Results

Out of 1550 patients who came to Benha university pediatric neurology clinic in the period between June 2008 to June 2010, 705 patients were included in our study who were meeting the inclusion criteria of : global developmental delay and age below 4 years.

845 did not meet the inclusion criteria and were excluded due to : age >4 years , absence of GDD or Down syndrome.

The mean age at initial evaluation was 28 ± 8.84 months and The mean age when delay was first suspected by the parents was 24 ± 6.25 months.There were 410 males and 295 females, corresponding with a male/female ratio of 1.39:1 as shown in **table (1)** and **figure (1).**

Overall, an etiology for GDD was found in 297 (42.1%) only of 705 children. The most common etiologic groupings were: perinatal asphyxia (198 [28.1%]), post kernicterus (28 [4%]), degenerative brain diseases (15 [2.1%]), post encephalitis (12 [1.7%]), post meningitis (11[1.6%]),hydrocephalus (10 [1.4%]),congenital brain malformation (8 [1.1%]), TORCHS (4[0.6%]), metabolic diseases(4 [0.6%]), hypothyroidism (3 [0.4%]), Sturge Weber syndrome (3 [0.4%]), chromosomal anomalies (1 [0.1%]) as shown in **table (2)** and **figure (2).**

Table (1) : distribution of the cases according to sex.

Sex	No	%
Male	410	58.1 %
Female	295	41.9 %
Total	705	100 %

Figure (1) distribution of the cases according to sex.

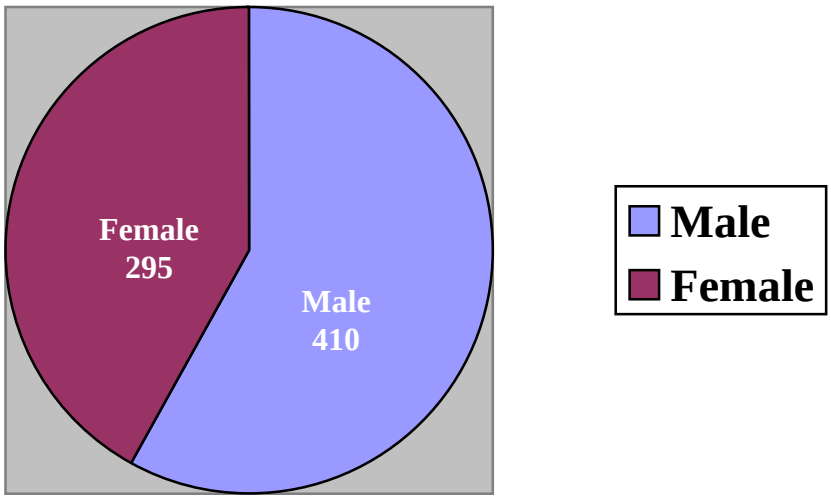


Table (2) Aetiological grouping of the cases with GDD.

Etiology	Total number (705)	Percent (%)
Hypoxic ischaemic encephalopathy	**198**	**28.1**
Hyperbilirubinemia and post kernicterus	**28**	**4**
Degenerative brain disease	**15**	**2.1**
Congenital brain malformation	**8**	**1.1**
hydrocephallus	**10**	**1.4**
Post meningitis	**11**	**1.6**
Post encephalitis	**12**	**1.7**
TORCHS infection	**4**	**0.6**
Metabolic diseases	**4**	**0.6**
Hypothyroidism	**3**	**0.4**
Sturge Weber syndrome	**3**	**0,4**
Chromosomal Translocation (21,15)	**1**	**0.1**
undiagnosed	**408**	**57.9**

Table (2) showed that The most common etiologic groupings were: perinatal asphyxia (198 [28.1%]), post kernicterus (28 [4%]), degenerative brain diseases (15 [2.1%]), post encephalitis (12 [1.7%]), post meningitis (11[1.6%]),hydrocephalus (10 [1.4%]),congenital brain malformation (8 [1.1%]), TORCHS (4[0.6%]), metabolic diseases(4 [0.6%]), hypothyroidism (3 [0.4%]), Sturge Weber syndrome (3 [0.4%]), chromosomal anomalies (1 [0.1%]).

Figure (2) Aetiological grouping of the cases of GDD.

