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Study of Amino Acid Disorders among a High Risk Group of Egyptian Infants and Children

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ABSTRACT

Aim of the work: The present work aimed at investigating infants (In neonatal and post neonatal period) and children suspected of having inborn errors of metabolism with unexplained mental retardation. The frequency pattern of the various amino acid disorders, in a group of selected infants and children was done to document the prevalence of various amino acid disorders among Egyptian children.

Patients and Method: In this study, recent methods to investigate such disorders have been carried out by amino acid analyzer which detects levels of amino acids. Extended metabolic screen which also detects amino acid disorders, organic acid disorders and the defects of fatty acid oxidation has been carried out. These recent methods have therefore the potential of yielding information on the physiological and pathophysiological status of different metabolic pathways, as well as their interrelationship.

Results: The total number of cases attending the outpatient clinic during the period of study were 1343 index cases, among them 50 index cases (3.72%) were suspected of having inborn errors of amino acid and, 20 cases (40%) of them have confirmed positive inborn errors of amino acid metabolism. Concerning the confirmed 20 cases, their ages ranged from 5 days to 11 years with a mean of 54.75±33.09 months with equally sex distribution. The overall consanguinity rate recorded was 65%, while the family history of the similarly affected cases was 30%. The main clinical findings included mental retardation 85%, convulsions 40%, and hypo pigmentation 75%, micro-cephally 15%. Associated anomalies were present in 35% of cases. Among them eye anomalies were the most common (8%).

Conclusion: The prevalence of amino-acido-pathies during the period of the study was 1.5% (Of 20 studied cases), among them PKU was found to be the commonest amino-acido-pathies 1.11%, while the remaining diagnosed cases representing 0.07% for each.

Key Words:
Amino acid disorders, high risk, children

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INTRODUCTION:

The inborn errors of amino acid metabolism are a family of genetic conditions in which an enzyme deficiency typically results in the toxic accumulation of substrates before the block, intermediates from alternative metabolic pathways, and defects in energy production and utilization caused by a deficiency of products beyond the block. Nearly every metabolic disease has several forms that vary in clinical severity and mode of inheritance.[1]

Mental retardation is a prominent finding of many hereditary metabolic diseases, but a fraction of mental retardation seen in daily practice is due to inborn errors of metabolism.[2] Many patients are referred for evaluation of suspected inherited metabolic disorders. The common causes for such referrals are the presence of motormental retardation, multiple deaths of sibs due to unidentified cause, or other disease with suspected metabolic cause.[3]

The availability of early diagnosis and treatment is fundamental to the prevention of neurological damage in patients affected by metabolic disorders with neonatal expression.[4]

The aim of the present study was to evaluate the frequency of amino acid disorders in a suspected group of Egyptian infants and children with suggestive clinical picture, unexplained mental retardation, or positive family history of relative or sib deaths with consanguineous marriages.

SUBJECTS AND METHODS

Subjects:

Subjects of the present study were selected from patients attending the out patient clinic of the Medical Genetic Center, Ain Shams University, for purposes of diagnosis, counseling and periodic follow up. During the period of study, the total number of cases attending the out patient clinic was 1343 cases.

The present work comprised 50 index cases belonging to 46 families fulfilling the inclusion criteria, 23 males ranging in age from 9 months to 10 years (Mean 43.87±26.65 months) and 27 females ranging in age from 5 days to 11 years (53.58±45.28 months).

Inclusion criteria:

Neonates presented with:

1. Lethargy, poor feeding, convulsions, vomiting, coma.
2. Clinical deterioration in a previously healthy neonate.
3. Positive family history of sibs or other relative deaths with consanguineous marriage.

Children presented with:

1. Unexplained mental retardation, developmental delay or convulsions.
2. Intermittent episodes of unexplained vomiting, acidosis, mental retardation or coma.
3. Hepatomegaly, renal stones.

Exclusion Criteria:
Post natal complications such as kernicterus, meningitis and head trauma.

