2 (3%)
Total	69

FREQUENCY OF INDIVIDUAL DISEASES

The break up of the individual diseases is given in Table-7.

PROGRESSIVE MYOCLONIC EPILEPSIES

Eight patients were diagnosed as progressive myoclonic epilepsies; all were between 4 and 9 years of age. Mean age was 5.25 yrs. There were 6 boys and 2 girls. Cognitive decline was seen in all except one and ataxia was present in half of the cases. One patient had classical clinical features suggestive of Juvenile NCL such as juvenile

Table-7. Frequency of individual diseases

Disorder	No of cases
POLIOENCEPHALOPATHY = 21	
Progresive myoclonic epilepsies	
NCL Juv	1
NCL Late inf	3
PME unclass	3
MLD	1
PDD	
Rett's S	6
PDD unclassified	4
Mitochondrial disorders	3
LEUKOENCEPHALOPATHY= 35	
SSPE	20
Leukodystrophies	
ALD	6
MLD	4
Other LD	5
CORENCEPHALOPATHY = 7	
HD	2
Wilson's Ds	1
Ataxia telangectiectasia	1
Probable Leigh's ds.	1
Sec. Dystonia. ?cause	2
MISCELLANEOUS = 6	
ADEM	1
Post encephalitic sequ.	1
Hypothyroidism	1
Osteopetrosis	1
?TORCH infection	1
Undiag neuro-met.ds	1

onset progressive visual loss followed by cognitive decline and myoclonus. Three were diagnosed as Late Infantile NCL, based on typical clinical features and EEG findings.

The remaining three were categorised as PME-unclassified. Biochemical and radiological features suggested a diagnosis of MLD in one case, whose presentation qualified for categorising as PME. Nerve conduction studies done in seven patients were normal. MRI showed cerebellar atrophy in 3 cases, diffuse cerebral atrophy in one and non-specific white matter hyperintensities in two. Work up for SSPE was available in one patient, which was negative. Four patients underwent biopsy study (skin/muscle). All were unyielding by routine light microscopic study. One sample was subjected to electron microscopic study, which was also normal.

PERVASIVE DEVELOPMENTAL DISORDERS

Ten cases were diagnosed as PDD. All these patients presented with the predominant features of behavioural problem in the form of autistic regression. 8 of them were categorized as Rett's syndrome at the time of discharge. All were girls and the mean age was 4.5 yrs. Retrospective analysis suggested a possiblilty of Rett's syndrome in 6 cases. However, only one patient had the typical features to satisfy the criteria for Rett's syndrome. The other two did not have microcephaly, which is a characteristic finding in this condition. One patient also had prominent extrapyramidal feature including chorea, dystonia and myoclonic jerks. One of the patients in this group had fasting hypoglycemia. MRI was unremarkable in three cases and showed cerebellar atrophy in one. EEG was done in all the patients and was found to be abnormal in nine out of ten cases (90%). Most frequent abnormality found was multi-focal epileptiform abnormalities commonly in the central and temporal regions.

SSPE

Twenty cases of SSPE were identified, 19 males and 1 female. Mean age of onset was 7.8 yrs. In 19 cases, correct diagnosis was suspected after the initial clinical evaluation. Myoclonic falls was the most common presentation in 12 cases (60%). One patient presented with ataxia as the initial symptom followed by the other typical features. Four patients had focal signs in the form of pyramidal (1), extra pyramidal (2) or cerebellar (1) features. Long interval periodic complexes were seen in 18 (90%)cases. The other two had multi-focal epileptiform discharges with a burst attenuation pattern. Three patients had MRI and the findings were non-specific. MRI findings noted in our study include hyperintensities in the white matter of frontal and occipital regions. One patient had unilateral putaminal hyperintensity in addition.

LEUKODYSTROPHY

Fifteen cases of Leukodystrophy were identified, 12 males and 3 females. Six were diagnosed as Adrenoleukodystrophy based on clinical and typical MRI features. All were boys. Mean age was 5.9 years. Mean age of onset was 3.5 yrs. Onset symptom varied from seizures, ataxia, deafness and spastic gait. All the cases had the typical features on MRI with brain stem involvement as well. Serum cotrisol levels were estimated in two patients and were found to be normal. Only one patient had hyperpigmentation on examination. Four of the 6 patients had a preceding febrile illness that resulted in neurological deterioration. Four cases were diagnosed as MLD. Mean age of onset was 2 years. All had suggestive MRI findings and low Arylsulphatase-A levels. In the remaining five patients, clinical and radiological features strongly suggested a

leukodystrophic process. In all cases MRI was interpreted as suggestive of MLD in view of the diffuse involvement. All these cases had a normal Arylsulphatase-A level. One infant had a low Hexosaminidase-B level along with hypotonia suggesting the diagnosis of Sandhoff's disease. This patient had early onset of motor regression along with hypotonia but had no organomegaly. The other four had a normal Arylsulphatase-A level. The clinical profile of a male infant with early onset visual impairment with nystagmus suggested a possibility of Pelizaeus-Merzbacher disease. One child had a delayed development without regression despite a four-year duration of illness.

CORENCEPHALOPATHY

Seven cases were categorized as corencephalopathy, 4 boys and 3 girls. Mean age was 9.4 yrs. Definitive diagnosis was possible in three cases, one case of Wilson's disease and two cases of Huntington's disease. Both patients with HD showed typical changes on MRI brain and were positive for the CAG repeats in the pathological range. One patient with HD did not have a family history. However, father was detected to have the genetic abnormality, which has not manifested till then. One had features of Ataxia telangiectasia and in the other case the features suggested a possibility of Leigh's disease. The remaining two patients were labelled as secondary dystonia of undetermined etiology.

CERTAINITY OF THE DIAGNOSIS

A definitive diagnosis was possible in 39 (56%) cases. Nine cases were categorized as having a "possible" diagnosis. 21 cases remained undiagnosed. Table-8 shows the degree of certainity of the diagnosis in the different subgroups.

Table-8. Frequency of confirmed and undiagnosed cases

Diagnostic Category	SSPE	LD	PDD	Mito	PME	Coren	Misc	Total
Confirmed	20	10	1	0	2	4	3	39
Possible	0	0	5	0	3	0	1	9
Undiagnosed	0	5	4	3	3	3	3	21

MRI

Forty patients (58%) underwent MRI study. (Table- 9). Out of this, MRI was found to be abnormal in 33 cases (82%) and diagnostically useful in 19 cases (47.5%). Conditions in which MRI was useful diagnostically were Leukodystrothies (13 cases) *(Fig-3),* Huntington's disease (2) *(Fig-4)*, Wilson's disease (1), Ataxia telangiectasia (1), probable Leigh's disease (1) and ADEM (1). MRI showed non-specific subcortical white matter hyperintensities in three patients with SSPE in whom it was done. MRI did not reveal any diagnostic clues in any of the 5 cases of PME. Four of the six MRIs in PDD group were normal and the other two showed non-specific changes. MRI was not found to be useful in any of the three cases with suspected mitochondrial cytopathy in our study. MRI in the two cases of secondary dystonia of uncertain etiology did not reveal

Fig-3. MRI appearance of Leukodystrophies

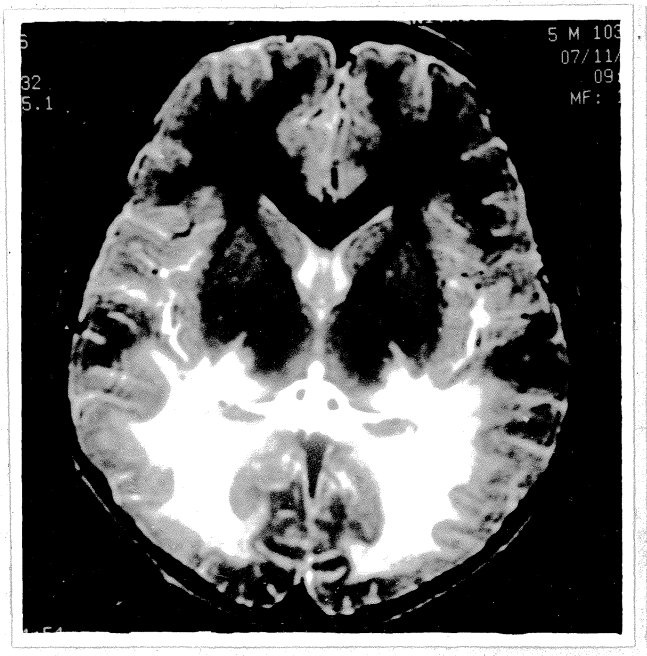


Fig-3a. Parieto-occipital demyelination in a case of ALD (MRI T_2 WI).