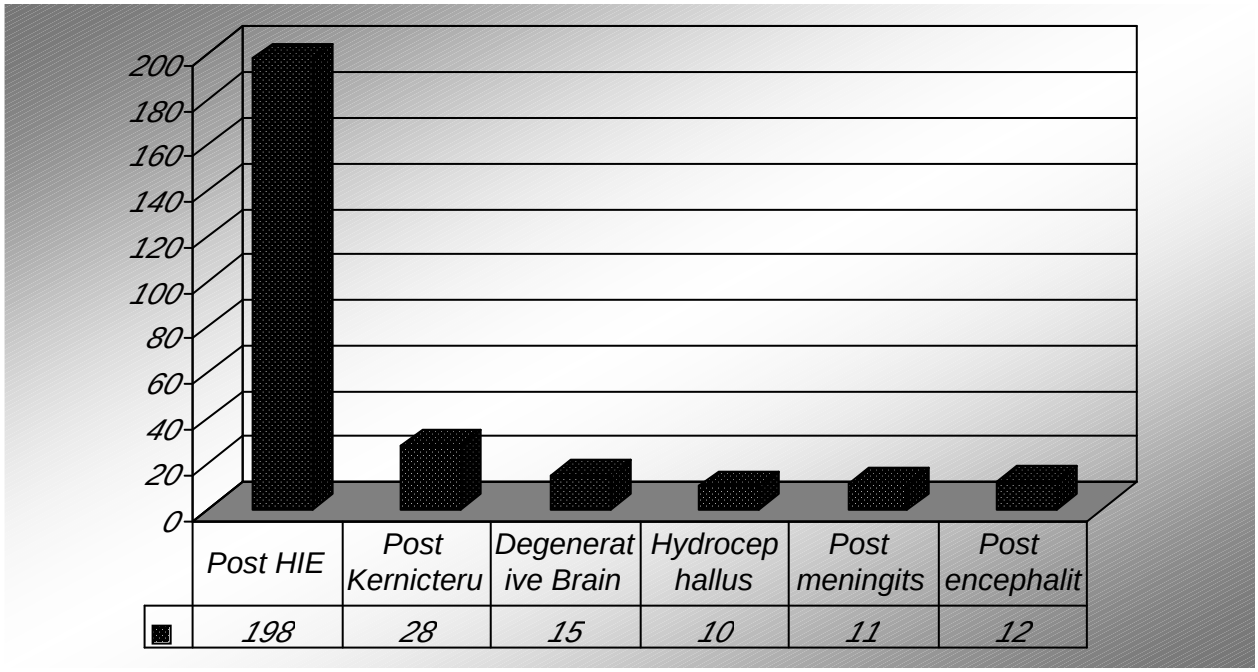
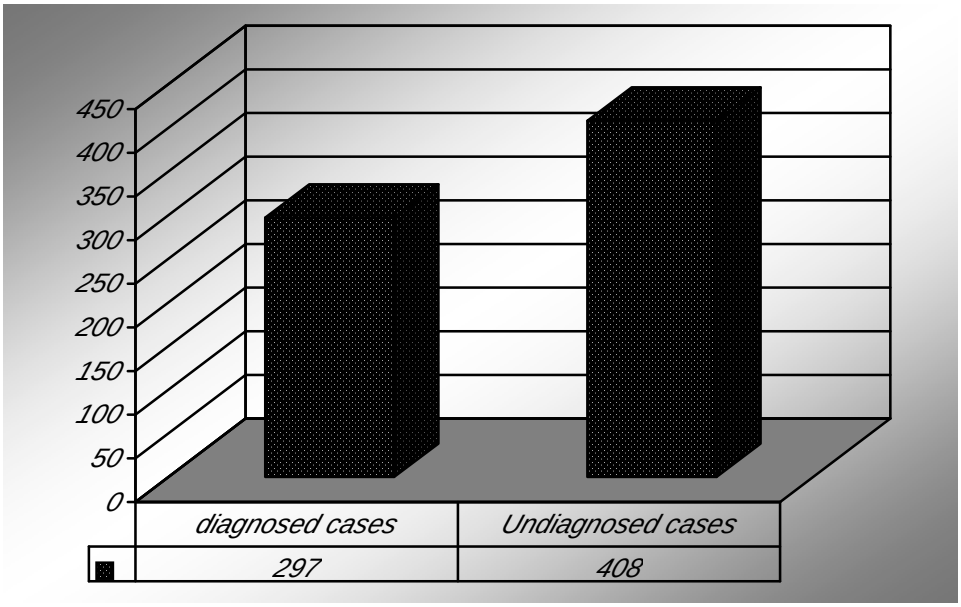


Table (3) : Percent of diagnosed cases to all patient with GDD

	No	**%**
diagnosed cases	297	42.1 %
Undiagnosed cases	408	57.9 %
Total	705	100 %

Figure (3) Comparison between number of diagnosed cases to undiagnosed cases.