Methods:
For each index case enrolled in the work, the following set of assessments and investigations was carried out:

1. Full clinical history.
2. Three generations pedigree analysis.
3. Thorough clinical examination.
4. Intelligent Quotient (IQ) assessment.[5]
5. Karyotype if indicated.
6. Biochemical evaluation, including calcium, glucose, liver and kidney function tests.
7. Blood gases, and electrolytes and pH.
8. Ferric chloride test.[6]
9. Quantitive determination of amino acids was done by different methods:
   a) Amino acid analyzer Sykam (S-433): based on the ninhydrin post - column derivatisation method.
   b) Extended metabolic screen.
   c) Quantitative determination of phenylalanine alone by quantase neonatal phenylalanine screening (Bio-Rad Laboratories, UK).

RESULTS

The total number of cases attending the outpatient clinic during the period of study were 1343 index cases, among them 50 cases (3.72%) were suspected of having inborn errors of amino acids and fulfilling the inclusion criteria, 20 cases (40%) of them have confirmed positive inborn errors of amino acid metabolism.

The results of the present study could be summarized in the following points:
The chronological age of the studied index cases ranged from 5 days to 11 years (Mean 49.11 months±37.83months). Index cases were 23 (46%) males ranging in age from 9 months to 10 years (Mean 43.87 months±26.65 months) and 27 (54%) females ranging in age from 5 days to 11 years (Mean 53.58 months±45.28 months).

The parental birth origin in Lower Egypt was higher (69.5%) than that in Upper Egypt (30.4%). A positive consanguinity was found in 32 families (69.56%), where 56.52% of the parents were 1st cousins and 13.04% were 2nd cousins, while 14 families (30.43%) were not consanguineous. 20 families out of 46 families (43.5%) had positive family history of affected relatives, among them 15 families (32.6%) had other affected siblings and 5 families (10.9%) had aunt or uncle affected, whereas 26 families (56.5%) had negative family history.

The clinical characteristics of the studied cases are summarized in (Table 1):

1. Presenting complaint: the most common presenting complaint was mental retardation with convulsions (42%), followed by mental retardation alone (20%) and mental retardation with hyperactivity (20%).
2. Course: it was progressive in 36% of cases, while it was stationary or regressive with treatment in 28% of cases in each. Rapid deterioration and death occurred in 4% of cases.
3. Anthropometric examination: micro-cephally was found in 10% of cases, while short stature was found in 12%.
4. Neurological features: hypertonia and hyperreflexia was found in 50% of cases, while only 4% were presented with hypotonia and hyporeflexia. Convulsions were found in 46% of cases. Mental retardation was recorded in 88% of cases, of which severe mental retardation was recorded in 34% of cases.
5. Hepatomegaly was found in only 2% of cases.
6. Dermatological features: fair complexion was found in 28% of cases, 4% of them had also eczema.
7. Associated anomalies were found in 30% of cases, among them eye anomalies were the most common (8%).

Table 1: Clinical Characteristics of the Studied Cases.

Presenting features	Number	%
Presenting complain*		
Mental retardation	10	20
Mental retardation with convulsions	21	42
Mental retardation with hyperactivity	10	20
Convulsions	1	2
Abnormal odor of urine	1	2
Discoloration of urine	1	2
Family history of unexplained neonatal deaths	3	6
Hepatomegaly	1	2
Failure to thrive, vomiting, tremors	2	4
Course		
Progressive	18	36
Stationary	14	28
Regression with treatment	14	28
Rapid deterioration and death	2	4
Anthropometric examination		
Microcephaly	5	10
Short stature	6	12
Neurological features		
Reflexes		
Hyperreflexia	25	50
Hyporeflexia	2	4
Muscle tone		
Hypertonia	25	50
Hypotonia	2	4
Convulsions	23	46
Mental retardation	44	88
Mild (IQ: 52-67)	7	14
Moderate (IQ: 36-51)	15	30
Severe (IQ: 20 - 35)	17	34
Profound (IQ<20)	5	10
Hepatomegally	1	2
Dermatological features		
Fair complexion	14	28
Eczema	2	4
Associated anomalies	15	30
Gastro-esophageal reflux	1	2
Meningocele	1	2
Undescended testicles	1	2
Bilateral hip dislocation	1	2
Umbilical hernia	2	4
Rocker bottom heel	1	2
Hemangioma on the abdomen	1	2
Mitral valve regurge	1	2
Postaxial polydactyly	1	2
Tongue tie	1	2
Eye anomalies	4	8
Optic atrophy	2	4
Optic atrophy with squint	1	2
Nystagmus	1	2

* Six cases presented with normal mentality.