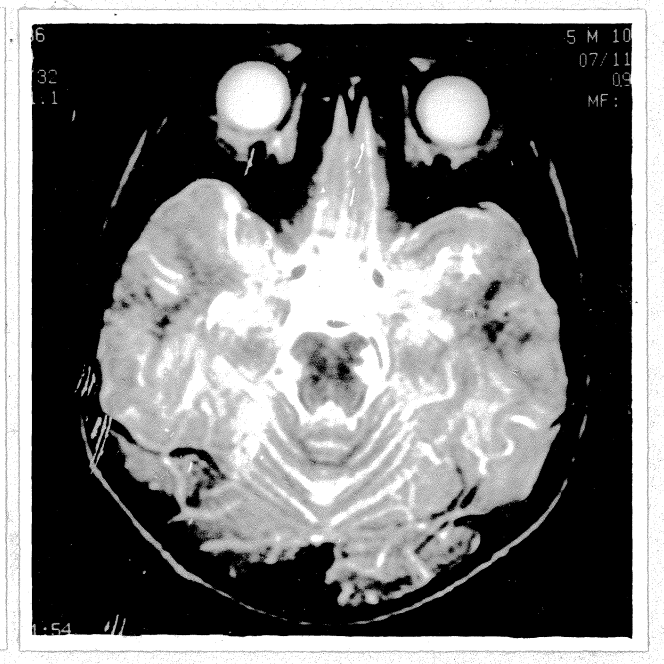


Fig-3b. Brain stem section showing lateral pontine involvement in ALD (MRI T_2WI).

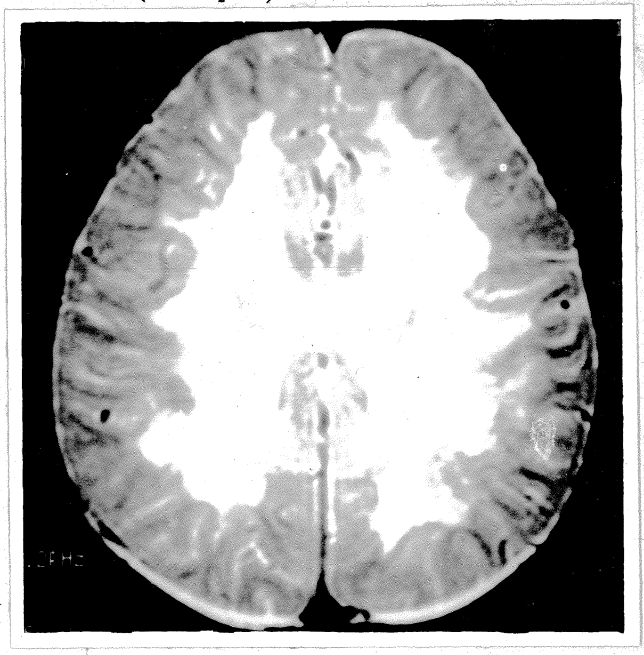


Fig-3c. Diffuse dysmyelination in case of 6 yr old boy with MLD. (MRI-T_2WI)

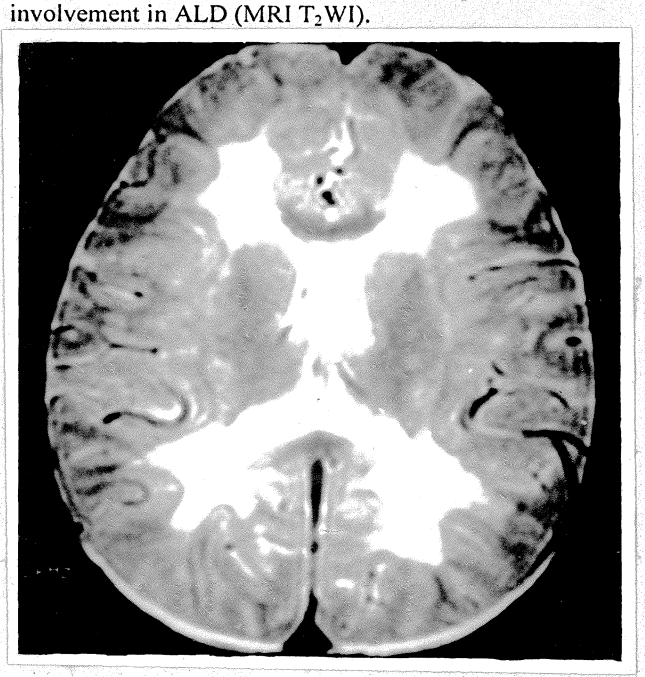


Fig-3d. Diffuse subcortical white matter dysmyelination in a case of MLD.(MRI T_2WI)

Fig-4. MRI appearance of Huntington's disease

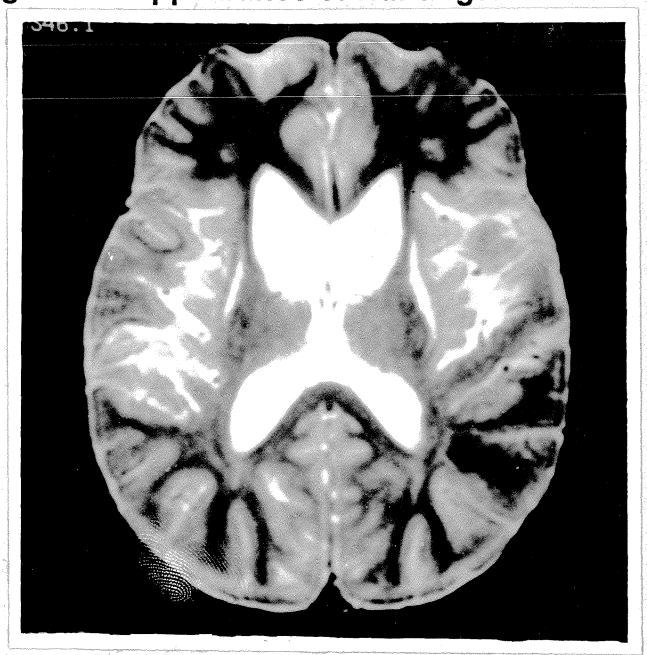


Fig-4a. Bilateral caudate atrophy with frontal horn dilatation in a case of Juvenile Huntington's disease. (MRI T_2WI)

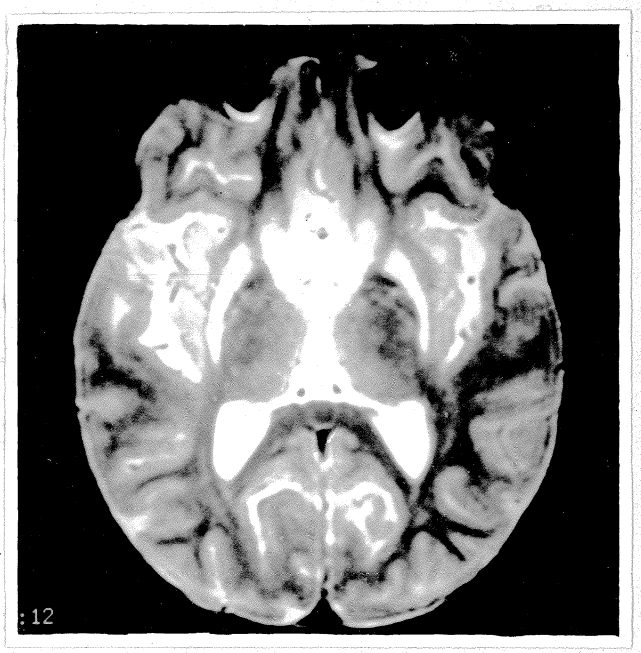


Fig-4b. Section showing bilateral putaminal atrophy with hyperintense signal changes. (MRI T_2WI)

any "eye of the tiger" sign as seen in Hallervorden-Spatz disease or "giant panda sign" as seen in Wilson's disease.

Table-9. MRI in different disease categories

Disease category	MRI		
	Total done	Abnormal	Diagnostic MRI
PME	5	4	0
SSPE	3	3	0
PDD	6	2	0
COREN	7	7	5
ALD	6	6	6
Non ALD-LD	7	7	7
Mito.Ds	3	3	0
Miscell.Ds	3	1	1
Total	40	33	19

EEG

Fifty patients (72%) underwent EEG monitoring. EEG was useful in the diagnosis only in two groups. 18 of the 20 patients (90%) with SSPE had the typical long interval periodic complexes thus clinching the diagnosis (Fig-5). The remaining two had atypical features, but consistent with the diagnosis of SSPE. Both had epileptiform abnormalities with a burst attenuation pattern. PDD was the other group where EEGs were done frequently and was found to be abnormal in nine out of ten cases (90%). Most frequent abnormality found was multi-focal epileptiform abnormalities commonly in the central and temporal regions (Fig-6). Findings were either unremarkable or non-specific in most other cases. Three patients with PME underwent evoked potential studies (VEP or SSEP), which was abnormal in all the three.

