Results and Analysis of DATA

This study comprised 45 infants and children with neurodegenerative disorders. The patients were 25 males [55.6%] and 20 females [44.4%] with their ages ranging from 6 months to 13 years.

The patients were classified into three subgroups based on clinical data, neuroimaging studies as well as specific laboratory diagnosis:

a) Demyelinating group comprising 30 patients [66.7%].

b) Neuronal storage group comprising 9 patients [20%].

c) Miscellaneous group comprising 6 patients [13.3%].

Demyelinating brain disorders group [table 10]:

The hallmark of this group is a demyelinating process demonstrated as low density changes of the white matter on CT brain or altered signal with white matter high signal intensity on T2-weighted MRI. These changes were demonstrated in symmetrical and often diffuse manner.

This group included 14 cases suffering from MLD, 1case from ALD, 2 from Canavan disease, 2 from Alexander's disease, 1 from PMD and 3 ones from glutathione synthetase deficiency. This group also included 2 cases with possible diagnosis of Krabbe disease and 5 cases with undefined etiology. One case with metachromatic leukodystrophy and two cases with possible diagnosis of Krabbe disease died after investigations were done.

Fourteen were males and 16 were females. The mean age at presentation was 45.10±32.2 months with the range from 6 months to 12 years and the mean duration of illness was 26.33±21.88 months.

Neuronal storage group [table 11]:

In this nine-patient group, 2 patients were diagnosed as having GM2 gangliosidoses, 4 patients with Niemmann-Pick's disease and 3 patients with mucopolysaccharidoses.

Six were males and 3 were females. The mean age at presentation was 62.67±36.39 months with the range from 18 months to 10 years and the mean duration of illness was 28.67±14.71 months

Miscellaneous group [Table 12]:

In this 6 patient group, 1 patient was diagnosed as having Wilson's disease, 1 patient with mitochondrial encephalomyopathy, 1 patient with Friedreich's ataxia and 1 patient with hereditary spastic paraplegia. Meanwhile, the other 2 cases were of unknown etiology but the clinical course was highly suggestive of neurodegrenerative disease.

Five were males and one was female. The mean age at presentation was 89.50±64.86 months with the range from 15 months to 13 years and the mean duration of illness was 27.50±9.38 monthes.

Table [10]: The etiological diagnosis in demyelinating group and the main diagnostic investigations .

Pt. No.	*Sex*	*Age at presentation (months)*	*Duration of illness (months)*	*Etiological Diagnosis*	*Main diagnostic investigation*
1	M	18	6	MDL	↓ arylsulphatase A enzyme
2	M	42	36	MDL	↓ arylsulphatase A enzyme
3	M	7	3	MDL	↓ arylsulphatase A enzyme
4	M	42	12	MDL	↓ arylsulphatase A enzyme
5	F	31	7	MDL	↓ arylsulphatase A enzyme
6	M	72	48	MDL	↓ arylsulphatase A enzyme
7	M	50	42	MDL	↓ arylsulphatase A enzyme
8	M	60	54	MDL	↓ arylsulphatase A enzyme
9	M	18	12	ADL	↑ VLC FA
10	F	32	26	MDL	↓ arylsulphatase A enzyme
11	F	78	4	MDL	↓ arylsulphatase A enzyme
12	M	42	12	Unknown	—
13	F	36	12	Alexander's disease	Diagnosis on the basis of clinical data.
14	M	60	50	Canavan disease	Diagnosis on the basis of clinical data and C.T brain
15	M	132	84	Canavan disease	Diagnosis on the basis of clinical data and C.T brain
16	F	6	3	Unknown	—
17	F	39	30	Krabbe disease	Diagnosis on the basis of clinical data and N.C.V

Continue:

Pt. No.	*Sex*	*Age at presentation (months)*	*Duration of illness (months)*	*Etiological Diagnosis*	*Main diagnostic investigation*
18	F	48	36	Unknown	---
19	F	12	6	MLD	↓ Arylsulphatase A enzyme
20	F	28	12	MLD	↓ Arylsulphatase A enzyme
21	F	43	12	Unknown	—
22	F	60	36	Alexander's disease	Diagnosis on the basis of clinical data.
23	M	144	60	Unknown	—
24	F	78	18	MLD	↓ Arylsulphatase A enzyme
25	F	42	36	Krabbe disease	Diagnosis on the basis of clinical data + NCV
26	M	48	42	PMD	Diagnosis on the basis of clinical data
27	F	24	18	MLD	↓ Arylsulphatase A enzyme
28	F	60	24	Glutathione synthetase deficiency	↓ Glutathione blood level
29	F	24	6	Glutathione synthetase deficiency	↓ Glutathione blood level
30	M	26	18	Glutathione synthetase deficiency	↓ Glutathione blood level
Mean & SD	-	45.10 ± 32.20	26.33 ± 21.88		

MLD = Metachromatic leucodystrophy.
ALD = Adrenoleucodystrophy.
↑VLCFA = Increased very long chain fatty acids.
PMD= Pelizaeus-Merzbacher disease.

Table [11]: The etiological diagnosis in neuronal storage group and the main diagnostic investigations.

Pt. No.	*Sex*	*Age at presentation (months)*	*Duration of illness (months)*	*Etiological diagnosis*	*Main diagnostic investigation*
1	M	48	36	G M2 Type III Gangliosidosis	↓↓ Hexosaminidase A enzyme
2	F	24	24	Tay-Sachs' disease	↓↓ Hexosaminidase A enzyme
3	F	30	30	Neimann-Pick's disease	Myelogram show abnormal cells*
4	M	66	12	Neimann-Pick's disease	Myelogram show abnormal cells
5	M	108	48	Neimann-Pick's disease	Myelogram show abnormal cells
6	M	18	6	Neimann-Pick's disease	Myelogram show abnormal cells
7	F	120	36	Mucopolysaccharidoses	Typical abnormality in skeletal survey + ↑ MPS in urine
8	M	66	48	Mucopolysaccharidoses	Typical abnormality in skeletal survey + ↑ MPS in urine
9	M	84	24	Mucopolysaccharidoses	Typical abnormality in skeletal survey + ↑ MPS in urine
Mean & SD	-	62.67 ± 36.39	28.67 ± 14.71		

* Abnormal cells = large cells with foamy cytoplasm and eccentric nuclei.

Table [12]: The etiological diagnosis in miscellaneous group and the main diagnostic investigations.

	Sex	*Age at presentation (months)*	*Duration of illness (months)*	*Etiological diagnosis*	*Main diagnostic investigation*
1	M	156	24	Wilson's disease	↑Copper in 24 h urine before & after D-penicillamine administration.
2	M	36	33	Mitochondrial encephalomyopathy	Muscle biopsy*.
3	M	42	24	Unknown	---
4	M	144	36	Friedreichs ataxia	Diagnosis on the basis of clinical data.
5	F	144	36	Hereditary spastic paraplegia	Diagnosis on the basis of clinical data.
6	M	15	12	Unknown	---
Mean & SD	-	89.50 ± 64.86	27.50 ± 9.38		

* Light and electron microscopic examination of muscle biopsy revealed subsarcolemmal aggregates of abnormal sized and shaped mitochondria.

Table [13]: Age at presentation (in months) in the 3 studied patient groups.

Group	*N*	*Mean & SD*	*Range*	*P-value*
Demyelinating	30	45.10±32.20	6-144	.036
Neuronal storage	9	62.67±36.39	18-120	
Miscellaneous	6	89.50±64.86	15-156	
Total	45	54.53±40.53	6-156	

- The mean age of the 3 studied patient groups showed significance difference.
- The mean age of the miscellaneous group was significantly higher than that of the demyelinating group [P-value = .013].

Table [14]: Duration of illness (in months) in the 3 studied patient groups.

Group	*N*	*Mean & SD*	*Range*	*P-value*
Demyelinating	30	26.33±21.88	3-84	.949
Neuronal storage	9	28.67±14.71	6-48	
Miscellaneous	6	27.50±9.38	12-36	
Total	45	26.96+19.13	3-84	

* P-value < 0.05 is significant.

There is no significant difference between the mean duration of illness among the 3 studied patient groups.

The comparative study of the clinical data in the 3 studied patient groups demonstrated [Table 15]:

- Positive consanguinity was elicited in 38 out of 45 cases [84.4%] whereas a positive family history of a similar condition could be elicited in approximately 50% of cases [23 out of 45 cases].
- Seventeen out of 45 [37.8%] patients were suffering from convulsion that has a higher percentage mainly in-patients suffering from neuronal storage disease. However, this was statistically non significant.
- All patients had severe psychomotor retardation:

- Speech was limited to a few words in the majority of patients. In demyelinating group [30 cases], three patients [10%] had staccato speech (1 case with MLD and 2 cases with the possible of Alexander disease) while in miscellaneous group [6 cases], two patients [33.3%] had slurred speech (1 case was suffering from Wilson's disease and the other from Friedreich's ataxia).

- Delayed achievement of motor developmental milestone was observed in 20 patients. Abnormal gait was found in 16 cases. Gait was ataxic in 10 cases, spastic in 4 cases and waddling in 1 case. 6.7% of cases were wheel chair bound.

In demyelinating group, 6 cases [20%] presented with ataxic gait (2 cases with MLD, 2 cases with the possible of Alexander disease and two cases with undefined etiology) and 1 case [3.3%] diagnosed Canavan disease presented with spastic gait. Meanwhile , in neuronal storage group, 2 cases [22.2%] presented with ataxic gait (1 case suffered from GM2 type III Gangliosidosis and the other

from Neimann-Pick disease) and 2 cases [22.2%] with spastic gait (1case with Neimann-Pick's disease and other with mucopolysaccharidoses).

In miscellaneous group, ataxic gait was found in 2 cases (one case diagnosed as Friedreich's ataxia variant and the other with undefined etiology) while spastic gait was seen in one case with hereditary spastic paraplegia and waddling gait was observed in case one diagnosed as mitochondrial encephalomyopathy.

- Movement disorders were observed in 12 out of 45 patients [26.6%]. Intention tremors were seen in 7 patients with demyelinating diseases (3 cases with MLD, 2 cases with Alexander's disease and two cases with undefined etiology), 2 cases with neuronal storage diseases (1 case suffered from GM2 type III gangliosidosis and the other from Neimann-Pick disease) and 2 cases in miscellaneous group (1 cases diagnosed as Fridreich's ataxia and the other case with undefined etiology). Static tremors were observed in the patient in whom the diagnosis of Wilson's disease was confirmed.
- As regard the skull size, macrocephaly was found in 10 patients: 6 cases in the demyelinating group, 3 cases in the neuronal storage group and 1 cases in miscellaneous group while microcephaly was found in 6 patients, all were belonging to the demyelinating group (4 cases diagnosed as MLD and 2 cases with the possible diagnosis of Krabbe disease).
- Cranial nerve affection in the form of bulbar palsy was found in 8 cases with demyelinating disease [3 cases with MLD, I case with ALD, 1 with the possible diagnosis of Krabbe disease, 2 cases with

glutathione synthetase deficiency and 1 case with undefined etiology] and only one case suffered from mucopolysaccharidoses.

- Neurological examination of the motor system revealed that 34 out 45 patients [75.6 %] had hypertonia while hypotonia was elicited in 11 out of 45 cases [24.2%].

In demyelinating group, only 6 cases presented with hypotonia [5 cases suffered from MLD & 1 case diagnosed as Canavan disease]. However, hyporeflexia was elicited in 7 cases: 5 cases suffered from MLD and 2 cases with the possible diagnosis of Krabbe disease.

In the neuronal storage group, only 2 cases diagnosed as Neimann-Pick disease presented with hypotonia and hyporeflexia.

- Dysmorphic facial features were observed in 2 cases with mucopolysaccharidoses and organomegaly was found in 2 cases suffering from Neimann-Pick disease.

- As regard ocular manifestations, cataract was elicited in one case with mitochondrial encephalomyopathy while nystagmus was seen in 5 patients with demyelinating disease [1 case diagnosed as PMD and 4 cases as MLD] and 1 patient with Tay-Sachs disease.

In addition, fundus examination revealed cherry-red spots of the macula in the 2 cases with GM2 gangliosidoses and retinits pigmentosa in 2 cases: 1 case diagnosed as Neimann-Pick disease and the other case as mucopolysaccharidoses.

Slit lamp examination revealed kayser-fleisher ring in the patient suffering from Wilson's disease.

Table [15]: The comparative study of the clinical data in the 3 studied patient groups.