Out of the 50 index cases suspected to have metabolic disease, 20 cases (40%) had amino-acido-pathies, among them 15 cases (30%) had PKU, one case (2%) had alkaptonuria, one case (2%) had citrullinemia, one case (2%) had nonketotic hyperglycinemia, and one case (2%) had trimethylaminuria (Fish odor syndrome) (Table 2).

Table 2: Aminoacidopathies detected over the period of this study.

Amino-acido-pathy	No of cases	%
Phenylketonuria	15	30
Urea cycle defects (Citrullinemia)	1	2
Hyperglycinemia	1	2
Maple syrup urine disease	1	2
Alkaptonuria	1	2
Trimethylaminuria (Fish odor syndrome)	1	2
Total	**20**	**40**

The Prevalence of amino-acido-pathies detected over the period of this study among 1343 cases attending the Genetics Clinic was 20 cases (1.5%). Phenylketonuria represented 1.11%, while the remaining diagnosed cases represented 0.07% for each table (2).

Concerning the confirmed 20 cases, it was found that their age ranged from 5 days to 11 years with a mean of 54.75±33.09 months. Their maximum age incidence was early childhood (60%). Both sexes were equally affected. Con-sanguinity was present in 65% of cases, of which 50% were first cousins, and 15% were second cousins. The family history of similarly affected cases was 30% of which 25% had other sibs affected.

The main presenting complain among examined cases was mental retardation with convulsions and mental retardation with hyperactivity (40%) in each. Clinical examination revealed micro-cephaly in 15% of cases, hypertonia and hyperreflexia in 35% of cases in each, convulsions in 40% and mental retardation in 85% of cases, of which severe mental retardation present in 55%. Associated anomalies were present in 35% of cases, among them eye anomalies were the most common in form of optic atrophy in 5% and nystagmus in 5%.

Case report of index case no 43:

Male patient, 4 years years old, the 2nd offspring of consanguineous parents, with negative family history (Figures 1, 2, 3) & parental birth origin was from Lower Egypt. His mother complained of darkening of the urine since birth to an almost black color when it was left standing exposed to air with stationary course.

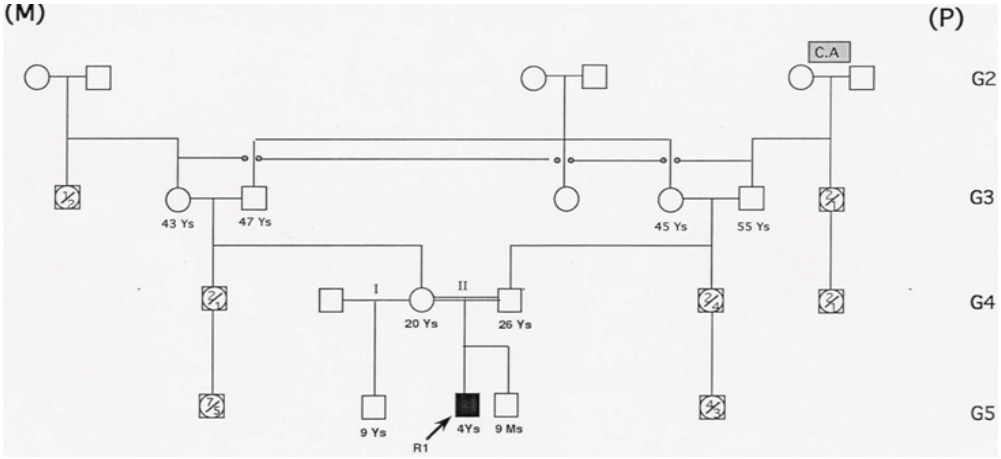

Fig. 1: Family pedigree of index case no (43).