Table(4) Main complaint and presentation of the cases.

symptoms	number	Percent
Failure to thrive	**226**	**32.1**
convulsions	**116**	**16.5**
delayed speech	**96**	**13.6**
Poor sphencteric control (urine and stool)	**75**	**10.6**
Delayed walking	**64**	**9.1**
Abnormal gait	**15**	**2.1**
abnormal level of consciousness		
(lethargy, stupor)	**35**	**5**
(coma)	**3**	**0.4**
(Poor vision)	**12**	**1.7**
(Squint,nystagmus)	**24**	**3.4**
(mouth deviation)	**6**	**0.9**
(deafness)	**14**	**2**
abnormal movement (head, limbs)	**22**	**3.1**

This table shows that in addition to GDD, about 32.1% of cases were complaining of failure to thrive, 16.5% had convulsions, 13.6% of cases had delayed speech, 10.6% with poor sphencteric control, 9.1% with delayed walking and 3.1% came with abnormal movement.

Table (5) Clinical examination in the cases of GDD.

examination	number	Percent (%)
Level of consciousness		
Conscious	**667**	**94.6**
lethargic	**35**	**5**
coma	**3**	**0.4**
Dysmorphic features		
(malformed, abnormal size or low set ear)	**4**	**0.6**
(hypertolerism, slanting)	**5**	**0.7**
(depressed nasal bridge)	**5**	**0.7**
(micrognathia, retrognathia)	**4**	**0.6**
(polydactyly, syndactyly, brachydactyly, semian crease)	**9**	**1.3**
(club feet, abnormal toes)	**8**	**1.1**
under weight	**226**	**32.1**
hypopigmented hair	**5**	**0.7**
Skin haemangioma	**3**	**0.4**
hepatosplenomegaly	**10**	**1.4**
skull size		
microcephaly	**492**	**69.8**
macrocephaly	**11**	**1.6**
normal skull size	**202**	**28.6**
muscle tone		
hypertonia	**680**	**96.5**
hypotonia	**25**	**3.5**

reflexes		
hyperreflexia	**547**	**77.6**
hyporeflexia	**25**	**3.5**
normal	**133**	**18.9**
Gait		
circumduction gait	**7**	**1**
scissoring gait	**8**	**1.1**
Ataxia	**8**	**1.1**
Autistic features	**11**	**1.6**

This table demonstrates clinical examination of the cases that revealed hypertonia (96.5%), hyperreflexia (77.6%), microcephaly (69.8%), under weight (32.1%), hepatosplenomegaly (1.4%), ataxia (1.1%), autistic features (1.6%) and dysmorphic features in (2.3%) of the cases.

Table (6) Neurophysiological tests in the cases with GDD.

test	Requested number	Percent %	results
Electroencephalogram (EEG)	**135**	**19.1**	Epileptogenic activity (116) Normal EEG (19)
Visual evoked response (VER)	**21**	**3**	Blind child (12) No blindness (9)
Auditory brainstem response (ABR)	**25**	**3.5**	Deafness (14) No deafness (11)

This table demonstrates that 116 cases had an epileptogenic activity (16.5%) of all cases with GDD, 12 cases are blind (1.7%), 14 cases had deafness (2%) of all cases.

Table (7) Neuroimaging findings of the cases with GDD.

findings	CT (442)	MRI (92)	diagnosis
Brain atrophy Periventricular leukomalacia Cerebellar anomalies	**78** 84 0	**15** 13 8	HIE (93) HIE (97) Ataxic CP (8)
Brain atrophy	**22**	**6**	Post kernicterus (28)
	9	**2**	Post meningitis (11)
	10	**2**	Post encephalitis (12)
Brain atrophy. Fronto temporal atrophy in glutaric type 1, central atrophy in maple syrup urine disease	**4**	**0**	IEM (4)
Brain atrophy, focal haemangioma, calcification	**3**	**0**	Sturge Weber syndrome (3)
Brain atrophy. Brain atrophy, hydrocephalus and calcification	**4**	**0**	Rubella (1) toxoplasma (1) Cytomegalovirus (2)
Brain atrophy	**1**	**0**	Translocation between chromosomes (21,15) (1)