Clinical data		*Patients group*						*Total [N =45]*		*P-value*
		Demyelinating [N =30]		*Neuronal storage [N =9]*		*Miscellaneous [N =6]*				
		N	*%*	*N*	*%*	*N*	*%*	*N*	*%*	
Consanguinity	+ ve	26	86.7	8	88.9	4	66.7	38	84.4	.074
	- ve	4	13.3	1	11.1	2	33.3	7	15.6	
Family history	+ ve	17	56.7	4	44.4	2	33.3	23	51.1	.521
	- ve	13	43.3	5	55.6	4	66.7	22	48.9	
Convuision	Atonic	1	3.3	-	-	-	-	1	2.2	.392
	Focal	2	6.7	-	-	1	16.7	3	6.7	
	Generalized tonic-clonic	4	13.3	3	33.3	1	16.7	8	17.8	
	Myoclonic	3	10	2	22.2	-	-	5	11.1	
	None	20	66.7	4	44.4	4	66.7	28	62.2	

Continue:

Clinical data		*Patients group*						*Total [N =45]*		*P-value*
		Demyelinating [N =30]		*Neuronal storage [N =9]*		*Miscellaneous [N =6]*				
		N	*%*	*N*	*%*	*N*	*%*	*N*	*%*	
Gait	Spastic	1	3.3	2	22.2	1	16.7	4	8.9	.007#
	Ataxic	6	20	2	22.2	2	33.3	10	22.2	
	Shuffling	-	-	-	-	1	16.7	1	2.2	
	Waddling	-	-	-	-	1	16.7	1	2.2	
	Delayed	17	56.7	3	33.3	-	-	20	44.4	
	Chair bound	2	6.7	1	11.1	-	-	3	6.7	
	Too young	4	13.3	1	11.1	1	16.7	6	13.3	
Speech	Dysarthria	22	73.3	9	100	4	66.7	35	77.8	.005#
	Staccato	3	10	-	-	-	-	3	6.7	
	Slurred	-	-	-	-	2	33.3	2	4.4	
	Too young	5	16.7	-	-	-	-	5	11.1	

Continue:

Clinical data		Patients group						Total [N =45]		P-value
		Demyelinating [N =30]		Neuronal storage [N =9]		Miscellaneous [N =6]				
		N	%	N	%	N	%	N	%	
Abnormal movements	Intension tremors	7	23.3	2	22.2	2	33.3	11	24.4	.124
	Static tremors	-	-	-	-	1	16.7	1	2.2	
	None	23	76.7	7	77.8	3	50	33	73.3	
Skull size	Macrocephaly	6	20	3	33.3	1	16.7	10	22.2	.48
	Microcephaly	6	20	-	-	-	-	6	13.3	
	Normal	18	60	6	66.7	5	83.3	29	64.5	
Cranial nerves affection	Bulbar palsy	8	26.7	1	11.1	-	-	9	20	.249
	None	22	73.3	8	88.9	6	100	36	80	
Tone	Hypertonia	24	80	7	77.8	3	50	34	75.6	.291
	Hypotonia	6	20	2	22.2	3	50	11	24.4	
Motor reflexes	Hyperreflexia	22	73.3	6	66.7	1	16.7	29	64.4	.014#
	Hyporeflexia	7	23.3	2	22.2	2	33.3	11	24.4	
	Normal	1	3.3	1	11.1	3	50	5	11.1	

Continue:

Clinical data		*Patients group*						*Total [N =45]*		*P-value*
		Demyelinating [N =30]		*Neuronal storage [N =9]*		*Miscellaneous [N =6]*				
		N	*%*	*N*	*%*	*N*	*%*	*N*	*%*	
Dysmorphic features	Present	-	-	2	22.2	-	-	2	4.4	.015#
	Absent	30	100	7	77.8	6	100	43	95.6	
Organomegaly	Present	-	-	2	22.2	-	-	3	4.4	.015#
	Absent	30	100	7	77.8	6	100	43	95.6	
Ocular manifestations	Nystagmus	5	16.7	1	11.1	-	-	6	13.3	.107
	Cataract	-	-	-	-	1	16.7	1	2.2	
	None	25	83.3	8	88.9	5	83.3	38	84.4	
Fundus examination	Cherry red spots	-	-	2	22.2	-	-	2	4.4	.005#
	Retinitis pigmentosa	-	-	2	22.2	-	-	2	4.4	
	Cone dystrophy	1	3.3	-	-	-	-	1	2.2	
	Optic disc pallor	2	6.7	-	-	-	-	2	4.4	
	Kayser fleisher	-	-	-	-	1	16.7	1	2.2	
	Normal	27	90.0	5	55.6	5	83.3	37	82.2	

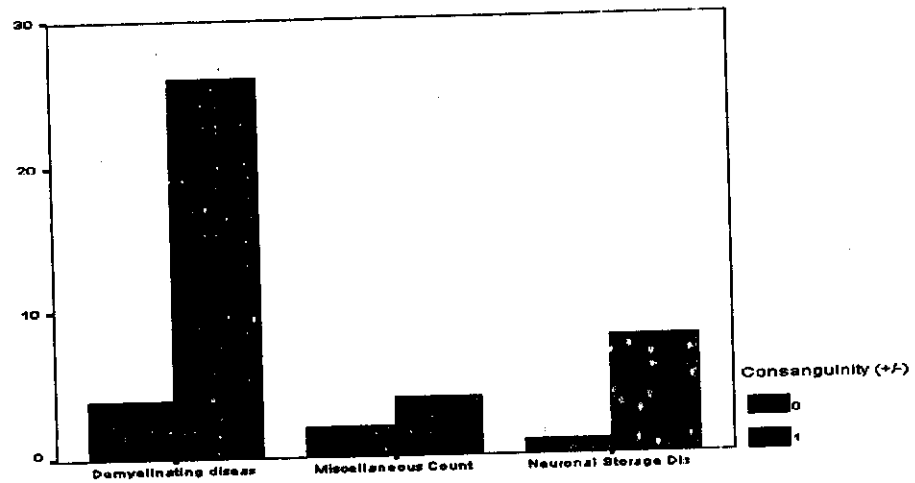


Figure [12]: The frequency of positive consanguinity in the 3 studied patient groups

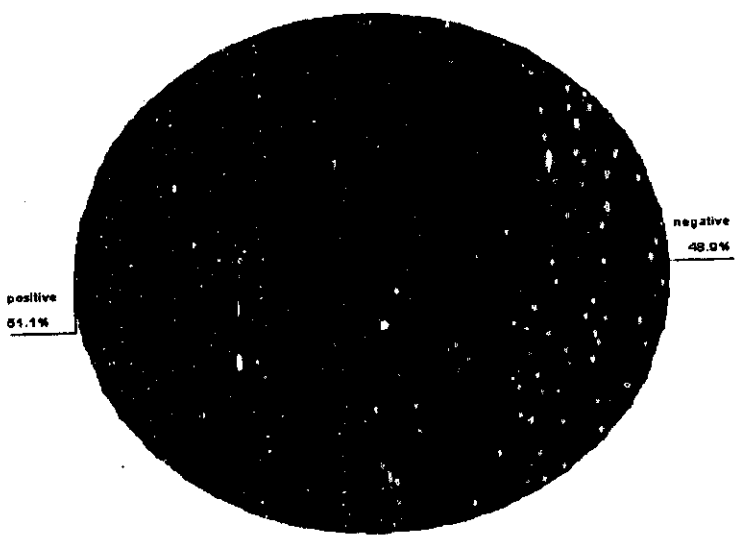


Figure [13]: Positive and negative family history in studied cases

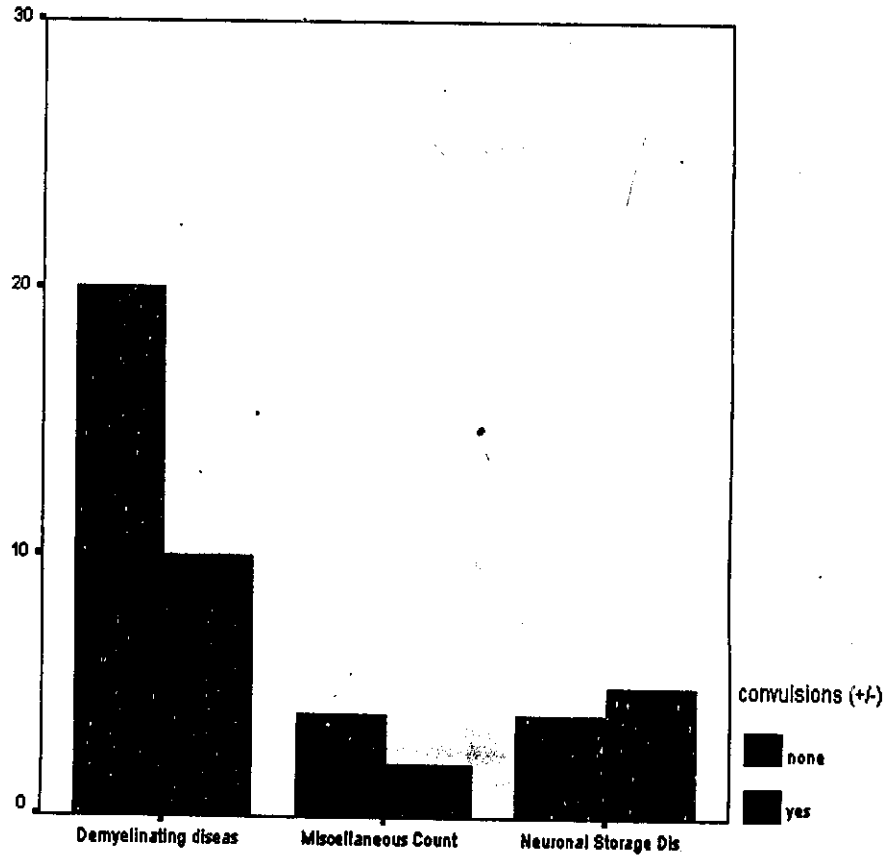


Figure [14]: The frequency of convulsions in the 3 studied patient groups

Results of the evoked potential studies:

❖ **Results of the somatosensory evoked potentials (SEPs):**

Table [16] shows the SEP measurements in patients with demyelinating disorders compared with normal control group. There is statistically significant increase in absolute latency of Erb's potential and of cortical potentials (N19/20). Similarly, there is statistically significant increase of N11/13-N19/20 interpeak latency.

Table [17] shows the SEP measurements in patients with neuronal storage disorders compared with normal control group. There is statistically significant increase in absolute latency of Erb's potential and of cortical potentials (N19/20). Similarly, there is statistically significant increase of N11/13-N19/20 interpeak latency.

Table [18] shows the SEP measurements in patients with miscellaneous neurodegenerative disorders compared with normal control group. There is statistically significant increase in absolute latency of cervical potentials (N11/13).

Table [19] shows the SEP measurements in the 3 studied patient groups as compared with each others. There is statistically significant increase in absolute latency of cortical potentials (N19/20) and N11/13-N19/20 interpeak latency in neuronal storage group as compared with miscellaneous group.

Table [16]: SEP measurements in-patients with demyelinating disorders and normal control group.

	Absolute latency						*Interpeak latency*			
	Erb's potential (Ep)		*Cervical N11/13*		*Cortical N19/20*		*Ep-N11/13*		*N11/13-N19/20*	
	Mean	*SD*	*Mean*	*SD*	*Mean*	*SD*	*Mean*	*SD*	*Mean*	*SD*
Demyelinating	7.766	1.418	12.787	1.346	19.451	2.640	4.863	1.991	6.832	3.172
Control	6.421	.7399	12.062	1.768	17.142	1.56	5.642	1.406	5.067	1.259
p-value	***.001 #***		***.096***		***.001 #***		***.090***		***.014 #***	

P-value < 0.05 is considered significant.

Table [17]: SEP measurements in patients with neuronal storage disorders and normal control group.

	Absolute latency						*Interpeak latency*			
	Erb's potetial (Ep)		*Cervical N11/13*		*Cortical N19/20*		*Ep-N11/13*		*N11/13-N19/20*	
	Mean	*SD*	*Mean*	*SD*	*Mean*	*SD*	*Mean*	*SD*	*Mean*	*SD*
Neuronal storage	7.852	1.504	12.743	1.334	20.808	2.057	4.836	1.905	8.120	1.642
Control	6.421	.7399	12.062	1.768	17.142	1.560	5.642	1.406	5.067	1.259
p-value	*.007 #*		*.257*		*.000 #*		*.174*		*.002 #*	

P-value < 0.05 is considered significant.