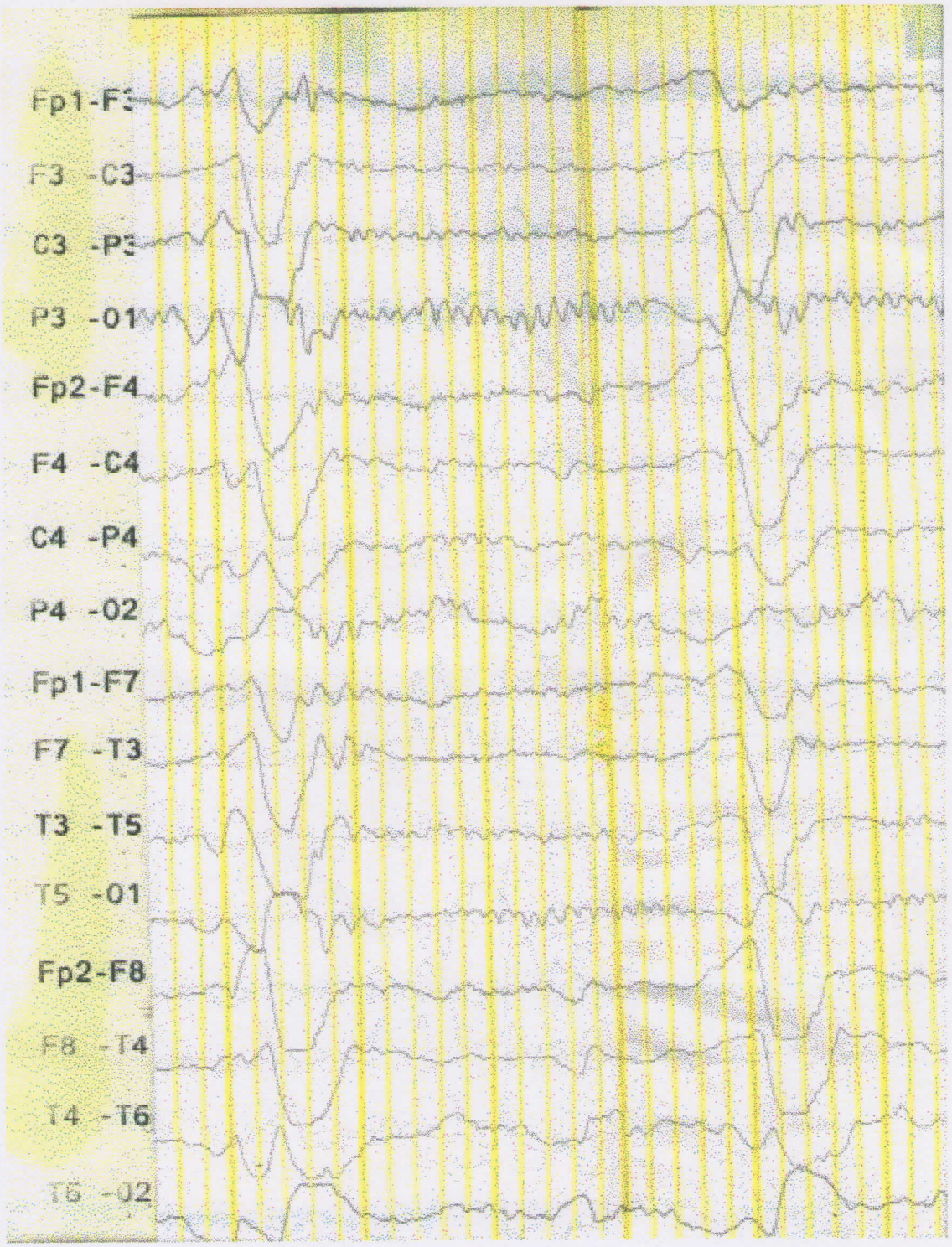


Fig:5. EEG in a patient with SSPE showing slow periodic complexes at 4 seconds interval

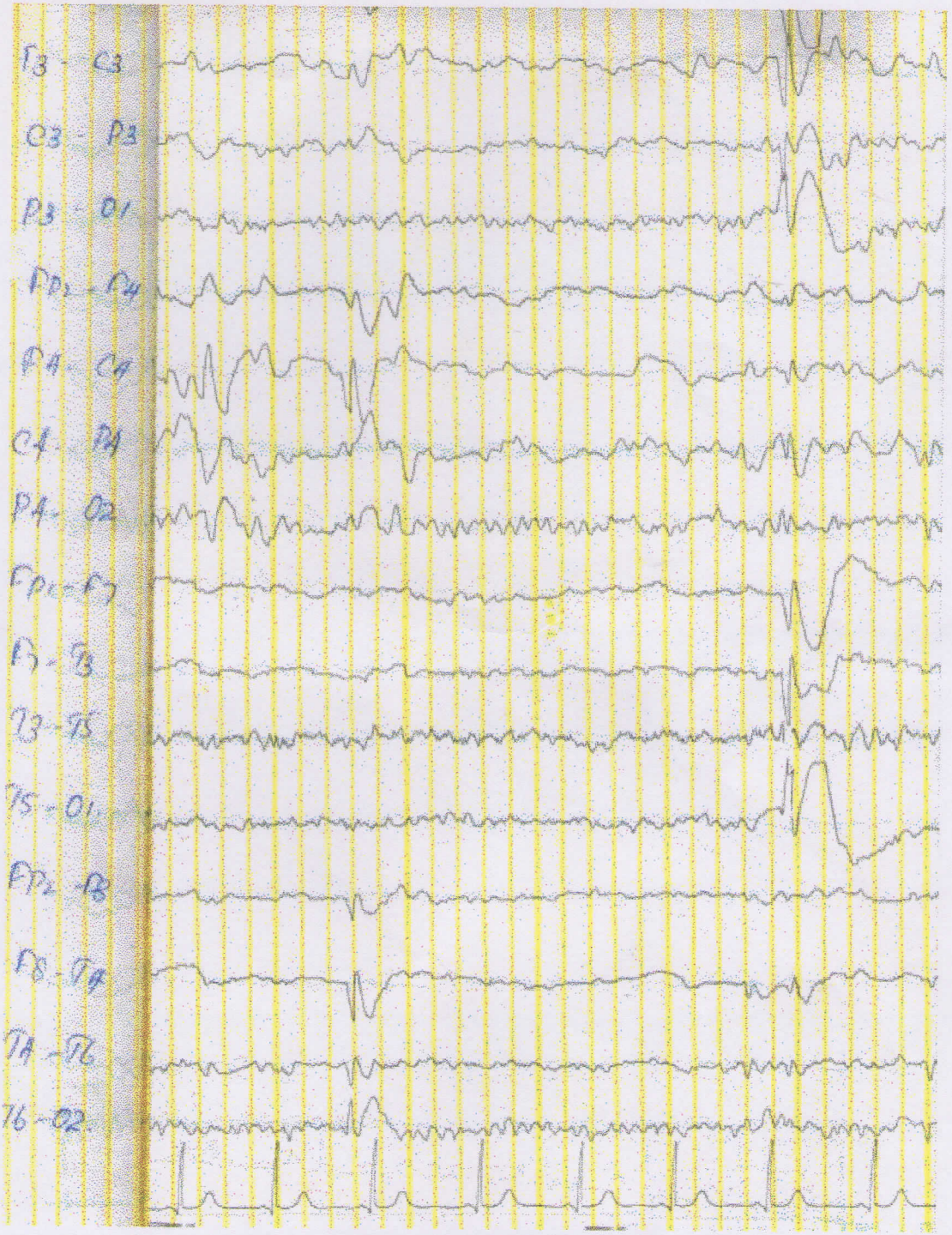


Fig:6.EEG of a patient with Rett Syndrome showing multi focal spikes

NERVE CONDUCTION STUDIES

Twenty-two cases underwent nerve conduction studies; ten in the leukodystrophy group, five in the corencephalopathy group and 7 in PMEs. Abnormal nerve conduction study was seen in only two studies, both in cases of metachromatic leukodystrophy. One of the patients had absent ankle jerks, but the other had brisk reflexes. Both showed features suggestive of demyelinating neuropathy.

BIOPSY STUDIES

Six cases underwent tissue biopsy- four in patients with PME and two in mitochondrial cytopathy. Three underwent skin biopsy and the other three, muscle biopsy. Three samples (two muscle and one skin) were subjected to electron microscopic analysis. None of them were diagnostically useful.

ANCILLARY METABOLIC TESTS

Fifteen patients had a thyroid profile done, of which one was abnormal, in the hypothyroid range. Twelve had a lactate level and was found to be abnormal in two cases of suspected mitochondrial cytopathy. Aminoaciduria screen was done in 13 cases and was found to be normal in all. 6 patients had a ceruloplasmin level and it was found to be low in one. 3 patients with MLD had urine positive for metachromatic granules. 5 patients had a serum ammonia level, which was normal. Two patients with ALD had a serum cortisol level done and both were normal. Two patients with HD had pathologic CAG repeats on genetic testing

Table- 10. Ancillary tests used for the diagnosis and their positivity.

Ancillary tests	Total no. done	No. abnormal
Thyroid function tests	15	1
Serum lactate	12	2
Urine aminogram	13	0
Sr. ceruloplasmin	6	1
Urine Metachro.granules	3	3
Sr. ammonia	5	0
Sr. cortisol	2	0
Genetic test for TNR in HD	2	2

FOLLOW UP RATES

Twenty-eight patients (37%) were available for follow up at least once (Table-11)

Table-11. Follow up rates in the major sub-groups

Disease category	No of follow up/ Total no.pts
PME	7/8
SSPE	4/20
PDD	1/10
COREN	5/7
LD	5/15
Mito.Ds	2/3
Miscell.Ds	4/6

Ten patients attended follow up clinic more than twice. Mean period of follow up was 11.3 months and the median period was 6 months. Follow up changed the diagnosis in

two patients. One had post encephalitic sequelae and the other had ADEM from which the patient had a near complete recovery. Follow up rates were high in the corencephalopathy group (71%).