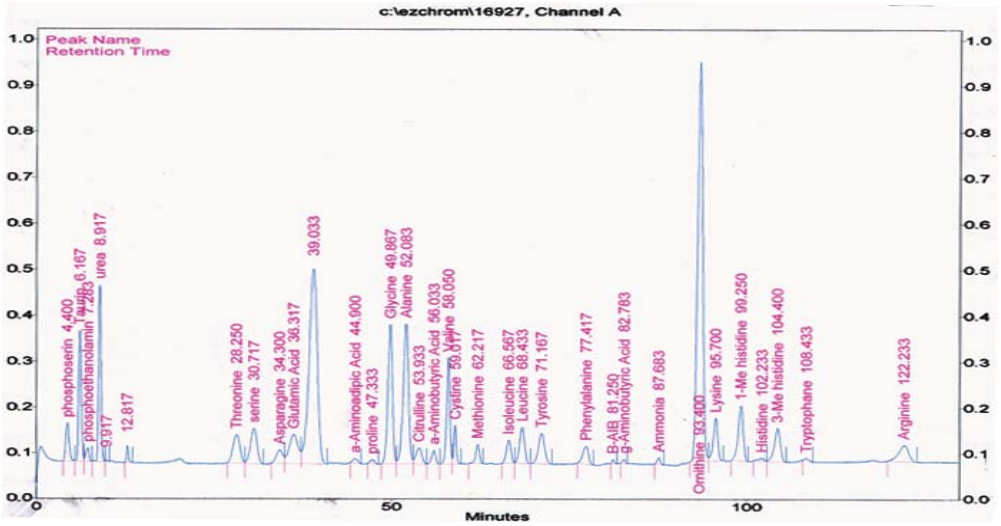

Fig. 2: Curve of amino acids separation of case (43).

A) **B)**

Fig. 3:a- Male patient no(43)with Alkaptonuria
b- Black colored urine of the patient.

Physical examination: Revealed a healthy child with normal mentality, growth and development, associated with umbilical hernia. There was no abnormal pigmentation of the sclera, conjunctiva, and cornea or ear cartilage. Joint examination was normal.

Investigations:

- Ferric chloride test: slight bluish discoloration which then disappeared.

- Kidney function tests were normal.
- Skeletal survey showed no degenerative changes.
- Echocardiography: revealed no abnormalities.
- Amino acids concentrations were normal as detected by amino acid analyzer figure (2).
- He was on vitamin C, currently, the patient is asymptomatic and is under follow up every six months in the outpatient clinic.

Diagnosis: Alkaptonuria.

Case report of index case no 35:

Female patient, 5 days old, the 4th offspring of consanguineous parents with positive family history (3 previous neonatal deaths) (Figures 4 & 5). Parental birth origin was from Lower Egypt. She was well until the sixth day, when she developed poor suckling, convulsions, difficulty in respiration and episodes of cyanosis. She was admitted to Neonatal Intensive Care Unit and died at age of 15 days. Blood gases and pH revealed metabolic acidosis.

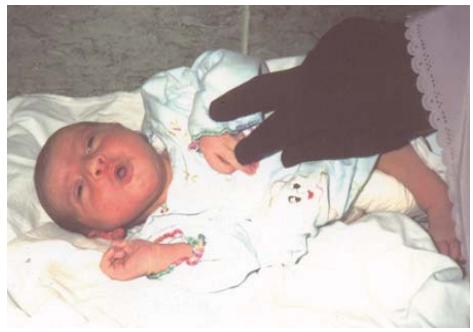

Fig. 5: A female patient no (35) with maple syrup urine disease (Poor suckling, convulsions and difficult breathing).

Amino-acids concentrations determined by amino-acid analyzer revealed raised levels of leucine, isoleucine and valine (Figure 6).

Diagnosis: Maple syrup urine disease.

Case report of index case no 18:

Female patient aged 11 years, the 2nd offspring of consanguineous parents with positive family history of affected 2 male sibs and the index mother (Figures 7 & 8). Parental birth origin was from Upper Egypt. Her mother