Table [18]: SEP measurements in patients with miscellaneous neurodegenerative disorders and normal control group.

	Absolute latency						*Interpeak latency*			
	Erb's potential (Ep)		*Cervical N11/13*		*Cortical N19/20*		*Ep-N11/13*		*N11/13-N19/20*	
	Mean	*SD*	*Mean*	*SD*	*Mean*	*SD*	*Mean*	*SD*	*Mean*	*SD*
Miscellaneous	7.182	1.661	13.510	1.280	18.435	1.320	6.328	1.237	5.344	.854
Control	6.421	.7399	12.062	1.768	17.142	1.560	5.642	1.406	5.067	1.259
p-value	*.208*		*.040#*		*.208*		*.317*		*.818*	

P-value < 0.05 is considered significant.

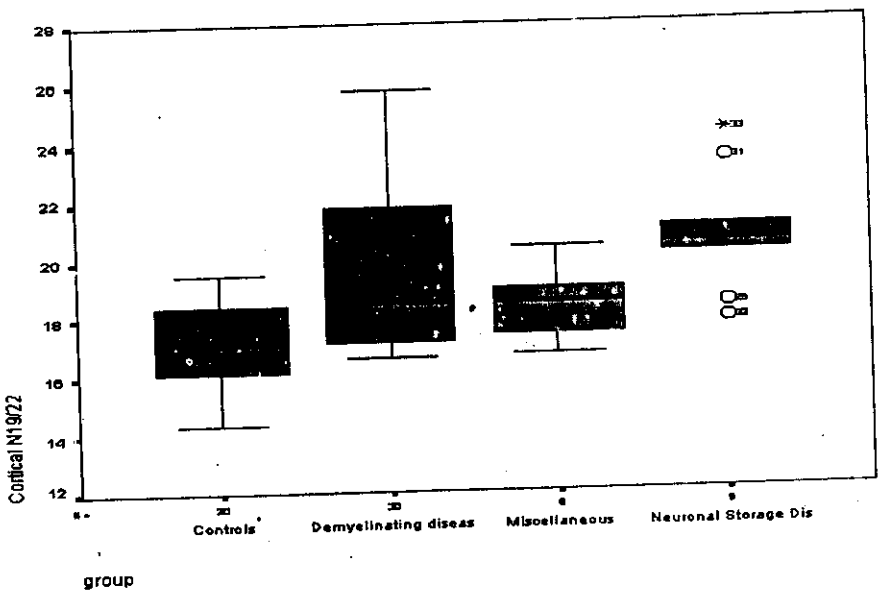
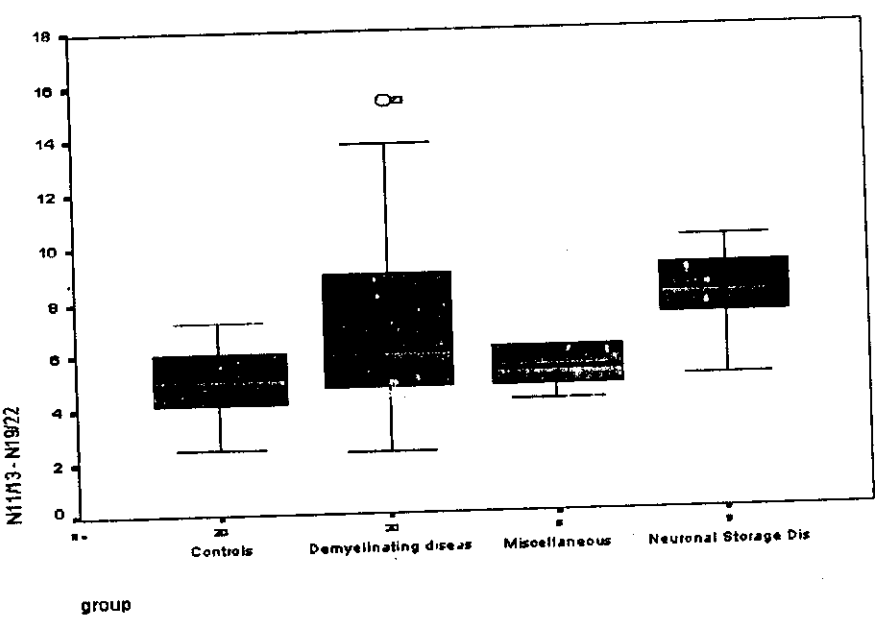


Figure [17]: The median and interquartile range of cortical N19/22 latency in the studied groups



Figure[18]: The median and interquartile range of N11/13-N19/20 in the studied groups

❖ **Results of the visual evoked potentials (VEPs):**

Table [20] shows the VEP measurements in patients with demyelinating disorders compared with normal control group. There is statistically significant decrease in amplitude of P100 in left eye.

Table [21] shows the VEP measurements in patients with neuronal storage disorders compared with normal control group. There is statistically significant increase in latency of P100 in right eye.

Table [22] shows the VEP measurements in patients with miscellaneous neurodegenerative disorders compared with normal control group. There is statistically significant increase in latency of P100 in both eyes.

Table [23] shows the VEP measurements in the 3 studied patient groups as compared with each others. There is statistically significant increase of P100 latency in miscellaneous group as compared with either demyelinating or neuronal storage groups.

Table [20]: VEP measurements in patients with demyelinating disorders and normal control group.

	Latency of P100				*Amplitude of P 100*			
	Rt.		*Lt.*		*Rt.*		*Lt.*	
	Mean	*SD*	*Mean*	*SD*	*Mean*	*SD*	*Mean*	*SD*
Demyelinating group	96.248	13.021	95.786	12.058	6.417	5.682	6.482	7.820
Control group	94.275	11.367	97.838	11.156	11.235	7.392	10.821	8.243
P-value	.590		.648		.187		.045#	

P- value < 0.05 is considered significant.

Table [21]: VEP measurements in patients with neuronal storage disorders and normal control group.

	Latency of P100				*Amplitude of P 100*			
	Rt.		*Lt.*		*Rt.*		*Lt.*	
	Mean	*SD*	*Mean*	*SD*	*Mean*	*SD*	*Mean*	*SD*
Neuronal storage	104.622	12.069	98.218	9.007	7.264	4.456	7.522	4.256
Control group	94.275	11.367	97.838	11.156	11.235	7.392	10.821	8.243
P-value	**.046***		**.939**		**.160**		**.268**	

P- value < 0.05 is considered significant.

Table [22]: VEP measurements in patients with miscellaneous neurodegenerative disorders and normal control group.

	Latency of P100				*Amplitude of P 100*			
	Rt.		*Lt.*		*Rt.*		*Lt.*	
	Mean	*SD*	*Mean*	*SD*	*Mean*	*SD*	*Mean*	*SD*
Miscellaneous group	113.683	15.440	113.257	20.013	6.093	3.524	5.535	4.254
Control group	94.275	11.367	97.838	11.156	11.235	7.392	10.821	8.243
P-value	**.002#**		**.009#**		**.381**		**.128**	

P- value < 0.05 is considered significant.

Table [23]: VEP measurements in the 3 studied patient groups.

		Latency of P100				*Amplitude of P 100*			
		Rt.		*Lt.*		*Rt.*		*Lt.*	
		Mean	*SD*	*Mean*	*SD*	*Mean*	*SD*	*Mean*	*SD*
Demyelinating group		96.248	13.021	95.786	12.058	6.417	5.682	6.482	7.820
Neuronal storage group		104.622	12.069	98.218	9.007	7.264	4.356	7.522	4.256
Miscellaneous group		113.683	15.440	113.257	20.013	6.093	3.524	5.535	4.254
P-value	***P****	**.086**		**.447**		**.712**		**.711**	
	P **	**.003 #**		**.011 #**		**.954**		**.774**	
	P* **	**.178**		**.024 #**		**.715**		**.610**	

P- value < 0.05 is considered significant
P* = significant difference between demyelinating and neuronal storage groups.
P** = significant difference between demyelinating and miscellaneous groups.
P*** = significant difference between neuronal storage & miscellaneous groups.

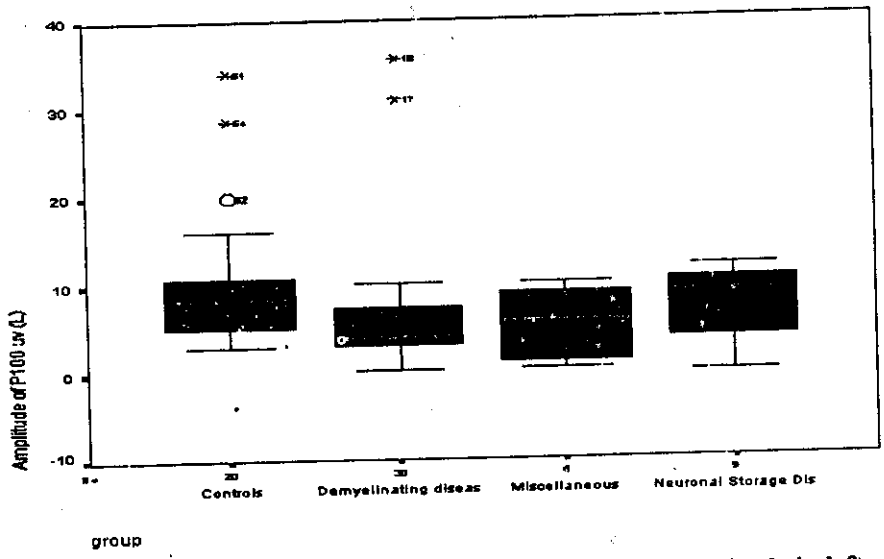


Figure [19]: The median and interquartile range of P100 amplitude in left eye

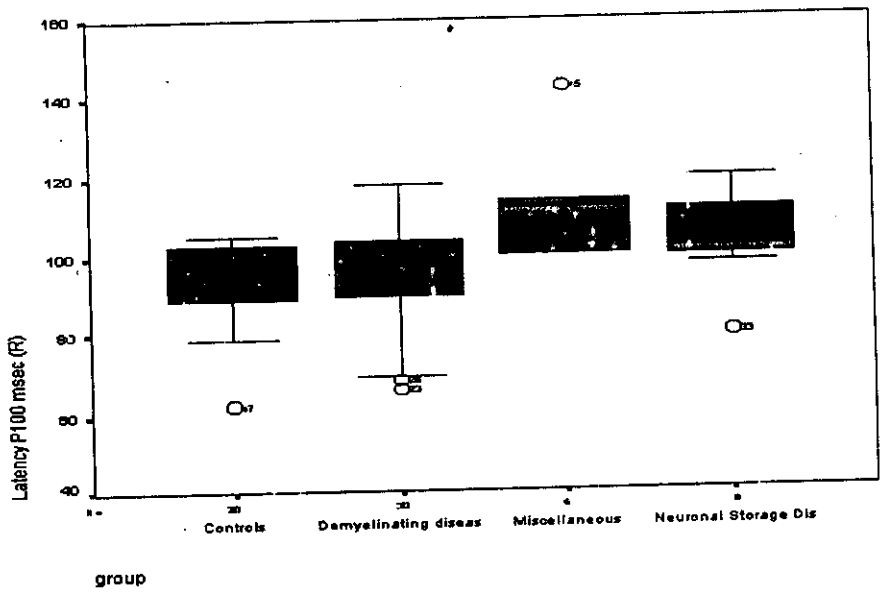


Figure [20]: The median and interquartile range of P100 latency in Rt eye

❖ **Results of the brain stem evoked potentials (BAEPs):**

Table [24] Shows the BAEP measurements in patients with demyelinating disorders compared with normal control group. There is statistically significant increase in the absolute latency of wave I, III and V.

Table [25] Shows the BAEP measurements in patients with neuronal storage disorders compared with normal control group. There is statistically significant increase in the absolute latency of wave I, III and V.

Table [26] Shows the BAEP measurements in patients with miscellaneous neurodegenerative disorders compared with normal control group. There is statistically significant increase in the absolute latency of wave I.

Table [27] Shows the BAEP measurements in the 3 studied patient groups as compared with each others. The multiple comparison of the BAEP findings revealed non-statistically significant difference among the 3 studied patient groups.

Table [24]: BAEP measurements in patients with demyelinating disorders and normal control group.