Cystic brain malformation, Agenesis of corpus callosum Dandy Walker malformation	**1** **0** **1**	**6** **2** **0**	Congenital brain malformation (10)
White and grey matter degeneration	**0**	**15**	Degenerative brain diseases (15)
Dilated ventricular system	**7**	**3**	Hydrocephalus (10)
Brain atrophy **normal**	**174** **44**	**13** 7	**No determined etiology**

This table shows that **CT** demonstrated brain atrophy in 129 cases including :HIE (78 cases 11.1%), post kernicterus (22 cases 3.1%), post meningitis (9 cases 1.3%), post encephalitis (10 cases 1.4%), IEM (4 cases 0.6%), Sturge Weber syndrome (3 cases 0.4%), rubella, toxoplasmosis and translocation between chromosomes 21,15 (1 case 0.14%).

CT demonstrated a diagnostic value in cases of hydrocephalus (7 cases 1%), and congenital brain malformation (2 cases 0.3%) .

CT demonstrated calcification in 2 children and by the aid of TORCHS screen represented 2 cases of cytomegalovirus (0.3%), (84 cases periventricular leukomalacia 11.9%) with history of perinatal asphyxia.

CT demonstrated brain atrophy in 174 cases but with no etiology determined.

MRI demonstrated brain atrophy in (15 cases of HIE 2.1%), 1n (6 cases of post kernicterus 0.6%), 2 cases of post meningitis and post encephalitis 0.3%). **MRI** was diagnostic in (8 cases of Congenital brain malformation 1.1%), (8 cases of cerebellar anomalies 1.1%),(3 cases of hydrocephalus O.4%), (15 cases of degenerative brain disease 2.1%).

Table (8) Tests for congenital infection and CNS infection of the cases.

Laboratory investigations	**number**	**results**	**diagnosis**
TORCHS	**9**	positive IGM and IGG for toxoplasma **(1)**	toxoplasmosis **(1)**
		positive IGM and IGG for rubella **(1)**	rubella **(1)**
		rising IGG titre for CMV **(2)**	cytomegalovirus **(2)**
		negative results **(5)**	
CSF examination and culture	**15**	Positive cases for meningitis (11) Negative cases (4)	Meningitis (11)

This table demonstrates that **TORCHS** screen was diagnostic in 4 cases of congenital infection representing (0.6%) of all cases of GDD.

CSF examination and culture was diagnostic in 11 cases of meningitis representing (1.6%)of all cases of GDD.

Table (9) Metabolic tests in our study

test	NO	%	results	diagnosis
Metabolic screen	**25**	**3.5**	increased level of leucine, isoleucine and valine **(1)**	Maple syrup urine disease **(1)**
			increased level of methylmalonic acid in urine and plasma **(1)**	Methylmalonyl acidemia **(1)**
			increased level, glutaric acid,glutaconic acid and 3 hydroxyglutaric acid) **(1)**	Glutaric aciduria **(1)**
			increased level of phenylalanine and phenylketone **(1)**	phenylketonuria **(1)**
			normal (21)	
Thyroid functions (T3), (T4) (TSH)	**5**	**0.7**	decreased level of T3 and T4, and increased level of TSH (3) **normal levels (2)**	hypothyroidism (3)

Table (9) demonstrates that 4 cases of inborn error of metabolism were diagnosed (0.6%) of the cases, 3 cases of hypothyroidism were diagnosed (0.4%) of the cases.

Table (10) Chromosomal study of the cases with GDD.

Karryotyping	**NO**	**Percent %**	**results**
Males with dysmorphic features	**9**	**1.3**	normal (8) failure of culture (1)
Males without dysmorphic features	**13**	**1.8**	normal (11) failure of culture (2)
Females with dysmorphic features	**7**	**1**	normal (6) **translocation between chromosomes 21,15 (1)**
Females without dysmorphic features	**11**	**1.6**	normal (11)

This table demonstrates that Karryotyping was diagnostic in one case (translocation between chromosomes 21,15) representing (0.14%) of all cases of GDD.

Table (11) Relation of some variables to determination of the etiology.