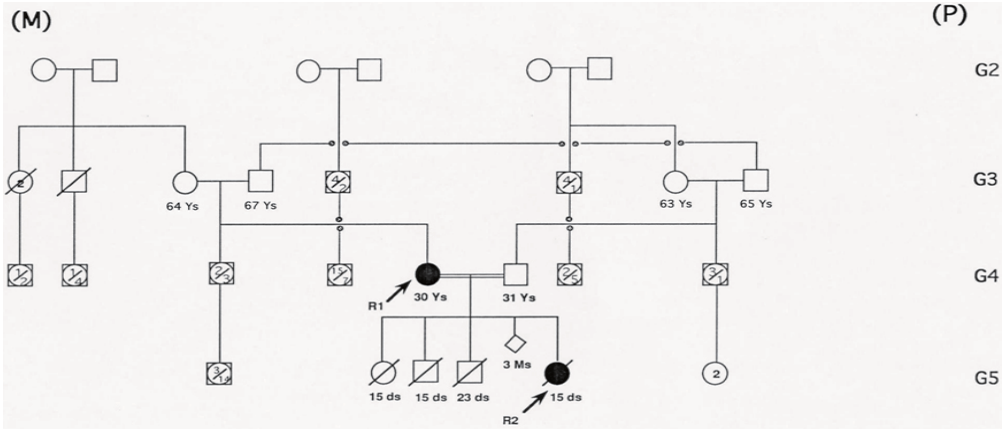

Fig. 4: Family pedigree of index case no. (35).

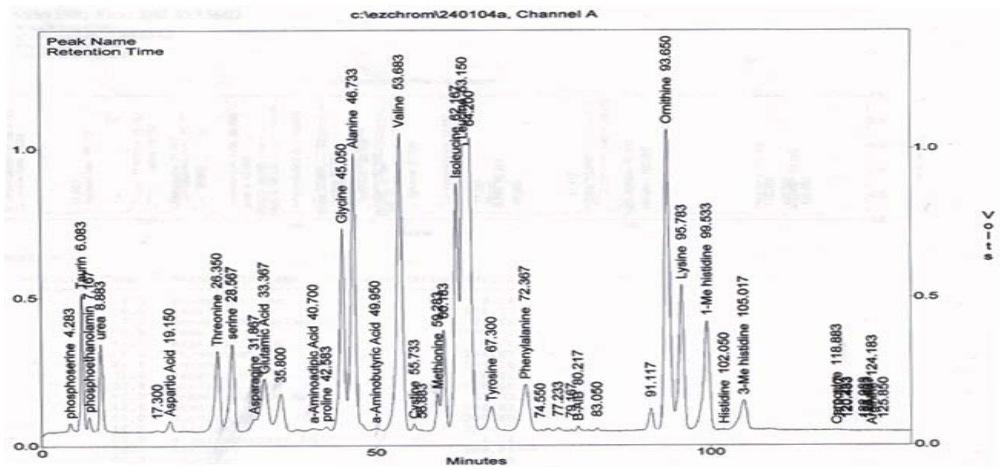

Fig. 6: Curve of amino acids separation of case (35).

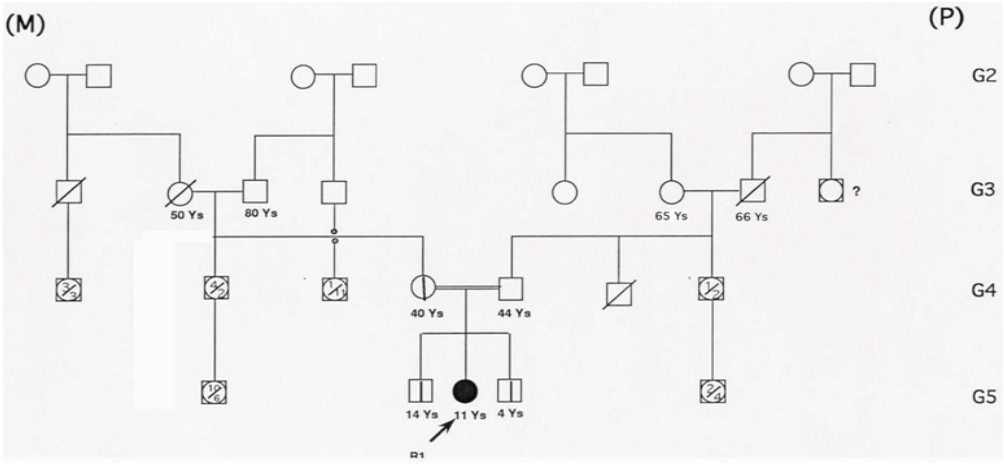

Fig. 7: Family pedigree of index case no 18.

noticed a fishy smell in urine, sweat and breath at the age of 4 years, stationary in course. The patient had normal mentality, growth and development without neurological abnormalities. She had anxiety and social isolation.