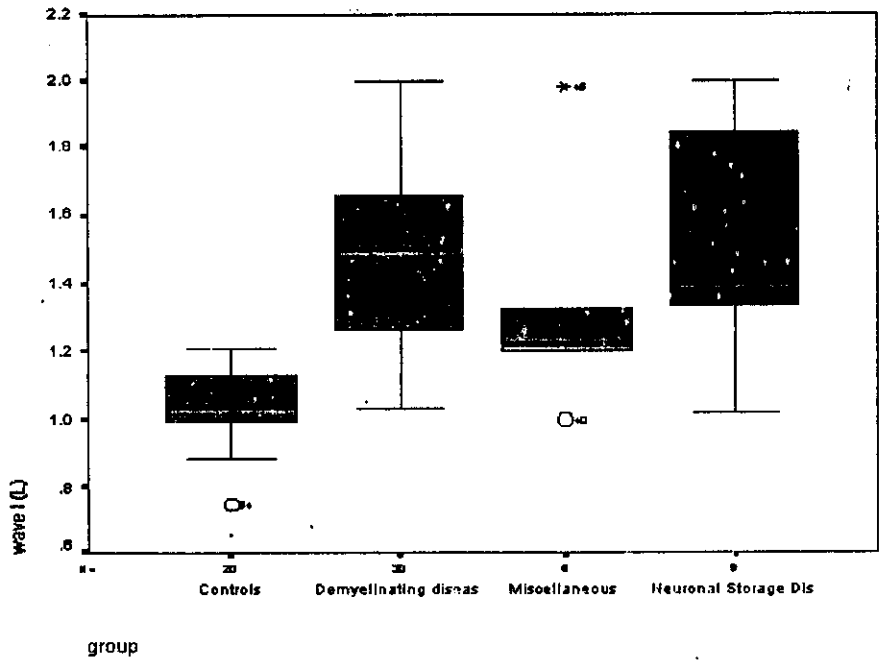
	Absolute latency												*Interpeak latency*									
	Wave I				*Wave III*				*Wave V*				*I-III*				*III-V*				*I-V*	
	Rt.		*Lt.*		*Rt.*		*Lt.*		*Rt.*		*Lt.*		*Rt.*		*Lt.*		*Rt.*		*Lt.*		*Rt.*	*Lt.*
	Mean	*SD*	*Mean*	*SD*	*Mean*	*SD*	*Mean*	*SD*	*Mean*	*SD*	*Mean*	*SD*	*Mean*	*SD*	*Mean*	*SD*	*Mean*	*SD*	*Mean*	*SD*	*Mean* *SD*	*Mean* *SD*
Demyelinating	1.46	.267	1.49	.292	3.57	.525	3.74	.463	5.22	.442	5.26	.529	2.10	.494	2.26	.492	1.65	.413	1.51	.492	3.77 .348	3.74 .5022
Control	1.03	.101	1.04	.106	2.99	.170	3.15	.383	4.67	.297	4.78	.331	1.96	.196	2.11	.336	1.68	.293	1.63	.346	3.64 .297	3.74 .263
P-value	.000#		000#		.000#		.000#		.001#		.001#		.197		.214		.877		.884		.345	.977

P-value < 0.05 is considered significant.

Table [25]: BAEP measurements in patients with neuronal storage disorders and normal control group.

	Absolute latency												*Interpeak latency*											
	Wave I				*Wave III*				*Wave V*				*I-III*				*III-V*				*I-V*			
	Rt.		*Lt.*		*Rt.*		*Lt.*		*Rt.*		*Lt.*		*Rt.*		*Lt.*		*Rt.*		*Lt.*		*Rt.*		*Lt.*	
	Mean	*SD*	*Mean*	*SD*	*Mean*	*SD*	*Mean*	*SD*	*Mean*	*SD*	*Mean*	*SD*	*Mean*	*SD*	*Mean*	*SD*	*Mean*	*SD*	*Mean*	*SD*	*Mean*	*SD*	*Mean*	*SD*
Neuronal storage	1.45	.266	1.49	.366	3.40	.438	3.76	.497	5.02	.540	5.28	.486	2.07	.403	2.27	.677	1.62	.322	1.54	.375	3.75	.634	3.81	.686
Control	1.03	.101	1.04	.106	2.99	.170	3.15	.383	4.67	.297	4.78	.331	1.96	.196	2.11	.336	1.68	.293	1.63	.346	3.64	.297	3.74	.263
P-value	.000#		.000#		.024#		.001#		.045=		.027#		.591		.140		.887		.869		.231		.197	

P-value < 0.05 is considered significant.



Figure[21]: The median and interquartile range of wave I absolute latency (L)

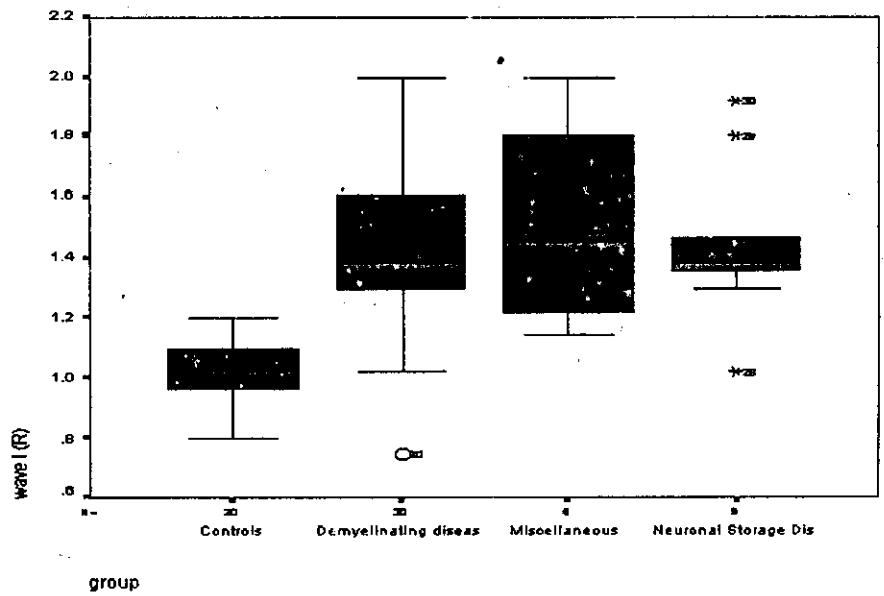


Figure [22]: The median and interquartile range of wave I absolute latency (Rt)

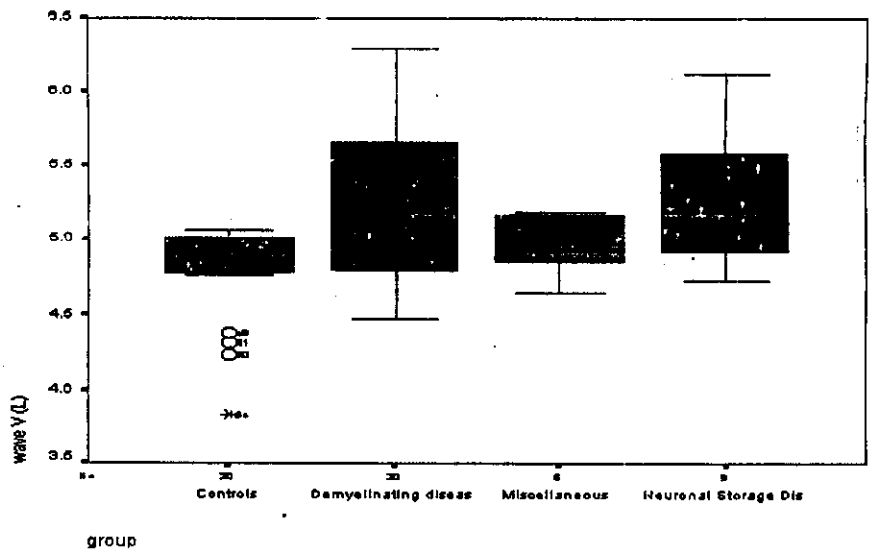
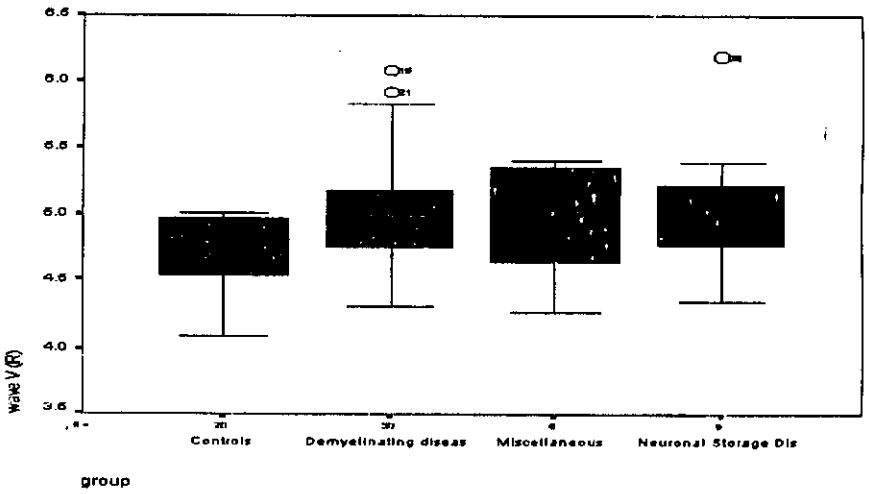


Figure [23]: The median and interquartile range of wave V absolute latency (Rt)



Figure[24]: The median and interquartile range of wave V absolute latency (Rt)

Results of the neuroimaging study:

Tables [28]: shows statistically significant difference in the percentage of normal and abnormal results of neuroimaging study in the 3 studied patient groups. Abnormal neuroimaging results were demonstrated in 37 out of 45 [82.2%] patients with a higher percentage in patients suffering from demyelinating diseases.

Table [28]: Results of neuroimaging study in the 3 studied patient groups: The percentage of normal and abnormal results.

CT and/or MRI brain	*Patients group*						*P-value*
	Demyelinating [N=30]		*Neuronal storage [N=9]*		*Miscellaneous [N=6]*		
	N	*%*	*N*	*%*	*N*	*%*	
Normal.	-	-	5	55.6	3	50	0.00005
Abnormal.	30	100	4	44.4	3	50	
Total	30	100	9	100	6	100	

Table [29]: Abnormal results of neuroimaging study in patients with degenerative brain diseases as regard etiological diagnosis.

Group	*Diagnosis*	*CT and/or MRI*
Neuronal storage group	Tay-Sachs' disease (2 cases)	-Cerebral& cerebellar atrophy [1 case]. -Cerebellar atrophy [1 case].
	Mucopolysaccharidoses [3cases]	Cerebral atrophy [2 cases]
Miscellaneous group	Wilson's disease [1 case]	Bilat. Basal ganglion and brain stem hypodensity
	Mitochondrial encephalomyopathy [1 case]	Cerebellar atrophy
	Unknown [2 case]	Cerebral atrophy [1 case]
Demyelinating group	Metachromatic leukodystrophy (MLD) [14 case]	-Bilateral symmetrical periventricular white matter demyelination (mainly frontal and occipital) [12 cases] -Bilat.occipital rather periventricular white matter demyelination [2 cases]
	- Alexander's disease [2 cases]. - Krabbe disease [2 cases]. -Glutathione synthetase deficiency [3 cases]. - Unknown [5 cases]	Bilateral symmetrical periventricular white matter demyelination (mainly frontal and occipital).
	Adrenoleukodystrophy (ALD) [1 cases]	Bilateral occipital rather periventricular white matter demyelination
	Canavan disease [2 cases]	Extensive demyelination involving central and peripheral white matter.
	Pelizaeus-merzbacher disease (PMD) [1 case]	Diffuse symmetrical demyelination of supratentorial white matter as well as the spino-cerebellar tracts down to the upper cervical cord.