DISCUSSION

In this retrospective review, 69 cases were initially diagnosed as neurodegenrative disorders. Two of them were categorised as "non" degenerative on subsequent follow up. Arbitrarily categorizing them in the different groups as proposed by Dyken and Krawiecki, [10] there were 35 cases of leukoencepahlopathy, 21 cases of polioencephalopathy, 7 cases of corenencephalopathy and 4 cases of diffuse encephalopathy and the remaining two were diagnosed as non degenerative conditions. Of the 69 cases, 39 could be classified to have a clinically most likely diagnosis, some with confirmatory laboratory evidence. 21 pateints remain undiagnosed and majority of these cases were in the polioencephalopathy group.

In a similar study by Dyken and Krawiecki, [10] in 1985, 341 cases of neurodegenerative disorders of infancy and childhood were found over a five year period in two pediatric neurology referral centers, constituting 28% of total admissions. Polioencephalopathy constituted 34% of cases, leukoencephalopathies and diffuse encephalopathies 21% each, and the spinocerebellopathies and corencephalopathies constituting the remaining cases. The six common conditions noted were SSPE, NCL, Tuberous sclerosis, West syndrome, Werdnig-Hoffman disease and hereditary spastic paraplegia. It is to be noted that almost one fifth of cases did not have a specific diagnosis. Of the 115 cases of polioencephalopathy, 35% did not have a specific diagnosis.

As regard to Indian experience, no similar studies have been published so far. In a review on the biochemical approach of inherited metabolic disorders by Christopher and

Shetty, from NIMHANS, [9] they report 240 cases of inherited metabolic disorders diagnosed based on biochemical studies from 7995 patients referred with a diagnosis of suspected inherited metabolic disorder. Two third of the cases were constituted by mucopolysacharidoses, one-fifth by sphingolipidoses, MLD being the commonest; the rest were aminoacidopathies and carbohydrate metabolism disorders. However this is not a clinical study and the data has to be interpreted with caution.

In our study, we did not include the lower motor neuron syndromes as we undertook the study mainly to address the issues of difficulties in the diagnosis of progressive cerebral degenerative disorders of childhood. Also, epileptic encephalopathies were excluded as the etiological factors are very much variable and would include non-progressive pathologies too, thus interfering with the final analysis. The problems and limitations in the diagnosis of these disorders are highlighted in the subsequent discussion.

POLIOENCEPHALOPATHIES

The group polioencephalopthy comprised of 8 cases of PMEs, ten cases of PDDs and 3 cases of mitochondrial cytopathies.

Progressive myoclonic epilepsies

Eight patients were diagnosed as progressive myoclonic epilepsies; all were between 4 and 9 years of age. Cognitive decline was seen in all except one and ataxia was present in half of the cases. One patient had typical clinical features suggestive of Juvenile NCL [16] and three were diagnosed as Late Infantile NCL and three were

categorised as PME-unclassified. Biochemical and radiological features suggested a diagnosis of MLD in one case, whose presentation qualified for categorising as PME.

Nerve conduction studies done in 7 patients were normal, adding little to the diagnostic work up. MRI showed cerebellar atrophy in 3 cases, diffuse cerebral atrophy in one and non-specific white matter hyperintensities in two. Work up for SSPE was done in only one patient, which was negative. Though the typical slow myoclonus is seen characteristically in SSPE, cases without this typical feature may be missed if not investigated appropriately. Though EEG is a sensitive test, serological evidence is the definitive diagnostic procedure. It was found that biopsy is often under utilised in the diagnostic work up of PMEs. Only four patients underwent biopsy study (skin/muscle). All were unyielding by routine light microscopic study. The only sample on which an electron microscopic study was available was normal. Among the causes of PMEs, MERRF, NCL and Lafora body disease can be diagnosed based on biopsy findings.[17, 18] Electron microscopy can provide additional information in the former two conditions [17] Genetic studies, which are not widely available yet can improve the diagnostic specififty as in NCL [19] and MERRF [20,21]. Among the biochemical studies enzyme assay for Sialidosis and urinary dolichol levels and oligosacharides could add to the diagnostic accuracy but were not available to us. According to Berkovic et al., [20,21] a specific diagnosis should be possible in virtually all case of PMEs. Common error in childhood onset PME is the failure to recognize clinical clues to MERRF. When this diagnosis is unlikely, a further careful search for Lafora bodies in eccrine sweat gland duct cells [18] should be performed. The yield of brain biopsy is less if preliminary studies have been carefully performed. Brain biopsy would be indicated when the clinical progression is

rapid, when the parents plan to have more children, when the family clearly wishes to understand the condition better, and when there is a possibility that accurate diagnosis will improve the management [20, 21].

Pervasive developmental disorders

Ten cases were diagnosed as PDD, 8 of them were categorized as Rett's syndrome at the time of discharge. Retrospective analysis suggested a possiblilty of Rett's syndrome in only 6 cases. However, only one patient had the typical features to satisfy the criteria for Rett's syndrome.[22] The other two did not have microcephaly, which is a characteristic finding in this condition. One patient also had prominent extrapyramidal feature including chorea, dystonia and myoclonic jerks. One patient in this group had fasting hypoglycemia suggesting a metabolic disease. However this finding had been overlooked during the evaluation of this case. MRI was unremarkable in three cases and showed cerebellar atrophy in one as reported in the past in autistic disorders [23]. EEG was found to be abnormal in 9 cases (90%).[24] The diagnosis of Landau-Kleffner syndrome was considered in two patients but none had the typical findings of continuos 1.5 to 5 Hz spike and wave discharges, distributed predominantly in the posterior temporal regions during slow wave sleep, which fragments or disappear in REM sleep. The higher percentage of (13%) of patients with PDD is probably because of referral bias as a project for survey of children with behavioural and learning disorders had been undertaken in the institute during the period of study.

LEUKODYSTROPHIES

This is another group of disorders where the diagnostic accuracy was high (66%). This is mainly because many conditions in this group have typical features like Addisonian features in Adrenoleukodystrophy [12,25] peripheral demyelinating neuropathy in late infantile MLD [13] and early onset symptoms with nystagmus in a male infant as in Palizeus Merzbacher disease [26]. Also the neuroimaging features have strong diagnostic specificity as in ALD. There were a total of 15 cases that were classified as leukodystrophy, which included six cases of ALD, four cases of MLD and the remaining were largely uncategorised.

Adrenoleukodystrophy

Six cases of ALD were identified. All were diagnosed based on the clinical features and characteristic imaging findings on CT or MRI. Only two of them had hyper-pigmentation to suggest Adrenal insufficiency. Other symptoms of adrenal insufficiency are less common. Hyper pigmentation is the single most important clinical clue [12,25]. One important feature that would suggest the possibility of a non-degenarative disease is the frequent exacerbation or the precipitation of the symptoms by a febrile illness which is reported earlier [25]. In such a setting, one tends to diagnose a post encephalitic or post ADEM sequelae as the likely possibility. It is to be noted that 4/6 patients had their symptoms precipitated by febrile illness. Among the neurological symptoms, the characteristic symptom that should alert the clinician as regard to the diagnosis of ALD is the hearing impairment. It is well known that ALD has a predilection to involve the brainstem auditory pathways (lateral leminiscus) as well as medial geniculate body and the temporal sub cortical white matter, [27,28] which leads to deafness. This feature is not a

common feature in other neurodegenerative disorders. Hearing impairment was noted in 5 of the six cases seen in our study.

MRI was done in four patients and all showed typical features of parieto-tempor-occipital inflammatory demyelination along with the involvement of brain stem, which is characteristic of ALD.[27, 28] Other leukodystrophies are very unlikely to affect the brain stem[28, 29]. The occurence of parieto-occipital demyelination alone can occur in other conditions like ADEM [30] and the long list of conditions that result in the "reversible posterior leukoencephalopathy syndrome" [31]. Serum cortisol level was done in only one patient and it was found to be normal. Only two were available for follow up and both had deteriorated compared to the previous visit.

Other Leukodystrophies

Among the nine non-ALD cases four were diagnosed as MLD based on clinical and radiological features confirmed by Arylsulphatase -A assay, which was low in all the cases. All these cases had onset between 1 and 3 years, thus falling in the late Infantile MLD group. One child had only a delayed development without a regression in milestones emphasising the need to suspect this diagnosis in the so-called 'static encepahalopathies'. The onset symptom in all of them were either as pyramidal or cerebellar dysfunction. Though this is an autosomal recessive disease, history of consanguinity was present in only two cases. Two patients had demyelinating neuropathy on nerve conduction study. One of them had clinical evidence of neuropathy in the form of absent ankle jerks. But the other patient had brisk reflexes despite the electrophysiological evidence for neuropathy. Thus the practise of screening with nerve conduction study in the absence of clinical evidence for neuropathy may be justified.