Fig. 8: Female patient no (18) with trimethylaminuria.

Investigations:
Extended metabolic screening: revealed no abnormalities in amino-acids, organic acids and fatty acids. Plasma ammonia, lactate, pyruvate were normal. Echocardiography: revealed mild mitral regurge (Rheumatic mitral valve).

Diagnosis: Most probably fish odor syndrome (Trimethylaminuria).

Case report of index case no 46:
Female patient aged 32/12 years old. She is the 1st offspring of consanguineous parents, with negative family history (Figure 9). Parents' birth origin was from Upper Egypt. Her mother complained of developmental delay of her daughter and convulsions not responding to anti-convulsants.

By examination, she had delayed physical and mental milestones, hypertonia with hyperreflexia and she had microcephaly, fair skin and hair, hypertelorism, depressed nasal bridge and severe mental retardation.

Investigations showed normal ferric chloride test for urine. Blood pH and blood ammonia were normal. MRI of brain showed brain atrophy and crescent like arachnoid cyst in left temporal pole. Slit lamp examination revealed normal fundus. Amino acids concentrations determined by amino acid analyzer revealed raised level of glycine (Figure 10).

Diagnosis:
Non-ketotic hypergly-cinemia (NKH).

Case report of index case no. 25:
Male patient aged 4.5 years. He is the 2nd offspring of consanguineous parents with positive family history (His brother was not examined) (Figure 11). Parental birth origin was from Lower Egypt. His mother complained of develop-mental delay, attacks of drowsiness, and tonic clonic convulsions of her son, progressive in course. During the study period the mother delivered a female baby who was also investigated. He had delayed mental and physical

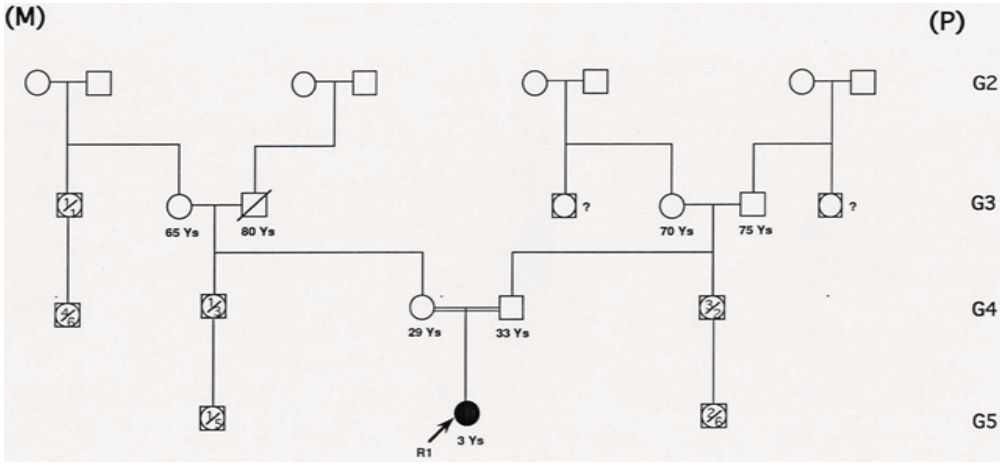

Fig. 9: Family pedigree of index case no (46).

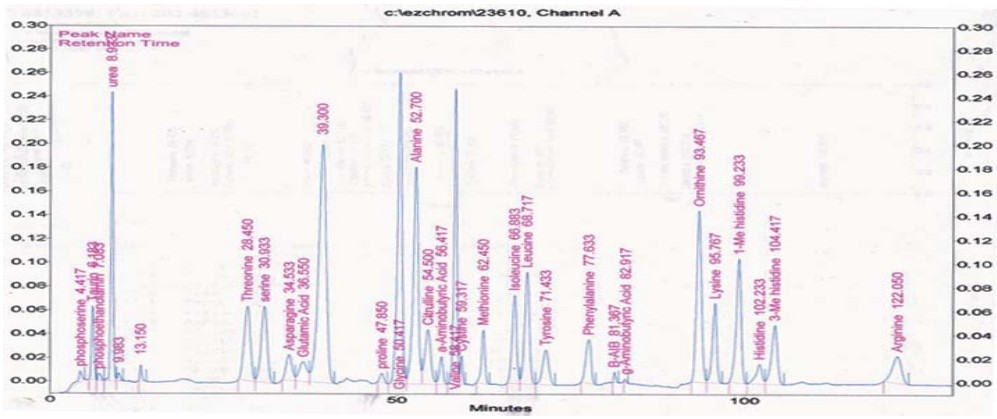

Fig. 10: Curve of amino acids separation of case (46)