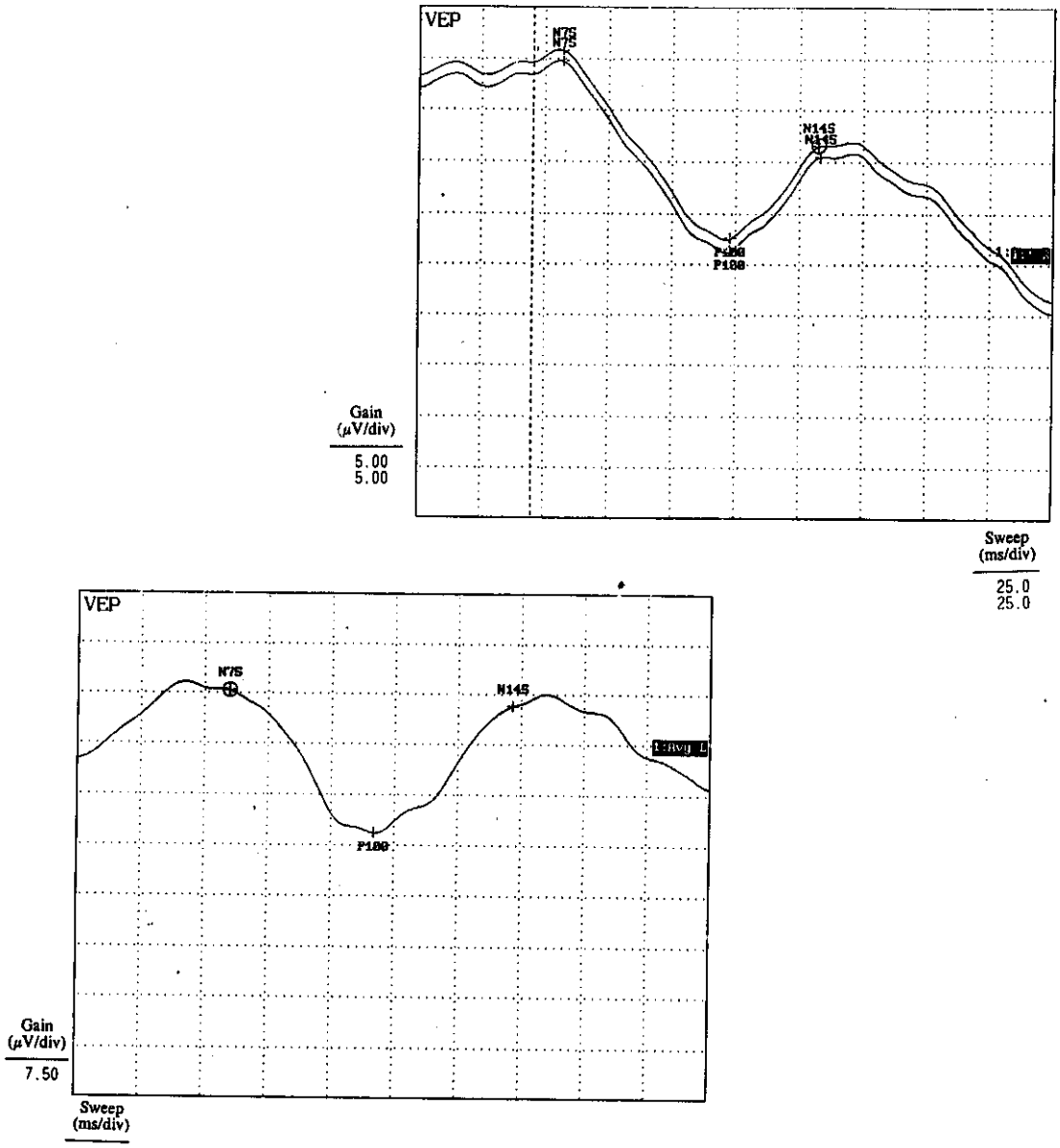


Figure [25]: Flash-VEP of a 4-years old male patient with GM2 gangliosidosis showing abnormal increase in the absolute latency of P100 with a non-significant interocular difference (postchiasmatic lesion).

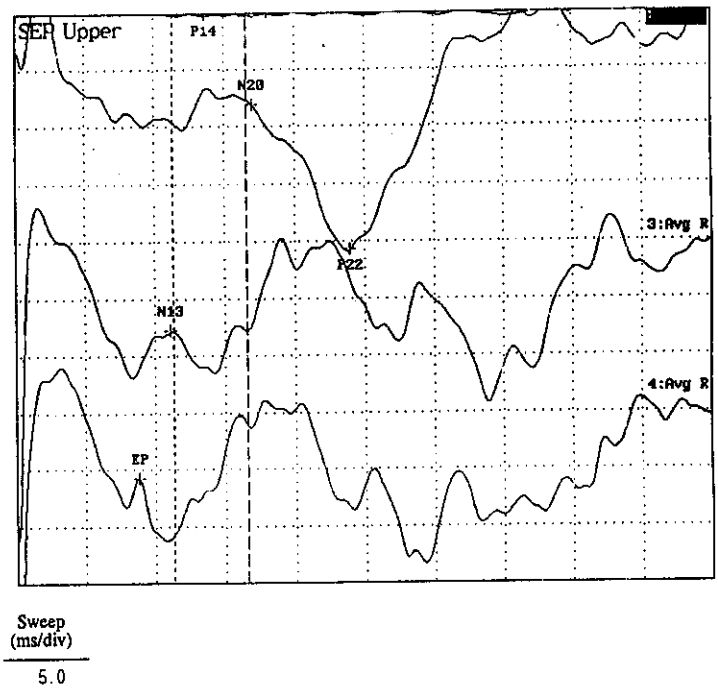
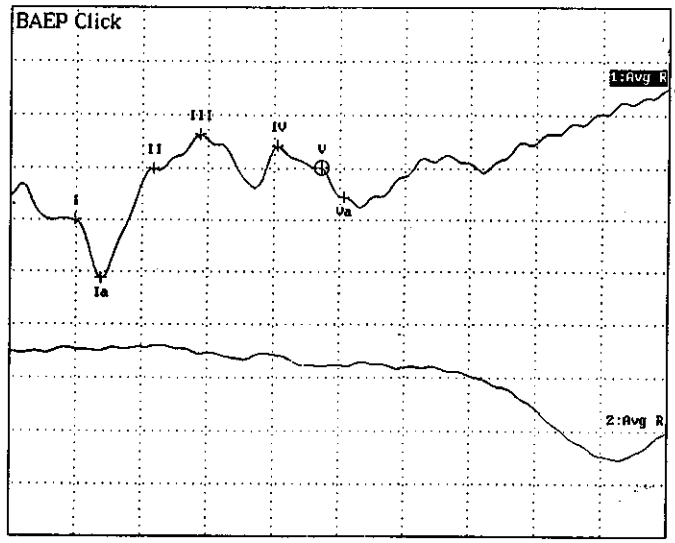


Figure [26]: Normal short latency SEPs following right median nerve stimulation of a 4-years old male patient with GM2 gangliosidosis .



Sweep (ms/div)
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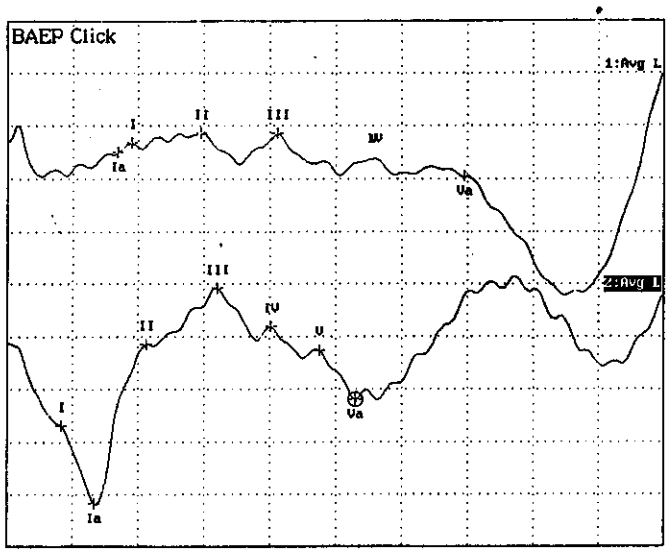
1.0



Sweep (ms/div)
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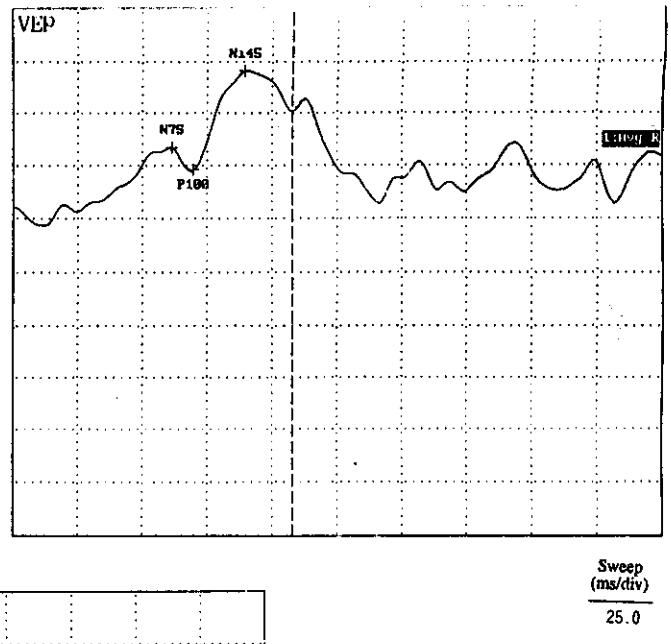
1.0

Figure [27]: BAEP of a 4-years old male patient with GM2 gangliosidosis showing abnormal increase in the interwave latency [I-III] on left monaural stimulation.



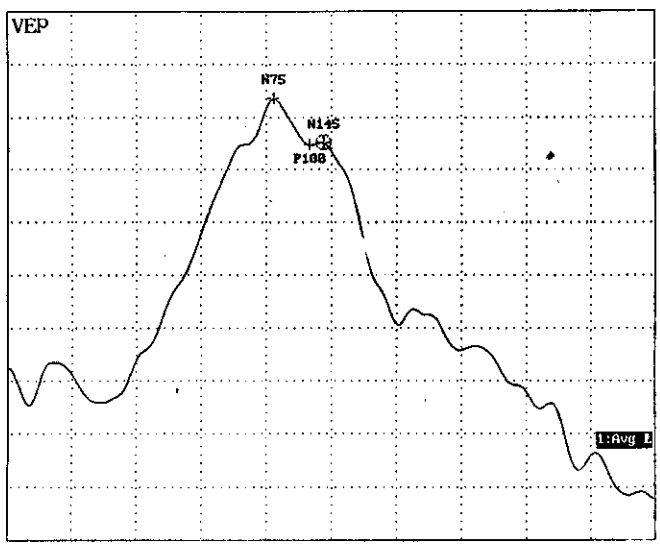


Figure [28]: Flash-VEP of a 2-years old male patient with adrenoleukodystrophy (ALD) showing abnormal increase in P100 latency after left sided stimulation (prechiasmatic lesion affecting the left visual pathway).