In the remaining five patients, clinical and radiological features strongly suggested a leukodystrophic process. In all cases MRI was interpreted as suggestive of MLD in view of the diffuse involvement. However, in late stages all the cases of leukodystrophy would appear similar clinically and radiologically. [29] All these cases had a normal Arylsulphatase-A level. One infant had a low Hexosaminidase-B level along with hypotonia suggesting the diagnosis of Sandhoff's disease.[13] The other four had a normal Arylsulphatase-A level thus ruling out the usual form of MLD. However, Arylsulphatase activator protein deficiency can result in features of MLD with a normal Arylsulphatase level.[13] The clinical profile of a male infant with early onset visual impairment with nystagmus suggested a possibility of Pelizaeus Merzbacher disease.[26, 13] One child had a delayed development without regression despite a four-year duration of illness raising a suspicion of a static encephalopathy. Only regular follow up and assessing the "velocity" of the development will help in the diagnosis of static encephalopathy, which has important implication in prognosis to the patient and the family. However this patient was not available for follow up. All except one were lost from follow-up.

CORENCEPHALOPATHIES

Childhood neurodegenerative disorders with predominant extra-pyramidal involvement are sometimes referred to as "corencephalopathies". [10] This is applicable to those cases with onset symptom as one of the movement disorders. In the seven cases seen in our study, four presented with dystonia and tremor on two and vocal tics in one.

Definitive diagnosis was possible in five cases- two cases of Huntington's disease, one case each of Wilson's disease, ataxia telangiectasia and probable Leigh's disease. The other two patients were labelled as secondary dystonia of undetermined etiology.

Both patients with genetically confirmed HD showed typical changes of bilateral caudate and putaminal atrophy on MRI brain. One patient did not have a family history, which is the main diagnostic clue in this autosomal dominant disease.[32] However, in this case also, the father was having the genetic abnormality, which however has not manifested yet. The other patient had a strong family history with an autosomal dominant pattern which in the presence of caudate atrophy on MRI makes the diagnosis fairly straight forward.[33] Only one case of Wilson's disease was observed in this study over a five year period, though this diagnosis is often suspected in any child with a extra-pyramidal disorder.[34, 13] The other two patients without a specific diagnosis had no characteristic features on MRI.

Ataxia telangiectasia was diagnosed in one patient base on the clinical features and conjunctival telangectasia. Evaluation of the same patient six years earlier did not reveal the telangiectasia. It is well known that telangiectasia can appear later in the course.[35] Moreover the initial presentation was with predominant involvement of the extrapyramidal system. This case underlines the importance of a careful and thoughtful general physical examination in any patient with neurodegenrative disease.

NON-METABOLIC NEURO-DEGENERATIVE DISORDERS

Though many authors tend to use "neurodegenerative disorders" and "neurometabolic disorders" synonymously, there are a definite group of disorders that do not fall under the rubric of "neuro-metabolic disorders". Conditions like SSPE, Progressive rubella encephalopathy, hydrocephalus, chronic fungal infection, battered baby syndrome are some of the conditions that are non metabolic but yet present with features simulating neurodegeneration. [2, 5, 36]

Subacute sclerosing panencephalitis.

The clinical diagnosis of SSPE is more often straightforward than many other similar disorders in centres where it is frequently seen as in our centre. SSPE often presents with myoclonic falls, behavioural disturbances, cognitive decline and occasionally the onset is heralded by seizures.[37] Being a "pan" encephalitic process, it has propensity to involve all the neuronal structures including the meningeal coverings. One of our patients had ataxia as the first manifestaion of the disease. Despite the similarity to the syndrome of PME, SSPE is not often included in the banner of PMEs. It is probably because all the other causes of PMEs are heritable in nature.[20, 21] However from a clinical viewpoint, it is preferable to consider SSPE in the differential diagnosis of PME syndromes.

Of the 20 cases, SSPE was considered as the most likely possibility in 18 cases after the clinical examination. The diagnosis is usually suggested by the characteristic myoclonus, which is typically a slow myoclonus. It is quite typical for this disorder and helps one to narrow the differential diagnosis in the evaluation of PMEs. The only case in

which the clinical diagnosis was not considered was a two and half year old child with atypical features and atypical EEG in the form of multifocal spikes with burst attenuation pattern, but had a positive CSF immunological test to confirm the diagnosis.

Myoclonic falls is the commonest presentation in 60 % of cases, followed by seizures, cognitive decline and ataxia (in one patient). Unlike other neurodegenarative disorders, "focal" signs are more common with SSPE.[37, 38] Four patients had focal signs in the form of pyramidal, extra-pyramidal or cerebellar features. It was surprising to note that there was a remarkable sex predilection in our case series. Male to female ratio was at 1.9:1. Though it has been recognised to be slightly more common in male children, female patients were being increasingly reported and the previous ratio of 2.3: 1 had declined to 1.8:1 in a series of 100 patients.[39, 40] Male preponderance may have implications in the pathogenesis of SSPE, which still remains to be an untreatable disorder with a uniformly poor prognosis except in rare cases where the progression may cease.[37]

Electroencephalography was very useful in the diagnosis of SSPE.[41] Typical pseudo periodic long interval discharges were seen in 18 patients. The remaining two patients had epileptiform abnormalities with a burst attenuation pattern which is a atypical pattern reported in SSPE.[42] MRI findings are not specific. MRI findings noted in our study include hyperintensities in the white matter of frontal and occipital regions. One patient had unilateral putaminal hyperintenity in addition. MRI adds little to the diagnosis in this disorder. One patient was very young and had atypical EEG findings. In another patient MRI was done as a part of PME work up.

Thus the diagnosis of SSPE is relatively easy once it is suspected clinically. It should be suspected in any patient with cognitive decline, unexplained falls, seizures and rapidly progressive extrapyramidal syndrome and it should always figure in the differential diagnosis of any patient with PME. EEG and CSF study for anti measles antibody titer are the only diagnostic tests required to confirm the diagnosis. Ruling out SSPE by a CSF and EEG study would be a more cost effective approach in the evaluation of PME. Only five patients were available for follow up and all had deteriorated since the previous visit.

MISCELLANEOUS CAUSES

Despite screening of 15 cases, only one patient was detected to have hypothyroidism. This patient had improved on follow up on thyroxine. The need for early diagnosis of hypothyroidism needs no special emphasis as it has been proven that only children detected and treated before the age of one month have a normal cognitive outcome.[43] Only of the patients thyroid function tests were available. Though the clinical features suggest alternate possibilities, it is necessary to screen for hypothyroidism in all the cases as it is a potentially treatable factor that may coexist in a given patient. The fact that in many developed countries hypothyroidism screening is done routinely for all new born babies should emphasise the importance of detecting it early. Screening for hypothyroidism should always be done in all cases of suspected neurodegenarative disorders [11, 43].

The diagnosis of osteopetrosis was interesting. This 7 yr old boy presented with progressive visual impairment from infancy with macrocephaly, mental retardation and 3

episodes of fracture of the humerus. X-rays of the long bones done for looking at the fracture clinched the diagnosis of Osteopetrosis. Extra cerebral causes of macrocephaly like skeletal causes and extra axial fluid collections need to be considered when evaluating such patients with macrocephaly.[13]

Another case, a one and half year old child presented with unequivocal features to suggest a TORCH infection. This child had rash at birth, congenital cataract, features of panophthalmitis and delayed development and subsequently was lost to follow up. These clinical features strongly suggested a possibility of an intra-uterine infection and syphilis is one of the treatable disorders in this group.[44] The diagnosis of rubella has implications for contacts at home especially women in the reproductive age group as these cases shed rubella virus almost life long and are potential sources for this devastating infection in pregnant women. Also, screening of the parents should be a part of the diagnostic evaluation.

The diagnosis of a 10 month-old child with feeding difficulty and predominant motor developmental delay and microcepahly with a strong family history of similar illness leading to early death of the two elder siblings at one and half and three years, remained elusive despite a fairly extensive diagnostic work up. MRI was considered normal for the age and the screening for aminoaciduria, galactosemia, organic acidemia were negative. This child progressively deteriorated on follow up. An extensive lysosomal enzyme screen might have helped in arriving at the correct diagnosis.

Three cases were diagnosed as possible mitochondrial cytopathy. All three had one first rank feature of mitochondrial disease. However none of them qualified for any definite phenotypic entities described so far. One patient with features suggestive of Leigh's diseases was categorized under corencephalopathy. None had a positive family history. None of the two patients who underwent biopsy study had any ragged red fibers or abnormal mitochondria on electron microscopy. These cases have to be labelled as undiagnosed entities and merits a close follow up for other features of the clinical phenotype to emerge. Three had dropped out of follow up. Mitochondrial cytopathies need to be considered whenever a patient present with one of the first rank features or two of the second rank features (Table- 12).[45]

Table-12. Clinical features useful in recognizing mitochondrial disease.

Rank-1	Rank-2	Rank-3
Progressive external ophthalmoplegia Raised lactate Maternal inheritance Low density in putamen on CT scan Sub sarcolemmal accumulation of mitochondria	Myoclonic epilepsy Ataxia Myopathy Stroke like episodes Deafness	Failure to thrive Small stature Dementia Developmental regression Retinal pigmentation Metabolic acidosis Cardiomyopathy Optic atrophy

FOLLOW UP RATES

It is noted that more than 60% cases have not turned for follow up. Two cases were diagnosed initially to have a neurodegenerative disorder, improved on follow up

thus negating a degenerative disorder. Both these cases had a subacute onset of illness; one was diagnosed as possible MLD and the other as ALD Vs ADEM. The first case started regaining the lost mile-stones at 1 yr follow up and the next case rapidly improved by more than 90% on follow up with in six weeks. Among the acute insults to CNS, ADEM has the propensity to mimic as leukodystrophy both clinically and radiologically[30]. As mentioned earlier, it is not unusual for ALD to have a fairly acute onset and associated with a febrile illness. Hence in cases where a firm diagnosis is not made on biochemical evidence, it is necessary to keep them under close follow up to further characterise the disease. Establishing a definitive diagnosis has important implications in prognosis and in genetic counseling for subsequent pregnancies with an option of pre-natal diagnosis, if available for the particular condition. Also, some of these disorders are treatable like hypothyroidism, Wilson's disease which have definitive therapy and dietary restrictions in may help in conditions like aminoacidurias, Refsum's disease, Sjogren-Larsen syndrome, ALD, etc.