Variable	(Etiology Determind) (N - %)	(Etiology not Determined) (N - %)	X^2	P. value
Gender				
Male (410)	145 (35.4)	265 (64.6)	**17.719**	**< 0.001**
female (295)	152 (51.5)	143 (48.5)		
perinatal history				
Presence **(238)**	233 (97.9)	5 (2.1)	**454.943**	**< 0.001**
Absence **(467)**	64 (13.7)	403 (86.3)		
Family history				
Presence **(49)**	15 (30.6)	34 (69.4)	**2.379**	**0.123**
Absence **(656)**	282 (43)	374 (57)		
Seizures				
Presence **(116)**	107 (92.2)	9 (7.8)	**140.574**	**< 0.001**
Absence **(589)**	190 (32.3)	399 (67.7)		
Microcephaly				
Presence **(654)**	280 (42.8)	374 (57.2)	**1.377**	**0.241**
Absence **(51)**	17 (33.3)	34 (66.7)		
Macrocephaly				
Presence **(11)**	11 (100)	0 (0)	**13.034**	**< 0.001**
Absence **(694)**	286 (41.2)	408 (58.8)		
Neurologic examination				
Normal **(0)**	0 (0)	0 (0)	**≈ 0**	**≈ 1**
Abnormal **(705)**	297 (42.1)	408 (57.9)		
Dysmorphic features				
Presence **(16)**	1 (6.3)	15 (93.7)	**7.204**	**0.007**
Absence **(689)**	296 (43)	393 (57)		
Autistic features				
Presence **(11)**	0 (0)	11 (100)	**6.474**	**0.011**
Absence (694)	297 (42.8)	397 (57.2)		

Table (11) demonstrated that the cases with GDD is more common among females (51.5%) than males (35.3%) with $\mathbf{X^2}$ value 17.719 and p. value < 0.001 that is strongly significant. perinatal history was associated with an etiology determination in (97.9%) of the cases with $\mathbf{X^2}$ value 454.943 and p. value < 0.001 that is strongly significant. positive family history was associated with an etiology determination in (30.6%) of the cases with $\mathbf{X^2}$ value 2.379 and p. value 0.123 that is non significant.

Seizures was associated with an etiology determination in (92.2%) of the cases with $\mathbf{X^2}$ value 140.574 and p. value < 0.001 that is strongly significant. microcephaly was associated with an etiology determination in (92.2%) of the cases with $\mathbf{X^2}$ value 1.377 and p. value 0.241 that is non significant.

Macrocephaly was associated with an etiology determination in (100%) of the cases with $\mathbf{X^2}$ value 13.034 and p. value < 0.001 that is strongly significant. abnormal neurologic examination was associated with an etiology determination in (42.1%) of the cases with $\mathbf{X^2}$ value $\approx$ **0** and p. value $\approx$ **1** that is non significant.

Dysmorphic features was associated with an etiology determination in (6.3%) of the cases with $\mathbf{X^2}$ value 7.204 and p. value 0.007 that is highly significant. autistic features did not lead to an etiology determination with $\mathbf{X^2}$ value 6.474 and p. value 0.011 that is significant.

Table (12) logistic regression model for successful identification of the etiology in the cases with GDD.

	Successful identification of Underlying Etiology			
	Beta values	**SE**	**Odds Ratio**	***P***
Presence of seizures	**0.411**	**0.26**	**24.967**	**< 0.001**
Absence of dysmorphic features	**0.110**	**0.09**	**11.236**	**0.003**
Female gender	**0.159**	**0.34**	**1.941**	**< 0.001**
Abnormal perinatal history	**0.628**	**0.36**	**293.434**	**< 0.001**
Absence of autistic features	**0.107**	**0.33**	**3.886**	**0.004**
Constant	**2.625**	**1.120**	**0.147**	**0.091**

This table of logistic regression model for significant variables demonstrated that Beta values of seizures, absence of dysmorphic features, female gender, abnormal perinatal history, absence of autistic features are equal to 0.411, 0.11, 0.159, 0.628, 0.107 respectively with constant value 2.625.

The odds ratio of seizures, absence of dysmorphic features, female gender, abnormal perinatal history, absence of autistic features are equal to 24.967, 11.236, 1.941, 293.434, 3.886 respectively with constant value 0.147.

- **Post HIE CP** :

HIE was diagnosed as an etiology in 198 cases of GDD, different perinatal history was obtained like cord around neck, knotting of the umbilical cord, ante-partum haemorrage, neonatel hypoxia due to RDS, history of meconium staind amniotic fluid, delayed first cry , cyanosis, convulsions and history of incubator admission are usually present.

abnormal neurolologic examination mostly there is hypertonia and hyper reflexia.