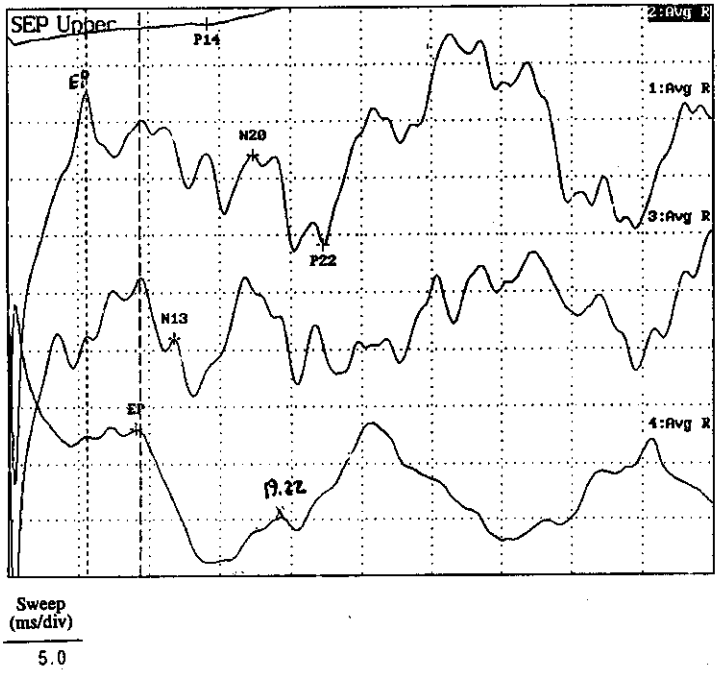
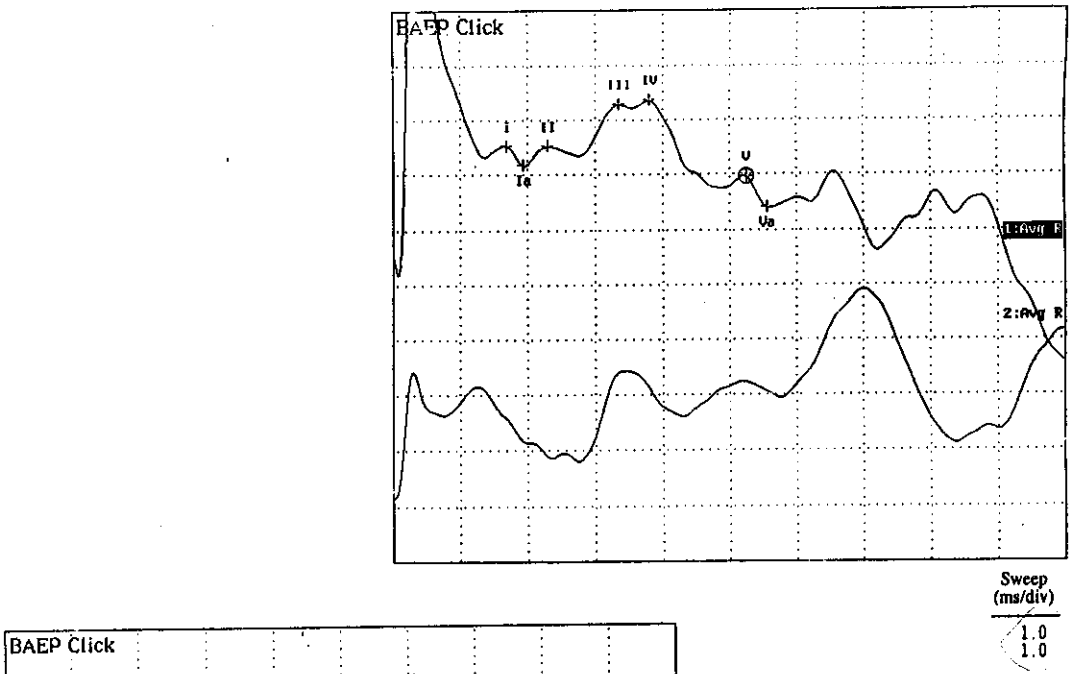


Figure [29]: Short latency SEPs following right median nerve stimulation of a 2-years old male patient with adrenoleukodystrophy (ALD) showing increase in the interwave latency cervical to cortical potentials & abnormal decrease in amplitude of the evoked responses.



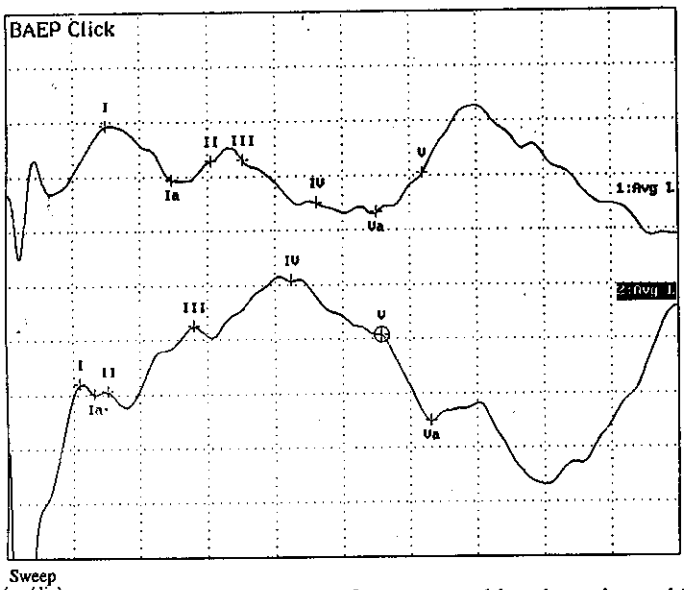


Figure [30]: BAEP of a 2-years old male patient with adrenoleukodytrophy (ALD) showing abnormal increase in the wave V/I ratio on right and left monaural stimulation.

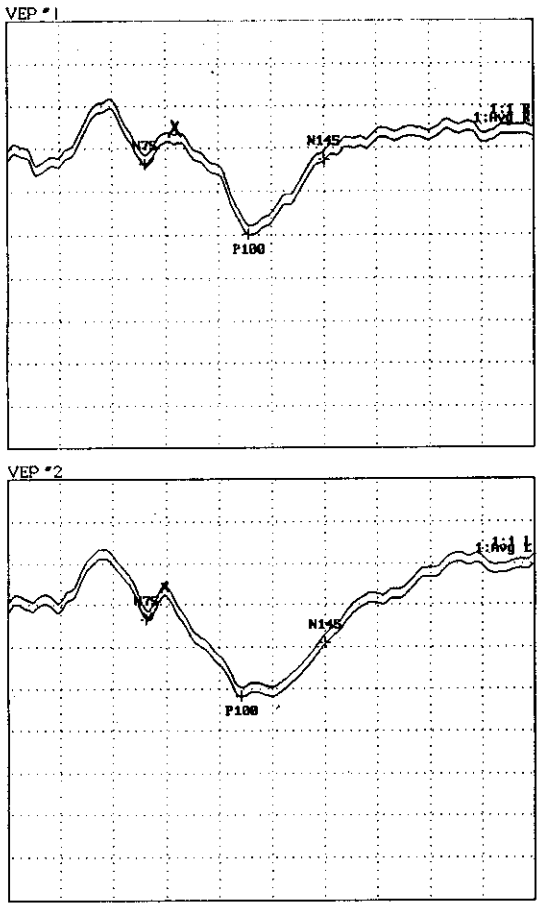


Figure [31]: Flash-VEP of a 13-years old male patient with Wilson's disease showing abnormal increase in the absolute latency of P100 responses with a non significant interocular difference denoting a postchiasmatic lesion affecting both visual pathways.

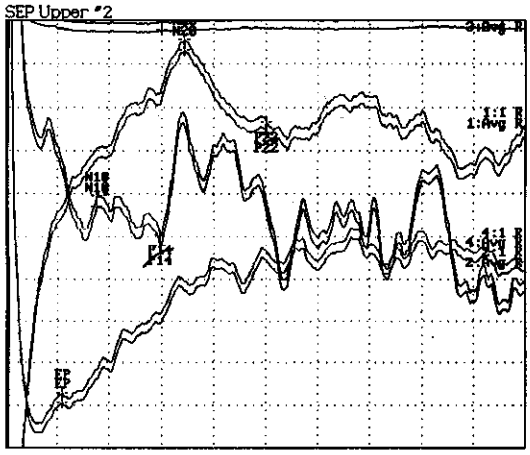


Figure [32]: Normal short latency SEPs following right median nerve stimulation of 13-years old male patient with Wilson's disease.

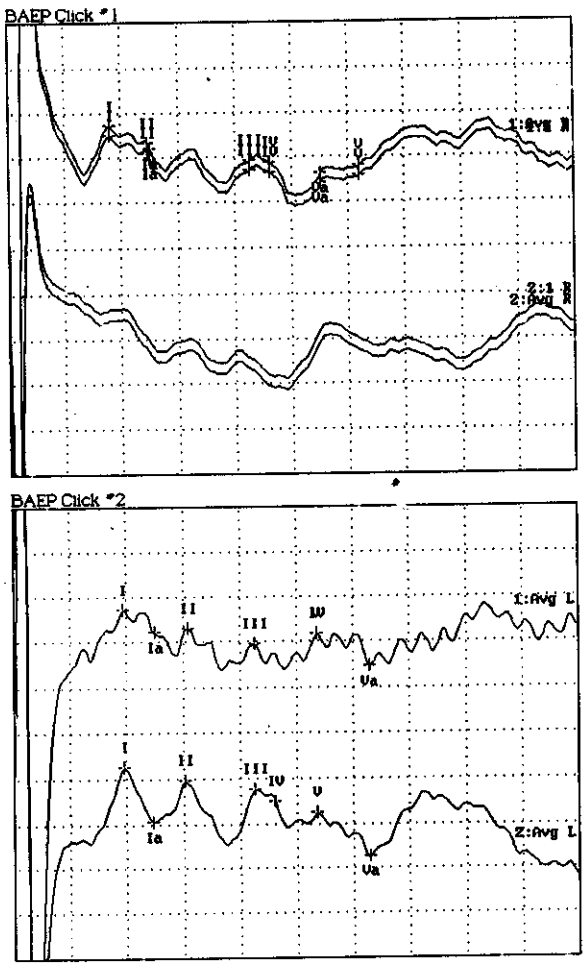


Figure [33]: BAEP of a 13-years old male patient with Wilson's disease showing abnormal increase in the interweave latency [I-III] on right and left monaural stimulation.

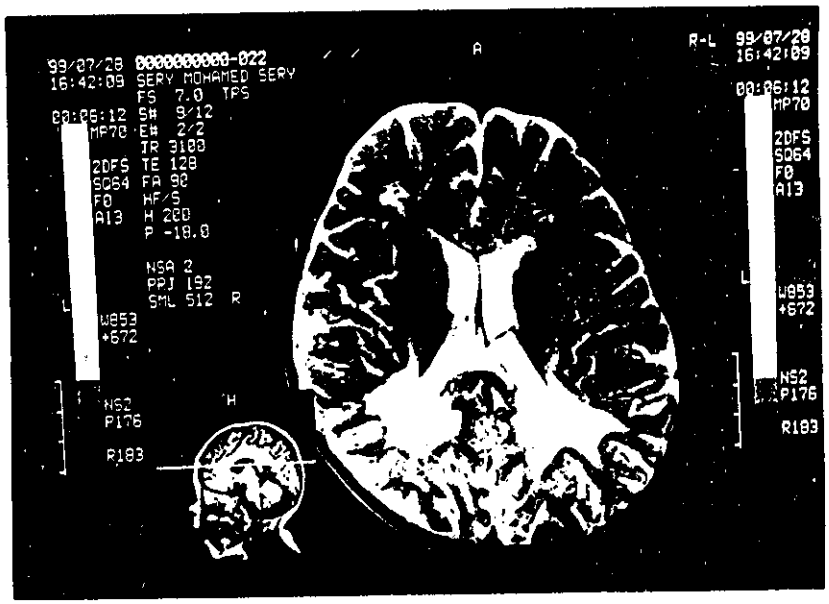


Figure | 34 |: T2-weighted MR image of a-2 years old boy with symptomatic adrenoleukodystrophy demonstrates bilat-occipital rather periventricular white matter demyelination.

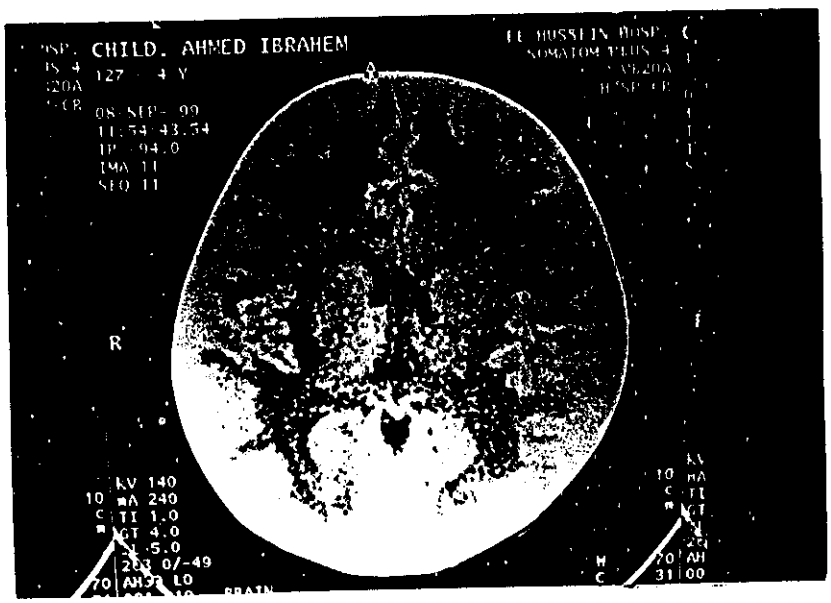


Figure | 35 |: Axial C.T. scan of a 4-years old boy with Canavan disease demonstrates extensive low density involving central and peripheral white matter.

