METABOLIC WORKUP
IN A NEURO – PEDIATRIC UNIT
FIRST ALARMING RESULTS

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INTRODUCTION

The pediatric department of AVH is a referral center for neurological, renal, and unresolved pediatric subspecialties cases in addition to general pediatric cases. The deserved geographical areas are the West Bank and Gaza. Most of referred cases are complicated, still undiagnosed and referred for diagnosis and possible therapy. Some of the cases were already investigated nearby countries without having yet specific diagnosis.

POPULATION AND METHODS:

Between 1/10/2002 and 1/10/2003, about 2000 patients were admitted to the pediatric department. Infants and children admitted to the Neuropediatric unit were 550. A metabolic screening study was conducted on newly admitted cases where no evident explanation was found for their neurological condition (trauma, infection …).

During this period, 101 pediatric patients were included. Their age ranged from few days to 15 years at time of screening. Indication for metabolic screening was to rule out underlying specific metabolic disorder with regards to clinical and/or radiological findings.

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In all cases, serum samples were taken for amino acid chromatography and urine samples for organic acids study. Specific enzyme assays, fibroblast culture for neurodegenerative diseases, very long chain fatty acids and respiratory chain enzymes in muscle were done according to suspected disorder.

RESULTS AND DISCUSSION

Indications for metabolic screening were multiple and patients were grouped according to the indication as shown in Table I.

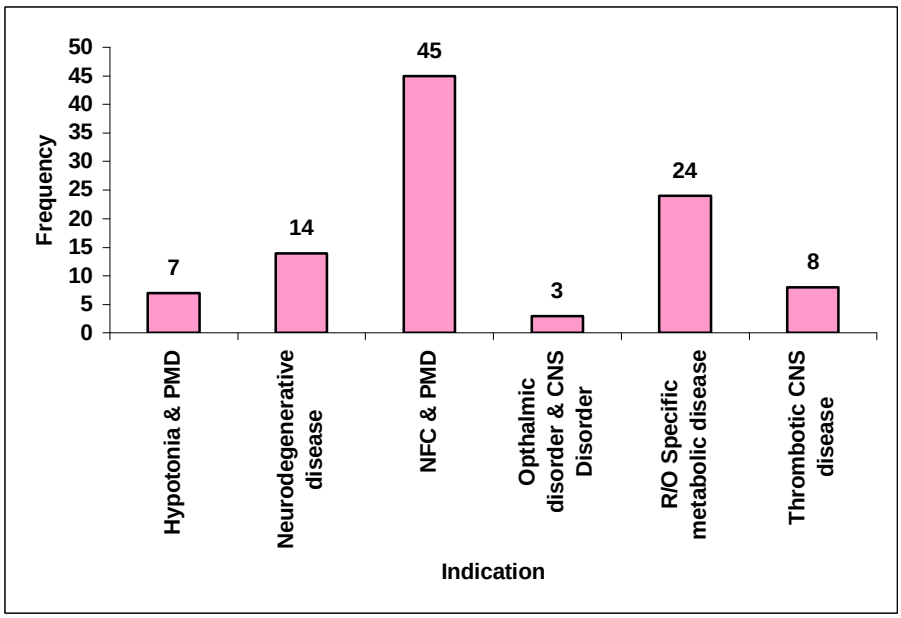

Table I

First group of patients presented with non febrile convulsions, psychomotor delay and/or cerebral or cerebellar signs and constituted about 45 % of patients. In 30% of patients, non febrile convulsions manifested as infantile spasm.

The second major group was represented by patients whose presentation whether clinical, laboratory or radiological , suggested a specific metabolic disorder.

Patients with clinical picture suggestive of neurodegenerative diseases represented the third group and constituted about 14 % of patients tested.

The fourth group was composed of patients who presented with thrombotic or bleeding CNS diseases and constituted 8 %.
3% was left for the fifth group in which presentation was specific ophthalmic findings in association with CNS disease.

Table II

AGE GROUP	***# Tested***	***Positive***
1d – 1y	*47*	*8 (17%)*
1y – 3y	*21*	*7 (30%)*
3y – 5y	*10*	*3 (30%)*
5y – 10y	*13*	*4 (31%)*
10y – 15y	*10*	*2 (20%)*

As shown in Table II, patients were grouped according to age. Those less than one year represented 47 % of the total and those who were less than 3 years 68 %.

Of the 101 patients investigated, 26 had positive results indicating underlying metabolic disorder, 16 were specific for a certain disorder and in 10 a diagnosis was suggested but still in need for final confirmation. As shown again in Table II, we had 15 positive results in the first two groups i.e. those less than 3 years of age.

The specific metabolic disorders diagnosed are shown in Table III.

One case of Cystinuria was diagnosed in a three-year-old female who was born to second-degree related parents, she presented with bilateral renal stones causing obstructive uropathy and renal failure with positive family history of kidney stones and renal failure of several other relatives.
Glutathione synthetase deficiency was diagnosed in a male infant born to third-degree related parents, he presented with infantile spasm and developmental delay without the classical picture of hemolytic anemia and episodic hypoglycemia as mentioned in the literature.

GM1 type gangliosidosis was diagnosed in a baby girl born to second-degree related parents, she presented with hypotonia, hepato-splenomegaly and cherry red spots, the mother got pregnant later on, CVS revealed the same disease in the new fetus and a therapeutic abortion was performed.