We conclude that, degenerative disorders of childhood constitute an important cause for admission to the pediatric neurology wards. A definitive diagnosis could be established in 56% of cases. SSPE and Leukodystrophies constituted majority of cases (51%). Majority of the undiagnosed cases belong to the category of porencephalopathy. Under utilization of the metabolic work up including the thyroid profile, amino acid screen and ammonia were noted. Also, the electron microscopic study of the biopsy specimen was found to be utilised less frequently. An algorithmic approach to these disorders with a proper utilization of the available metabolic screening facilities and

appropriately done biopsy studies would help to arrive at a definitive diagnosis in majority of cases (*Appendix-II).*

SUMMARY AND CONCLUSIONS

1. Sixty-nine cases of probable progressive cerebral degenerative disorders were detected by screening through over 230 case files of children admitted to the pediatric ward of Sri Chitra Tirunal Institute for Medical Sciences and Technology, between Jan 1996 and June 2000.
2. There were 35 cases of leukoencephalopathy, 21 cases of porencephalopathy, 7 cases of corencephalopathy, 4 cases of diffuse encephalopathy and two cases were found to have a non-degenerative disorder on follow-up

   SSPE was the most common condition followed by ALD, MLD, NCL and Rett's syndrome.
3. A definitive diagnosis could be arrived in 39 cases (56%). A possible diagnosis in 9 cases (13%) and 21 cases (30%) remained undiagnosed. The majority of the undiagnosed cases belong to the porencephalopathy group
4. MRI was the single most important investigation that provided evidence for the diagnosis. MRI was done in 40 cases and was found to be diagnostically useful in 19 cases.
5. Metabolic work-up was found to be under utilized. A thyroid screen was available for only one fifth of the cases.
6. Biopsy studies were noted to be under utilized.
7. More than 60% cases did not turn up for follow-up. Follow-up rates were found to be high in corencephalopathy group (71%).
8. An algorithm that helps to diagnose these disorders has been formulated from the available literature and our experience. *(Appendix- II).*

Appendix I

A DESCRIPTIVE STUDY OF PROGRESSIVE CEREBRAL DEGENERATION IN CHILDHOOD (Hospital based Analysis)

Name:
Age:
Sex:
Address:

Hosp. No: ☐☐☐☐☐☐☐
DOA:
DOD:
Diagnosis code: ☐☐☐☐☐☐

1) ☐ Age of onset of disease (yrs/ months)

2) ☐ First symptom reported
1=cognitive decline 2=seizures 3=ataxia
4=visual impairment 5=motor symp 6=extra pyramidal
7=others

3) Developmental delay 1=Mild 2= Mod 3=Severe

☐ Gross motor ☐ Personal social ☐ fine motor ☐ Language
☐ Nature of Devel.delay: 1=Slow acquisition 2=regression.

4) ☐ Seizures: 0= none 1= SP 2=CPS 3= PGTC
4= SGTC 5= Myoclonic 6= Absence 7= Spasms
Age of onset ☐/

5) ☐ Cognitive decline 0=absent; 1=present.
Age of onset ☐/

6) ☐ Spasticity 0=absent;1=present

7) ☐ Visual impairment 0=absent,1=decreased VA;2=night blindness

8) ☐ Deafness 0=absent;1=present

9) ☐ Extrapyramidal movements 0=absent;1= Tremor; 2=chorea; 3= athetosis;
4=dystonia5=tics; 6=myoclonus;7=Stereotype

10) ☐ Ataxia 0=absent;1=present
Age of onset ☐/

11) ☐ Dysarthria 0=absent;1=present

12) ☐ Hypothroid symptoms 0=absent;1=present

FAMILY HISTORY

1. ☐ Consanguinity 0=non consang., 1= consang.

2. ☐ Degree of consanguinity 1=first, 2=second, 3=third.

3. ☐ Similar illness 0=absent; 1=present.

Nature of illness ☐

Relation to patient ☐

Age of onset ☐

Diagnosis if any: ☐

☐ Outcome: 1= independent; 2=dependent 3=vegetative 4= dead 5=no follow up.

☐/☐ If dead, age of death

4. ☐ Any other member with MR, SEIZURES, or any other neurological illness 0=none, 1=present

ANTENATAL HISTORY

☐ 1. Infection 0=none, 1=UTI, 2=exanthem, 3=LNE 4=arthralgia, 5=Rubella, 6=nonspecific

2. ☐ Drugs 0=none, 1=present.

Name of the drug ☐

3. Other maternal illness if any

☐

PERINATAL HISTORY

1. ☐ Birth asphyxia 0=no, 1=asphyxiated, 2=details NA

2. ☐ Neonatal jaundice 0=absnet, 1=present [TSB level>20mg% or required exch.trasfusion.]

3. ☐ Neonatal meningitis 0=absent, 1=presumptive, 2=proven.

4. ☐ Seizures 0=absent, 1=present

probable cause: ☐

OTHER SIGNIFICANT PAST ILLNESSS

☐ 0=none, 1=measles, 2=others.

☐

EXAMINATION:

General physical:

1. ☐ Weight: [kg]
2. ☐ Height/Length:[cm]
3. ☐ Head circumfernce:[cm].
   ☐ Normal=0;Microcephaly=1;macrocephaly=2.
4. ☐ Skin / hair changes
   0= none 1= ashleaf 2= shagreen patches 3 = angiokeratomas
   4= neurofibromas 5= alopecia 6= kinky hair 7= rash
   8= photosensitivity 9= icthyosis 10= xanthomas
   11= incontinenta.pigmenti 12= hypomelanosis of ito
   13= xeroderma.pigmentosum 14= F/O hypothyroidism.
   15=others
5. ☐ Ocular findings
   0= none 1= cataracts 2= keratitis 3= KF ring
   4= corneal clouding 5= microphthalmia 6= others

6.CVS:

☐ cong.heart disease(Yes=1;No=0)
diagnosis: ☐

7. RS : ☐

8. ☐ Abdomen
   0= no organomegaly 1= hepatomegaly 2=splenomegaly
   3= renomegaly 4= inguinal hernia 5= umbl.hernia
   6= others

9.CNS

a) Intelligence
   ☐ IQ: if done___
   ☐ SQ:___

b) ☐ Speech 0= normal 1= dysarthria

c) ☐ Stereotype 0= absent 1= present

d) ☐ Behaviour 0=nil specific 1= autistic
   2=hyperkinetic 4=self mutilating

f) Visual

1. ☐ Ocular movements 0= normal 1= Restricted
2. ☐ Pupillary reflex 0= normal 1= abnormal

g) ☐ Fundus
0= normal 1= Optic atrophy 2= Ret. Pig.deg.
3= Cherry red spot 4= Macular degeneration
5= Any other findings (specify)
☐

h) ☐ Hearing
0= normal 1=deafness 2= hyperacusis

i) MOTOR:

1. ☐ Bulk 0= normal 1= wasting 2= hypertrophy
Specify pattern/group. ☐
2. ☐ Tone 0= normal 1= spastic 2= rigid 3= hypotonia
3. ☐ Power/weakness 0= normal 1=LL 2= all limbs
4. ☐ DTRs 0= normal 1=a/hyporeflexia 2=brisk
☐ Ankle jerk 0= normal 1=a/hyporeflexia 2=brisk

j) SENSORY 0= normal 1= impaired
1. ☐ touch 2. ☐ pain 3. ☐ temp
4. ☐ position 5. ☐ vibration___ 6. ☐ cortical

k) CEREBELLAR 0= absent 1= present

1. ☐ Nystagmus
2. ☐ Tremor
3. ☐ Ataxia
4. ☐ Dysarthria
5. ☐ Finger nose in co-ord
6. ☐ Heel knee in co-ord

l) EXTRAPYRAMIDAL MOVEMENTS 0= absent 1= present
1. ☐ Chorea 2. ☐ Athetosis 3. ☐ Dystonia
4. ☐ Tremor 5. ☐ Tics 6. ☐ Others(specify)
☐

m) SEIZURES if observed 0= absent 1= present

1.☐ SPS 2.☐ CPS 3.☐ Prim.GTCS
4.☐ Sec. GTCS 5.☐ Myoclonic 6.☐ Infantile spasms

n) Others:

CLINICAL DIAGNOSIS

INVESTIGATIONS

1.Haemogram:Hb- PCV- TLC-
DLC- P L E M B
Platelets-
Smear-
Vacoulated lymphocytes ☐ 0=absent;1=present.