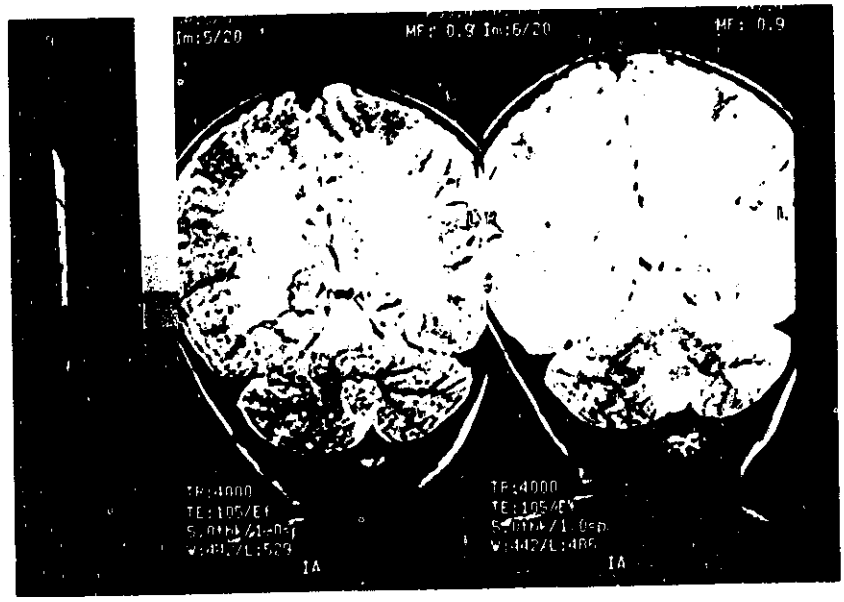
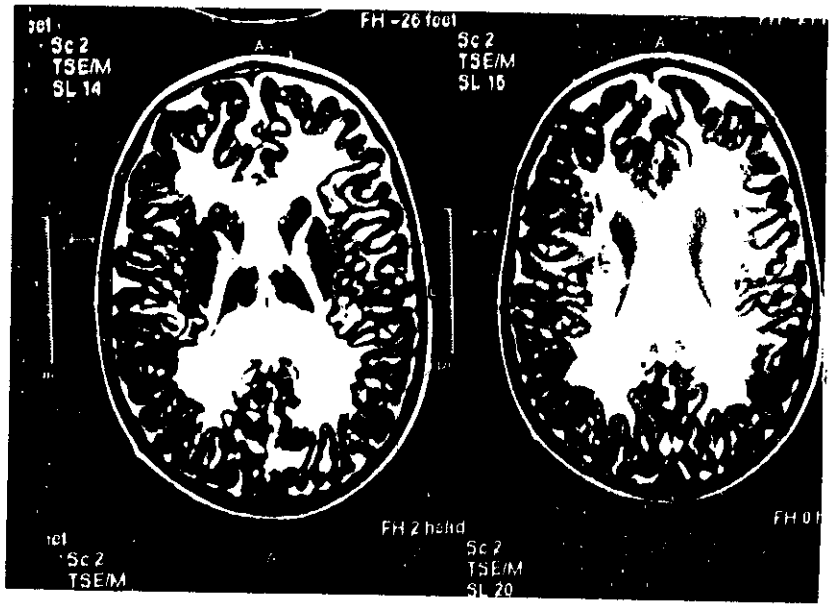


Figure [36]: T2-weighted MR image of a- 2 ½ years old female patient with metachromatic leucodystrophy demonstrates bilat. symmetrical diffuse periventricular white matter demyelination.



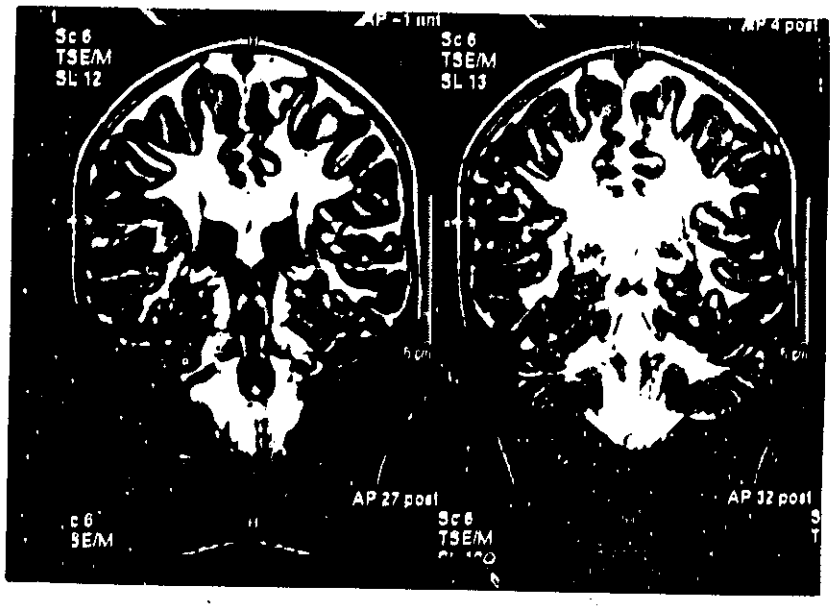


Figure / 37 /: T2-weighted MR image of a 4-years old boy with pelizaeus-merzbacher disease demonstrates diffluse symmetrical demyelination of supratentorial white matter as well as the spino-cerebellar tracts down to the upper cervical cord.

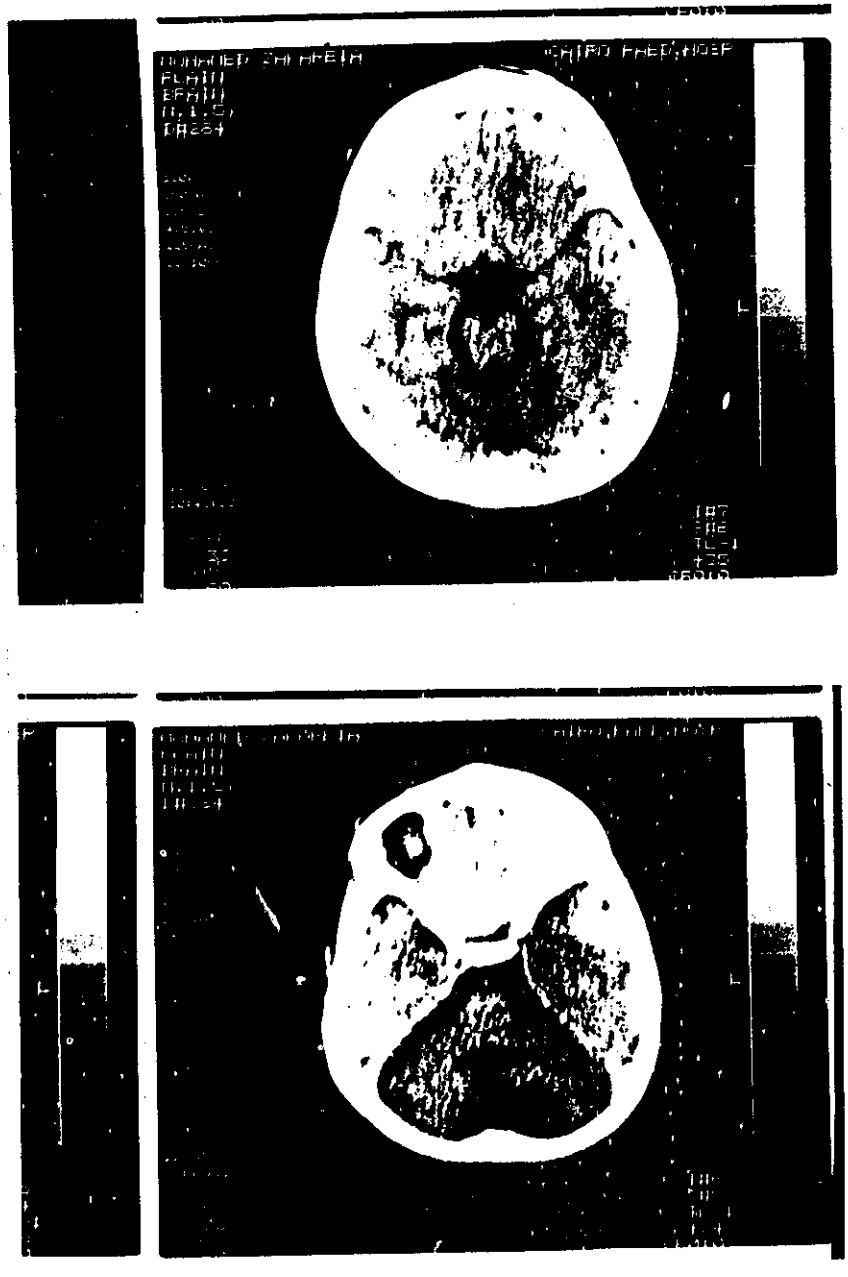


Figure [38]: Axial C.T. scan of a-2 years old boy with mitochondrial encephalomyopathy demonstrates cerebellar atrophy

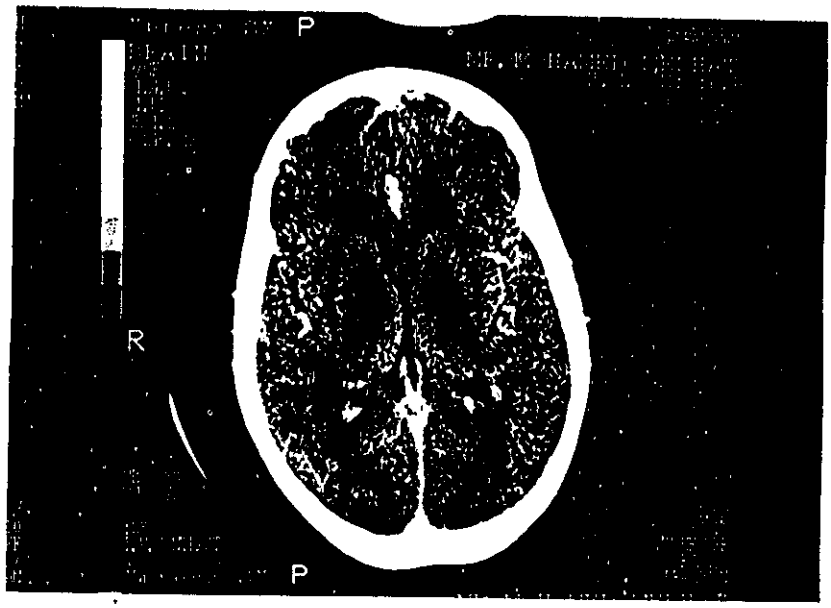


Figure [39]: Axial C.T. scan of a 12-years old patient with Wilson's disease demonstrates bilateral basal ganglion and brainstem hypodensity.

Discussion

Neurodegenerative disorders of childhood encompass a large number of heterogeneous diseases that result from specific genetic and biochemical defects, and a significant group of conditions of unknown cause. Most are inherited in an autosomal recessive fashion and show involvement of different parts of the central and sometimes peripheral nervous system with a variety of progressive deficits, especially dementia, epilepsy, blindness, ataxia and disorders of tone and reflexes ***(Brett and Lake, 1997).***

In primary neurodegenerative conditions, diagnosis is based on clinical patterns of illness, age of onset, nature of genetic transmission, and, increasingly, specific biochemical and chromosomal determinations. So, primary neurodegeneration conventionally have been divided into gray matter and white matter diseases based on early clinical symptoms and presumed primary site of pathologic involvement. Because gray matter diseases affect neurons, early symptoms include seizures, intellectual deterioration, and visual changes. White matter diseases manifest with evidence of that involvement, including loss of motor skills, spasticity, or ataxia ***(Swaiman & Dyken, 1999).***

Neurologic evaluation of the pediatric patients is one of the most challenging problems in clinical medicine. Too often, limited cooperation hinders the performance of the neurological physical examination, thus demanding reliance on more objective laboratory measures.

Evoked potentials are very useful clinical tools and its clinical value is fourfold:

- Demonstration of abnormal sensory system function when the history and neurologic examination are equivocal.
- Disclosure of clinically unsuspected malfunction in a sensory system when symptoms or signs in another area of the central nervous system (CNS) suggest demyelinating disease.
- Aid in definition of the anatomic distribution of a disease process.
- Objective monitoring of changes over time in a patient's status.