CT or MRI: periventricular leukomalacia and brain atrophy are common findings.

- **Post kernicterus CP :**

there was 28 cases of post kernicterus CP with history of high level of serum bilirubin in first days of life, incubator admission and sometimes exchange transfusion was done, presented by convulsion or abnormal movement , sometimes there is deafness.

ABR: was done for detection of deafness.

CT or MRI : show brain atrophy

- **Bacterial meningitis:**

It was the cause in 11 cases of GDD, there were history of fever, convulsions, vomiting, loss of consciousness and history of admission to fever hospital. The cases presented with GDD , convulsions, hearing loss.

CSF examination: showed increased leukocytic count, increased proteins, decreased glucose level.

CSF culture : positive

neuroimaging: demonstrated brain atrophy.

ABR: demonstrated deafness in many cases.

- **Autistic child:**

It started at infancy and pre-school children, the cases had impaired communication with others, impaired social interaction , restricted range of activity and interests, no eye contact with others and stereotypic behaviour.

Neuroimaging: no specific pattern, brain atrophy or normal CT.

- **congenital infection (TORCH)**

toxoplasmosis: one case presented with maternal history of fever, malaise, and the child presented with GDD,blindness**.**

CT: demonstrated brain atrophy and calcification.

Serological tests: positive IGM and IGG antibodies against toxoplasma.

Rubella : one case presented with history of maternal fever and her child presented with GDD,hepatosplenomegaly, vision and hearing impairment.

CT: demonstrated brain atrophy.

Serological tests: rising IGG antibodies titre against rubella.

Cytomegalovirus: 2 cases presented with history of IUGR, and the child presented with GDD, hepatosplenomegaly, deafness.

CT: demonstrated periventricular calcification.

Serological tests: positive IGM and rising IGG antibodies against CMV.

- **Inborn errors of metabolism:**

The cases did not present immediately after birth but after few weeks of normal development of the baby, threre was failure to thrive , , vomiting, lethargy .

Maple syrup urine disease:

one case presented with poor feeding, vomiting, lethargy, incubated as neonatal sepsis but CRP was negative.

Metabolic study: demonstrated increased level of leucine, isoleucine and valine.

CT: shows brain atrophy.

Methyl malonyl acidemia :

One case presented with vomiting, lethargy , ketoacidosis and coma.

Metabolic study : demonstrated hyperammoneamia , hypoglycemia , increase level of blood methyl malonyl acid and metabolic acidosis.

Glutaric aciduria:

One case presented by GDD, poor activity and feeding, macrocephaly and coma that was precipitated by gastroenteritis

Metabolic study: increased level of glutaric acid in plasma and urine, metabolic acidosis.

CT: showed brain atrophy.

Phenyl ketonuria:

One case presented by blond hair ,blue eyes, hyperactivity .

metabolic study: show increased level of blood phenyl alanine and there is phenyl ketone in urine.

CT: showed brain atrophy

- **Neuro cutaneous syndrome:**

3 cases of Sturge Weber disease Presented with GDD, convulsions and cutaneous manifestations in the form of facial nevus which wes port-wine coloured.

CT: showed unilateral brain atrophy and calcification.

- **Congenital hydrocephalus**

10 Cases presented by large sized head in early infancy , sun set eyes and GDD, there was wide anterior fontanelle and separated sutures in early infancy.

neuroimaging: demonstrated dilated ventricular system.

- **Neurodegenerative disorders:**

15 Cases presented with progressive GDD after a period of normal development, diagnosis was confirmed by enzyme assay.

Metachromatic leukodystrophy

12 cases presented by age below 2 years, GDD after a period of normal development and abnormal movements.

Laboratory tests: deficiency of Arylsulfatase enzyme.

MRI: white matter degeneration.

Rett syndrome

1 female case presented with GDD at one year age after a period of normal development and associated with abnormal hand movement.

Laboratory tests: deficiency of methyl-CPG-binding protein 2.

MRI: grey matter degeneration.

Adrenal leukodystrophy

2 male cases presented with GDD, behaviour changes, convulsions associated with adrenocortical insufficiency and vomiting after a period of normal development.

Laboratory tests: elevated hexacosanoate level in plasma.

MRI: white matter degeneration.

- **Hypothyroidism:**

3 Cases presented with GDD , poor activity, lethargy and distended abdomen.

Hormonal assay: decreased blood T3 and T4 level and increased TSH.