Others ☐

2.Biochemistry:

FBS-	BUN-	Cr.-	Uric acid
Na-	K-	Ca-	P-
SGOT-	SGPT-	Alphos-	Acid phos-
Cholesterol-	TG-	HDL-	VLDL
Sr.Copper-			
Sr.Ceruloplasmin-			

3.Urine(Positive=1;Negative=0)

a) ☐ aminogram
b) ☐ Fe Cl test
c) ☐ Nitroprusside test
d) ☐ Reducing sugars:0=none; 1=galactose; 2=fructose
e) ☐ Mucopolysacharidesf) 0ligosacharides
e) ☐ Metachromatic granules

4. ☐ Thyroid function test: 0=normal; 1=hypo; 2=hyper
a)T 3 ☐ b)T4 ☐ c)TSH ☐

5.CSF:
a)sug- b)prot- c)Ig G- d)lactate

e)cells-TLC-_____cells/cmm DLC-P___% L___%

f) [ ] VDRL 0=negative;1=positive;2=not done.

g) [ ] Anti measles Ab 0=negative;1=positive;2=not done

h)Others if any:

[ ]

6.Enzyme assay: 0=normal; 1=reduced; 2=not done

a) [ ] Arylsulphatase A
b) [ ] Hexosaminidase A
c) [ ] Hexosaminidaes B
d) [ ] Other enzymes if done

7.TORCH TITRES 0=negative; 1=positive; 2=not done

a) [ ] toxo
b) [ ] rubella
c) [ ] CMV
e) [ ] VDRL
e) [ ] Others

8. [ ] NCV/EMG study
0= Normal; 1= Myopathy; 2= Neuropathy.

[ ]

9. [ ] EEG study:
Dys [ ] Delta [ ] Asy [ ]
Supp [ ] Sleep [ ]

[ ]

10. [ ] VEP 0=normal; 1=abnormal; 2=not done

[ ]

11. BAEP: 0=normal; 1=abnormal; 2=not done
[ ]

[ ]

12. [ ] CT Head 0=normal; 1=Cer.atrophy; 2=White matter hypodensity
3=Others

Report: [ ]

13. [ ] MRI 0=normal; 1=Cer.atrophy; 2=White matter hyperintensity
3=Others

Report:

14. [ ] Biopsy if any:
0=none 1=Muscle 2=Skin
3=Nerve 4=Rectal 5=Bone marrow

15. [ ] Autopsy:(If death in hospital)
0=not done 2=done

Report:

DISCHARGE DIAGNOSIS:

ANY CHANGE IN DIAGNOSIS ON FOLLOW UP:

STUDY DIAGNOSIS:

CATEGORISATION OF THE DIAGNOSIS:

[ ] 1= Confirmed 2= Probable
3= Possible 4= Undiagnosed

ANY FOLLOW UP DATA:

[/]
[ ]

Upto what age followed up:
Outcome: 1=status quo 2=deteriorated 3=died

Appendix II

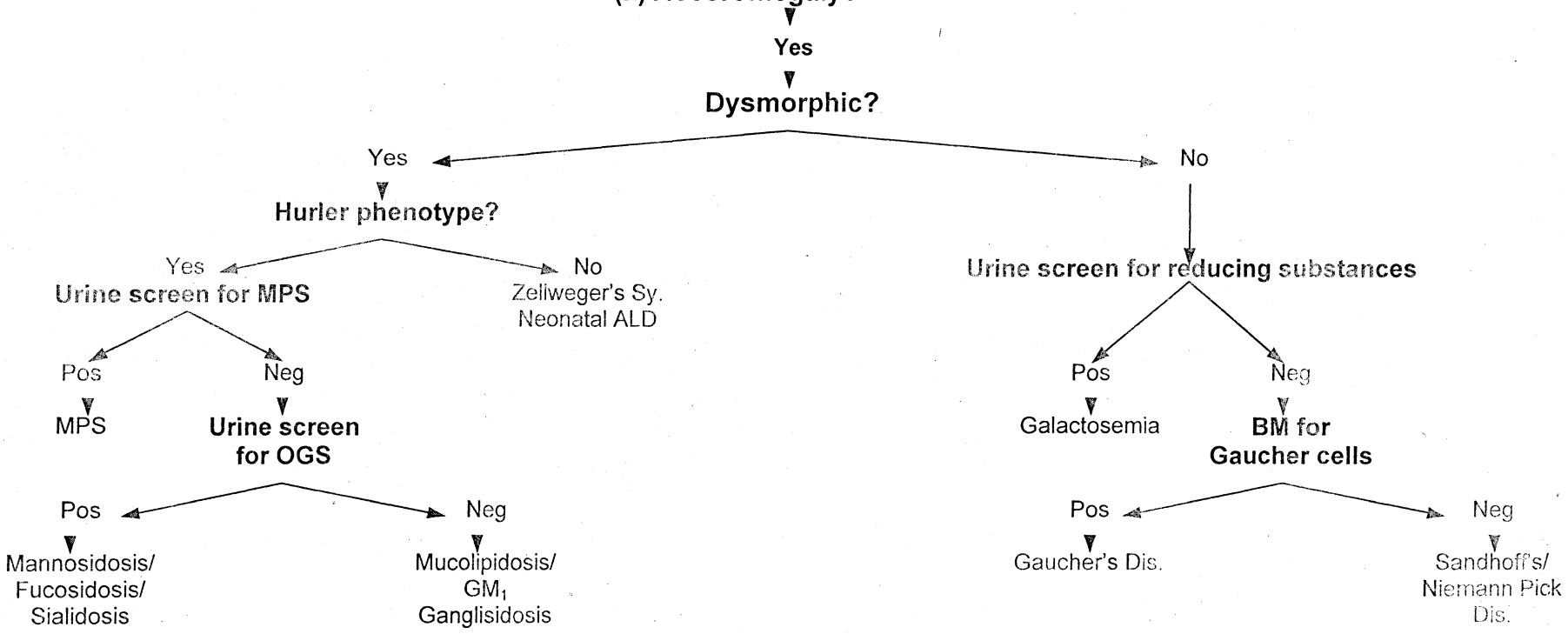
Diagnostic Evaluation

Once the child's history and physical examination are completed, formulation of differential diagnosis and further work up are initiated. The following flow-sheet is recommended for further evaluation

(1)Screen for remediable causes

Rule out hydrocephalus/hyperammonemia/hypothyroidism/aminoacidopathies/ organic acidurias (Table 3., Fig. 1)

(2)Visceromegaly?



Cont'd.

Appendix II (Cont'd)