Thus they provide sensitive, primarily quantitative, extension of the clinical neurologic examination ***(Chiappa et al., 1997).***

Multimodality evoked responses provide more information regarding the functional integrity of several afferent systems in their course from peripheral nerves, through spinal cord and brain stem to the cerebral cortex. These findings when correlated with the results of other conventional tests such as EMG, nerve conduction velocities, EEG and CT scan are helpful in the diagnosis and total functional assessment of the nervous system in patients suspected to have degenerative neurological disorders ***(Markand et al., 1982).***

Whereas evoked potentials are useful reliable tools to measure the function of specific parts of the CNS , brain radiography [CT, MRI] reflects morphological abnormalities. CT and MRI are of value in the

differential diagnosis of neurodegenerative brain diseases *(Vanhanen et al., 1994).*

The aim of this study is a trial to evaluate the importance of different modalities of evoked potential in the detection of degenerative brain disorders and to asses the benefits obtained when adding neurophysiological modalities to neuroimageing procedures in order to refine our knowledge about the pathophysiology of these diseases.

Although the outcome is invariable fatal, and current therapeutic attempts have been unsuccessful, it is important to make the correct diagnosis so that genetic counseling may be offered and prevention strategies can be implemented.

To reach the goal 45 patients were the subject of this study and 20 normal volunteers acted as a control matched with the same age and gender for the patients.

All patients were chosen from those showing progressive loss of previously aquired motor and mental milestones or failure of achievement of normal milestone of development associated with positive family history. All patients were subjected to thorough clinical examination and neuroimageing studies [CT or/and MRI].

The patients were categorized into demyelinating, neuronal storage and miscellaneous groups based on clinical data, neuroimageing studies as well as specific laboratory diagnosis. Multiple comparison study of multimodality evoked potentials [SEPs, VEPs, BAEPs] were carried out in the 3 studied patient groups and the normal control group.

All patients had severe psychomotor retardation. Seventeen out of 45[37.8%] patients were suffering from convulsion that has a higher percentage mainly in-patients suffering from neuronal storage disease [55.6%] and were of myoclonic [22.3%] and generalized tonic clonic types [33.3]. This is in accordance with other auther ***(Neil Gorden, 1993)*** who reported that seizures are common in the primarly affected gray matter diseases and are usually of myoclonic or grand mal type.

Among the demyelinating group, 14/30 patients [46.7%] were suffering from metachromatic leukodystrophy as showen by deficiency of arylsulfatase in WBCs. This is in accordance with other authors ***(Baker et al., 1994)*** who reported that this disorder of myelin metabolism is the most common white matter degeneration of childhood.

Leukodystrophies are genetically determined conditions. The pathological hallmark is widespread, often symmetrical, demyelination, or failure of normal formation of myelin central white matter of the brain. In some members of the group peripheral nerves are affected and show segmental demyelination ***(Swaiman, 1999).***

In view of these pathological changes, it is not unexpected to observe severe alteration in those evoked response components, which arise, in the central neural elements.

The Erb's potential (EP) recorded by median nerve stimulation is due to the action potentials generated in the median fibers as they transverse the brachial plexus. The cervical potential (N11/13) is usually considered to arise in the dorsal column or the dorsal column nuclei of the medulla oblongata. Where as the cortical potentials (N19/20) are

supposed to arise in the thalamo-cortical radiation or cerebral cortex ***(Chiappa, 1983).***

In the present work, the patients suffering from demyelinating diseases [Table 16] were found to have a statistically significant delayed cortical response in addition to prolonged central conduction time between cervical and cortical potentials. This suggests a conduction defect in the large fiber sensory system above the lower medulla and below the thalamus.

This findings agree with previous findings in several SEP studies of children with neurodegenerative disorders affecting white matter ***(Markand et al., 1982; Tobimatsu et al., 1985; DeMeirleir et al., 1988).*** These authors reported abnormalities of central components, delay in latency or absence of components, seen in degrees proportional to the severity of the disease.

In the present study, there was statistically significant delay in Erb's potential. This can be simply a reflection of peripheral nerve involvement. This explanation also agrees with postulation of ***Markand et al., (1982)*** who reported absence of Erb's point potentials in the patients with MLD.

SEP study in the patients with neuronal storage disorders [Table 17] showed the same abnormalities as in the patients suffering from demyelinating diseases without any significant difference between these two groups [Table 19].

This is in accordance with ***Cracco et al (1980)*** who had similar results when studied patients with neuronal storage and demyelinating

diseases. The responses over rostral spinal cord segments, brain stem, and cortex were abnormal. Delay in latency or absence of components were seen in degrees proportional to severity of illness.

Delayed Erb's potential could be explained by the presence of peripheral neuropathy in agreement with ***Gumbinas et al (1975)*** who reported the occurance of peripheral neuropathy in some patients with type A Neimman-Pick disease presenting clinically with hypotonia,a reflexia and slowed conduction velocities.

In the present study, the patients with miscellaneous neurodegenerative disorders [Table 18] were found to have a statistically significant delayed cervical potential, pointing to involvement of the large fiber sensory system central to the brachial plexus and below the lower medulla.

These findings agree with previous findings in SEP studies ***(Taylor et al, 1985) & (Rossini et al., 1986, 1987)*** in patients with miscellaneous neurodegenerative disorders.

Rossini et al., (1986, 1987) reported abnormal SEP in 25 of 33 patients including all patients with Friedreich's ataxia, hereditary motor neuropathy I & II and in one with olivopontocerebeller atrophy. As in other studies, patients with Friedreich's ataxia had impaired central conduction and normal or slightly prolonged peripheral nerve potential latencies ***(Taylor et al., 1985).***

SEPs are generally normal in acute cerebeller ataxia and in chronic ataxia of unknown etiology ***(Fagan et a., 1987 A,B).***

Also a recent study of multimodal evoked potentials in mitochondrial encephalomyopathy ***(Scaioli et al, 1998)*** revealed signs of involvement of the peripheral and central nervous system in 14 of 16 patients suffering from this diseases.

Abnormal visual-evoked responses can be encountered in neurodegenerative disorders that involve the visual system ***(Harden and Pampiglione, 1977).*** The response is composed primarily of the summated postsynaptic potentials of the pyramidal cells of the primary visual cortex ***(Ducati et al., 1988).*** VEP reflects the end result of a long neural pathway that starts at the photoreceptors and passes through synapses in the retina, the lateral geniculate body in the thalamus, and the primary visual cortex ***(Baker et al., 1995).***

In the present work, the 3 studied patients groups were found to have statistically significant abnormalities in the visual evoked responses. Either the response was significantly attenuated or had marked prolongation of the latency of P100.

Significantly attenuated visual evoked responses were found in the patients with demyelinating diseases [Table 20] with no significant prolongation of latency. However, amplitude is much less reliable than latency because it shows a greater interindividual variability. Because VEP amplitude is directly related to visual acuity, any process producing changes in visual acuity (e.g. changes in pupil size, refractive errors, and medical opacities) affects it. Other patient's factors that affect amplitude are related to poor fixation such as nystagmus, excessive blinking, or looking away ***(Chiappa et al, 1997).***

on the contrary, ***Markand et al., 1982***, reported abnormal VEP responses with pattern reversal and flash stimuli in 13 of the 17 patients with leukodystrophy [PMD, 12; ALD, 3;MLD, 3] with their ages ranging from 2.5 to 39 years. Either there was no identifiable VEP or the response were attenuated, poorly defined and had marked prolongation of latency of P 100.

The possible explanation of this discrepancy is the early stage of disease at the time of recording in the present study as compared to previous Markand'study and another explanation is the difficulty of applying pattern reversal stimuli to obtain VEP for these uncooperative, mental retarded, pediatric group which is a preferred stimulus for clinical investigation of the visual pathways. Flash induced VEP is easy to obtain and require no cooperation of the patients, although, show wide inter and intra-individual variability.

In agreement with this explanation ***Boyd&Harden (1997)*** reported that "although flash VEP abnormalities (usually loss of earlier components) may be found in all types of leucodystrophies, they are not invariably seen at any particular stage and in cases where pattern reversal VEPs are feasible, the P100 latency may be prolonged".

In this study, the patients with neuronal storage diseases had statistically significant increased of P100 latency in right eye [Table 21]. This is in accordance with ***Harden and Pampiglione [1977]*** who studied VEPs, electroretinogram and electroencephalogram in progressive neurometabolic "storage" diseases of childhood. They reported that abnormal visual - evoked responses could be encountered in

neurodegenerative disorders that involve the visual system

In the present study, the patients with miscellaneous neurodegenerative diseases had statistically significant increased of the latency of P100 in both eyes [Table 22].

In agreement with this result, ***Bird & Crill (1981)*** described VEP findings in a series of 24 patients with hereditary ataxia and spinal degeneration. Abnormally delayed latencies were found in 3 of 5 patients with classic friedreich's ataxia, in 1 patient with dominant spastic paraparesis, and in 1 patient with recessive dentatorubro-spinal degeneration. Fifteen other patients with various dominant and recessive hereditary ataxia had normal VEP latencies.

Also, ***Scaiali et al., (1998)*** reported the utility of multimodal evoked potentials study in 16 patients with various forms of mitochondrial encephalomyopathy, with a high incidence of VEP alternation, indicative of visual pathway vulnerability in mitochondrial disease.

Moreover, in recent study of visual pathway abnormalities in Wilson's disease ***(Satishchandra & Ravishankar, 2000),*** VEP latencies were found prolonged in comparison to the control group ($p<0.001$).

Based on these previous reports, the statistically significant increase of P100 latency in the miscellaneous group as compared with either demyelinating or neuronal storage groups could be explained [Table 23].

The BAEP is a subcortical response that reflects conduction along the auditory brain stem pathway. Five component waves are routinely measured: wave I and II arise from the distal and rostral portions of the eight nerve respectively, wave III is from pons and wave IV and V are from the midbrain ***(Chiappa et al,1997)***

In neurologic application of the BAEP, relative latency measurements have greater diagnostic values, since wave I reflects 8th cranial nerve activity, the latency interval between wave I and subsequent components is a measure of auditory brain stem transmission time because interpeak latencies are essentially unaffected by changes in stimulus intensity and by disorders of peripheral hearing apparatus ***(Chiappa et al, 1997).***

In this study, wave I who is generated by the activity essentially of the extra-medullary portion of the 8th nerve was statistically significant delayed in the patients with demyelinating diseases [Table 24].

This is in accordance with ***Rachel et al (1979)*** who suggested that subclinical demyelination of the eight nerve may be responsible for the prolonged latency of wave I recorded in the patient with MLD although clinical signs of cranial nerve involvement are usually lacking. Also ***Markand et al (1982)*** reported that demyelinating changes in the peripheral nerves, including the auditory nerve, can certainly result in prolonged latency of wave I in MLD. Moreover ***Wang et al (1992)*** reported that peripheral conduction time as absolute latency of wave I were abnormal in 4 of 6 patients with MLD.

Also in the present study there was statistically significant delay in absolute latency of wave III & V in the patients with demyelinating diseases. However we did not found any statistically significant delay in the interpeak latencies.

In contrast, ***Markand et al (1982)*** reported severe alteration in BAEP in their patients with leucodystrophies [PMD, 12; ALD, 3; MLD,3] due to demyelination of brain stem structure with the exception of two patients who had milder form of ALD.

Also serial auditory evoked responses were investigated in 3 children with Krabbe disease ***(Yamanouchi et al, 1993).*** ABR disclosed progressive deterioration in wave configuration as well as prolonged latencies. Later components disappeared and wave I was the last remaining component in the advanced stage of the disease.

In the present study, the overall ABR abnormalities in patients with demyelinating diseases were less severe probably due to the early presentation of their diseases at the time of recording.

This explanation agree with the postulation of ***Wang et al (1995)*** who reported that BAEP are more profoundly altered in PMD probably due to widespread dysmyelination of the brain at the early stage and in other genetic leucodystrophies demyelination is more pronounced in the periventricular white matter, brain stem becomes involved subsequently.

As regard the BAEP study in patients with neuronal storage diseases [Table 25], we found a statistically significant delay in absolute latency of waves I, III and V with no delay in the interpeak latencies.

This is in accordance with ***Markand et al (1978)*** who reported that the BAEP are normal or only minimally altered in primary gray matter diseases that involve cortical and subcortical structures. Also ***Boyd and Harden [1997]*** reported that " Although BAEP abnormalities may be found, this is variable in both Gm1 and Gm2 gangliosidoses".

As regard the BAEP study in patients with miscellaneous neurodegenerative diseases [Table 26] we found a significant delay in wave I with no delay in interpeak latencies.

This is in accordance with another study ***(Rossini et al, 1987).*** SEP has been found to be more severely altered than BAEP and serial testing parallels this clinical progression of disease.