Two cases were diagnosed as Homocystinuria. The first one was a boy who had lens subluxation without any other manifestation. His parents were not relatives. The second one was a girl who presented with dystonia, mainly facial, and in whom Segawa disease was the provisional diagnosis. Her parents were not relatives.

Isovaleric acidemia was diagnosed in a three-year-old girl who presented with severe unexplained acidosis and a specific odder. Her parents were first-degree cousins with other affected children who died before reaching diagnosis and who had the same picture.

Krabbe disease was diagnosed in two patients who presented with progressive encephalopathy. They were diagnosed by Specific enzyme assay in Lymphocytes. Both were born to second-degree related parents.

L-2OH Glutaric aciduria was diagnosed in a boy who presented with convulsions secondary to perinatal insult and who developed ataxia and myoclonic epilepsy after a significant period of improvement and while off therapy for 2 years. Parents were first-degree cousins with positive family history for different types of epilepsy and unexplained deaths. This type of disorder belongs to the organic acidemias that are inherited as autosomal recessive. The defect results in build up of 2-hydroxyglutaric acid without knowing the pathology or enzyme deficiency. There are less than 50 reported cases worldwide having this disorder and patients usually presented with fits, cerebellar signs, psychomotor delay and macrocephaly. Brain MRI shows subcortical leukodystrophy. The severity of the disorder looks to be dependent on the degree of enzyme deficiency and this may explain the time of presentation as well(1, 2, 3).

Metachromatic Leukodystrophy was diagnosed in three patients who presented with progressive encephalopathy. In two of them, the diagnosis was made in late infancy by both lymphocyte and fibroblast enzyme assay. The third one was a young girl who was diagnosed by enzyme assay in blood.

A school aged girl presented to us with mild ataxic gait and convulsions. She was born to second-degree relative parents. Results of screening showed Methionine Adenosyl Transferase deficiency. This is, the first step in methionine metabolism to form homocysteine, the result is hypermethioninemia. Three distinct forms are known according to biochemical properties: Alpha, Beta and Gamma. MAT Alpha and MAT Beta are not deleterious but complete deficiency can lead to neurological abnormalities as demyelination. The Gamma form is widely distributed in non-hepatic tissue like brain, kidney and lymphocytes. Its inheritance is either recessive or dominant. For this particular case, we are waiting for the specific form as still we are working on (4, 5, 6, 7, 8).

Non Ketotic hyperglycinemia was diagnosed in two male newborns presented with severe hypoactivity, hypotonia and hiccups, both were born to second-degree related parents.

β Ketothiolase deficiency was diagnosed in an infant who presented with unexplained developmental delay and optic atrophy. His parents are first-degree cousins.

Table III: RESULTS

Diagnosis	**Number**
Cystinuria	1
Glutathione synthetase deficiency	1
GM1 Gangliosidosis	1
Homocystinuria	2
Isovaleric acidemia	1
Krabbe disease	2
L-2-OH-glutaricaciduria	1
Metachromatic leukodystrophy	3
Methionine Adenosyl Transferase Deficiency	1
Non Ketotic hyperglycinemia	2
β-Ketothiolase deficiency	1

The other 10 remaining cases have results suggestive of mitochondrial disorder. An extensive workup is still needed to determine the exact diagnosis.

CONCLUSION

These initial results are very alarming as, through the relatively short period, since the beginning of the activity of the neuropediatric unit and the small number of patients screened, we had a high percentage of positive results indicating a high degree of consanguinity and clusters of metabolic disorders in the Palestinian community.

Public and health authority awareness of the problem is the first step in prevention. The medical and health professionals are to be informed to suspect these cases and to refer them for proper diagnosis in order to prevent their recurrence later.

REFERENCES

1-Barth, PG, Hoffmann GF, Jaeken J. et al . L-2-hydroxyglutaric acidemia: a novel inherited neurometabolic disease. Ann Neurol 1992;32:66-71.

2-Divry P, Jakobs C, Vianey-Saban C, et al. L-2-hydroxyglutaric aciduria: two further cases. J Inherit Metab Dis 1993;16: 505-7.

3-Duran M, Kamerling JP, Bakker HD, van Gennip AH , Wadman SK. L-2-hydroxyglutaric aciduria: an inborn error of metabolism? J Inherit Metab Dis 1980;3: 109-12.

4-Alvarez L, Corrales F, Martin-Duce A, Mato J M. Characterization of a full-length cDNA encoding human liver S-adenosylmethionine synthetase: tissue-specific gene expression and mRNA levels in hepatopathies. Biochem J 1993;293: 481-6.

5-Blom HJ, Davidson AJ, Finkelstein JD, et al. Persistent hypermethioninaemia with dominant inheritance. J Inherit Metab Dis 1992;15: 188-97.

6-Chamberlin ME, Ubagai T, Mudd SH, Levy HL, Chou JY. Dominant inheritance of isolated hypermethioninemia is associated with a mutation in the human methionine adenosyltransferase 1A gene. Am J Hum Genet 1997;60: 540-6.

7-Chamberlin ME, Ubagai T, Mudd SH, et al. Methionine adenosyltransferase I/III deficiency: novel mutations and clinical variations. Am J Hum Genet 2000;66:347-55.

8-Chamberlin ME, Ubagai T, Mudd SH, et al. Demyelination of the brain is associated with methionine adenosyltransferase I/III deficiency. J Clin Invest. 1996;98:1021-7.