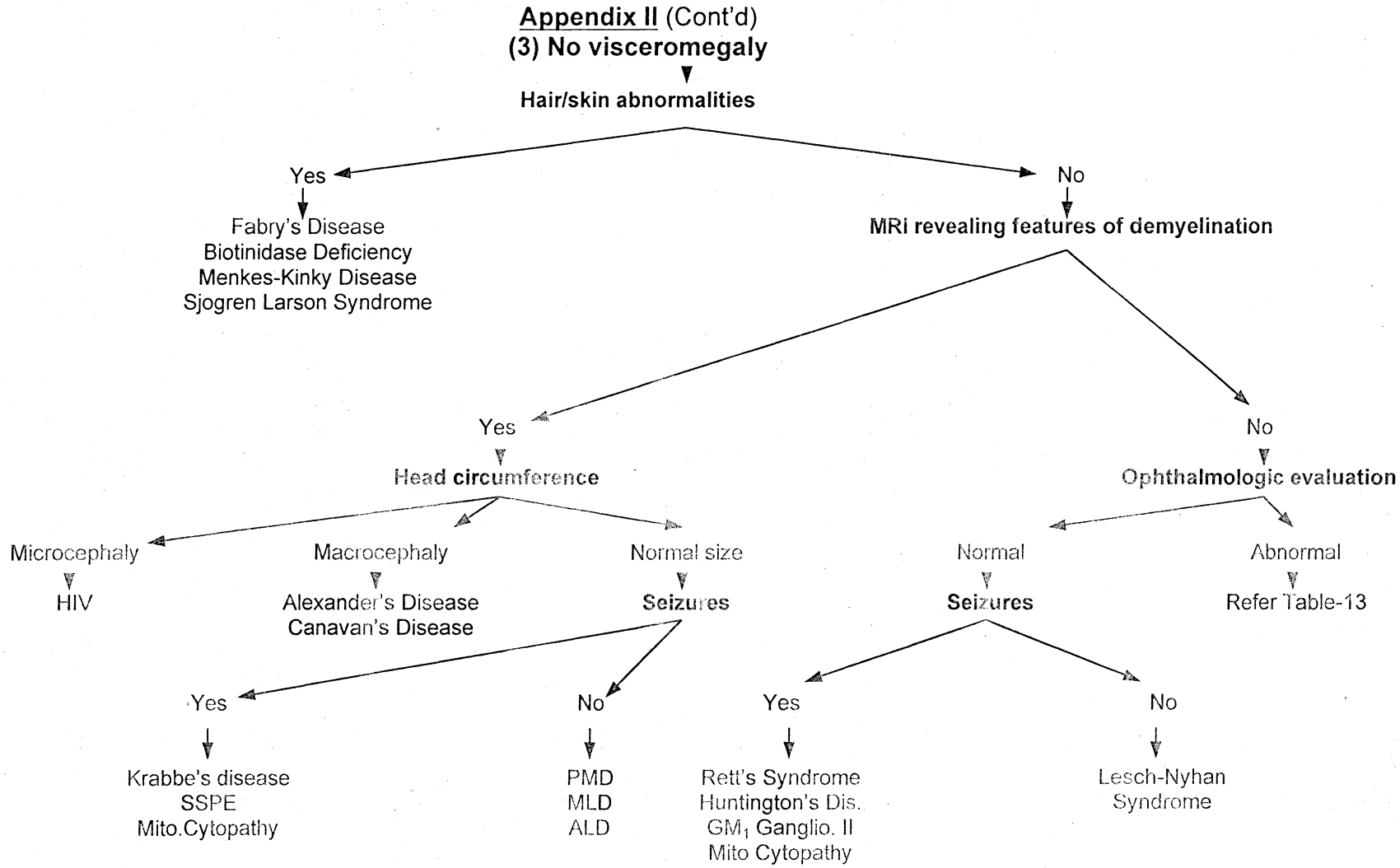


Table-13. Ocular findings

Findings	Disorders relevant
Galucoma	Lowe's syndrome
Corneal dystrophy	Lowe's syndrome, Hurler's syndrome
Cataract	Lowe's syndrome, congenital rubella, Cerebrotendinous xanthomatosis
KF ring	Wilson's disease.
Macular degenartion-	NCL (infantile/late infantile)
Retinal pigmentary degeneration-	NCL, mitochondrial cytopathy, Hallervorden- Spatz syndrome

REFERENCES

1. Cervos-Navarro J, Urich H. Fundamentals of metabolic diseases. In: Metabolic and degenerative diseases of central nervous system.1 edn. Cervos-Navarro J and Urich H. Eds., Academic press, 1995, p 4-12.
2. Needleman HL, Gunnoe C, Leviton A, et al. Deficits in psychologic and class-room performance of children with elevated dentine lead levels. NEJM 1979; 300: 689-94.
3. Kolodny EH, Cable WJL. Inborn errors of metabolism. Ann Neurol 1982; 11: 221-32.
4. Gray RGF, Preece MA, Green SH, Whitehouse W, Winer J, Green A. Inborn errors of metabolism as a cause of neurological disease in adults: an approach to investigation. JNNP 2000; 69: 5-12
5. March DO, Myers GJ, Clarkson TW, et al. Fatal methyl mercury poisoning: clinical and toxicological data on 29 cases. Ann Neurol 1980; 7: 348-53.
6. Evans OB, Block OH, Parker C, Hanson RR. Inborn errors of metabolism of the nervous system. In :Neurology in clinical practise.3rd edn. Bradley WG, Daroff RB, Fenichel GM, Marsden CD. Eds., USA, Buttersworth- Heineman, 2000, 1595-1663.
7. Amit N, Soffer D, Shaler RS, El-Pelego O, Gomori M. Glutaric aciduria:pathological findings and magnetic resonance features of symptomatic and asymptomatic homozygotes. Ann Neurol 1991; 30: 468-9.

8. Swanson PD. Diagnosis of inherited metabolic disorders affecting the nervous system. JNNP 1995; 59: 460-70.

9. Christopher R. Shetty KT. Diagnosis of inherited neurometabolic disorders: A biochemical approach. Ann Of Indian Acad Of Neurology 1999; 2: 87-97.

10. Dyken P, Krawiecki N. Neurodegenerative disorders of infancy and childhood. Ann Neurol 1983;13: 351-64.

11. Goldstein EM, Naidu S. Degenerative disorders of the brain. -A clinical and biochemical approach. Indian J Pediatr 1990; 57: 499-516.

12. Moser HW. Adrenoleukodystrophy: phenotype, genetics, pathogenesis and therapy. Brain 1997; 120: 1485-1508

13. Brett EM, Lake BD. Progressive neurometabolic brain diseases. In: Pediatric Neurology.Brett EM ed., London, Churchil Livingstone, 1997, 143- 199

14. Singer HS, Rorke LB.Clinicopathological correlation. Pediatr Neurosci 1985; 12:31- 7.

15. Chaudhry V, Moser HW, Cornblath Dr. Nerve conduction studies in Adrenoleukodystrophy. JNNP 1996; 61: 181-5.

16. Santavouri P, Pinko H, Sainio K, et al. The spectrum of Jansky-Beilschowsky's disease. Neuropediatrics 1991; 22: 92-6.

17. Carpenter S. Skin biopsy for the diagnosis of hereditary neurologic metabolic diseases. Arch Dermatol 1987; 123: 1618-21.

18. Carpenter S, Karpati G. Sweat gland duct cells in Lafora body disease: diagnosis by skin biopsy. Neurology 1991; 31: 1564-8.

19. Goebel HH, Sharp JD. The neuronal ceroid lipofuscinoses. Recent advances. Brain Pathol 1998; 8: 151-62.

20. Berkovic SF, Andermann F, Carpenter S, Wolfe LS. Progressive myoclonic epilepsies: specific causes and diagnosis. NEJM 1986; 315: 296-305.

21. Berkovic SF, Cochius I, Andermann E, Andermann F. Progressive myoclonic epilepsies: clinical and genetic aspects. Epilepsia 1993; 34 (suppl 3); s19-30.

22. Hagberg B. Rett syndrome: clinical peculiarities and biological mysteries. Acta Paediatr 1995; 84: 971-6.

23. Courchesne E, Townsend J, Saitoh O. The brain in infantile autism: posterior fossa structures are abnormal. Neurology 1994; 44: 214-23.

24. Glaze DG, Frost JD, Zoghbi HY, Percy AK. Rett''s syndrome. Correlation of electroencephalographic characteristics with clinical staging. Arch Neurol 1987; 44: 1053-6.

25. Van Geel BM, Assies J, Wanders RJA, Barth PG. X-linked adrenoleukodystrophy: clinical presentation, diagnosis and therapy. JNNP 1991; 63: 4-14.

26. Renier WO, Gabneels FJM, Hustinx TWJ, et-al. Connotal Pelizaeus-Merzbacher disease with congenital stridor in two maternal cousins. Acta Neuropathological 1981;20:71-7.

27. Loes DJ, Hite S, Moser H, et al. Adrenoleukodystrophy: a scoring method for brain MR observation. Am J Neurorad 1994; 15: 1761-6.

28. Demaerel P, Faubert C, Wilms G, et al. MR findings in leukodystrophy. Neurorad 1991; 33: 368-71.

29. Nowell MA, Grossman RI, Hackney DB, et al. MR Imaging of white matter disease in children. AJNR 1998; 9: 503-9.

30. Singh S, Alexander M, Korah IP. Acute disseminated encephalomyelitis. MR Imaging features. AJR 1999; 173: 1101-7.

31. Hinchey J, Chaves C, Appigani B, et al. A reversible posterior leukoencephalopathy syndrome. NEJM 1996; 334: 494-500.

32. Young AB, Shoulson I, Penney JB, et al. Huntington's disease in Venezuela: neurological features and functional decline. Neurology 1986; 36: 244-9.

33. Haris GJ, Pearlson GD, Peyser CE, et al. Putamen volume reduction on MRI exceed caudate in mild Huntington's disease. Ann Neurol 1992; 31:69-75

34. Dobyns NB, Goldstein NP, Gordon H. Clinical spectrum of Wilson's disease. (Hepatolenticular degeneration). Mayo Clin Proc 1979; 54: 35-42

35. Garcia UD, Campos J, Varela de seijas E, de yebenes JG. Movement disorder in Ataxia telangiectasia. Neurology 1989; 32: suppl (1): 321-23

36. Rall DP, Tower Db. Environmental hazards and neurological diseases. Ann Neurol 1977; 1: 209-10.

37. Dyken PR. Subacute sclerosing panencephalitis- current status. Neurology clinic 1985; 3:179-95

38. Billeter MA, Cattanco R, Spielhofer P, et al. Generation and properties of measles virus mutation typically associated with SSPE. Ann N Y Acad Sci 1994; 724: 367-77

39. Jabbour JJ, Duenng DA, Sever JL, et al. Epidemiolgy of Subacute sclerosing panencephalitis- A report of SSPE registry. JAMA 1972; 220: 959-62

40. Modin JF, Halsey NA, Eddins DL,et al. Epidemiolgy of SSPE. J Pediatr 1979; 94:231-6

41. Markand ON, Panszi JG. The electroencephalogram in subacute sclerosing panencephalitis. Arch Neurol 1975; 32: 719-26.

42. Santoshkumar B, Radhakrishnan K. Periodic electroencephalographic pattern modified by pre-existing damaged cerebral hemisphere. Electroencephalogr Clin Neurophysiol 1996; 99(5): 440-3.

43. Hulse JA, Grant DB, Clayton BE,et al. Population screening for congenital hypothyroidism. BMJ 1980; 280: 675-8.

44. Marcola L, Pelosi R, Blount Jh, et al. Congenital syphilis revisited. Am J of Dis in Child 1985; 139: 575-80.

45. Jackson MJ, Schafer JA, Johnson MA, et al. Presentation and clinical investigation of mitochondrial respiratory chain disease. A study of 51 patients. Brain 1995: 118: 339-57.