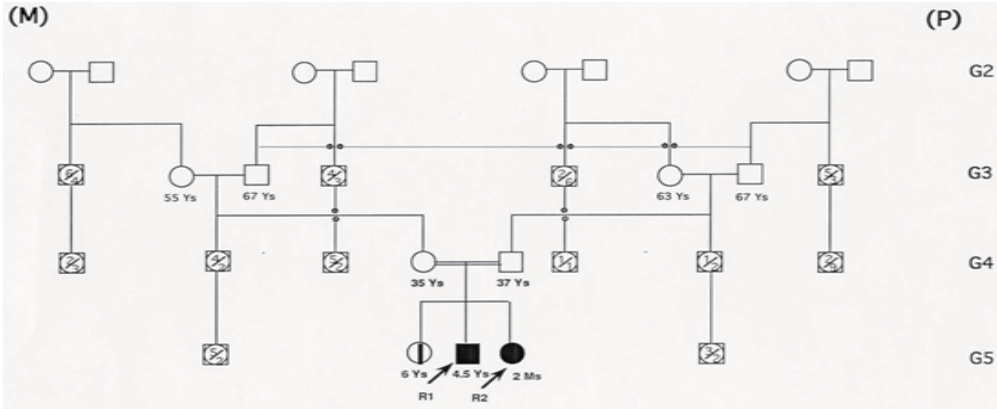

Fig. 11: Family pedigree of index case no (25).

milestones of development, hypertonia, hyperreflexia and severe mental retardation. There was mild elevation of blood ammonia (320 µmol/L), while blood pH, lactate and pyruvate were normal. MRI of the brain showed hypoplasia of cerebellum.

Extended metabolic screen revealed high level of citrulline 730 µmol/L (Normal:5–95 µmol/l). The female infant (Two months) was also investigated by extended metabolic screen and showed no abnormalities in amino acids, organic acids or fatty acids.

Diagnosis: Urea cycle defect (Citrullinemia).

PKU cases:

PKU cases were classified into classical type [11 cases (73.3%)] with blood phenylalanine>1200 mmol/l and atypical type [4 cases (26.7%)] with blood phenylalanine<1200 mmol/l. Their blood phenylalanine ranged from 810-1673 mmol/l with the mean of 880.58 mmol/l (Normal: 41–86 µmol/L). FeCl3 test was dark green in all PKU cases.

The maximum age incidence at time of examination was early childhood [9 cases (60%)], with approximately equal sex distribution. Consanguinity was found in 8 families (66.67%) and first cousins were the most prevalent (58.33%). Four families (33.33%) had positive family history of affected members.

The main clinical findings among our cases included mental retardation in 100%, hyperactivity in 53.33%, convulsions in 40%, microcephaly in 13.33%, hypo pigmentation in 86.7%, and associated anomalies in 26.7%, in the form of meningocele in 1 patient, bilateral optic atrophy in1 patient, gastroesophageal reflux in 1 patient and undescended testes in1 patient.

(Figure 12a & b) shows case no. 9, a 6 years old male with PKU.

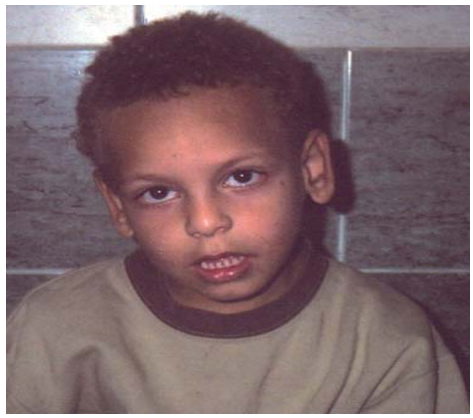

Fig. 12a: Case no. 9 a 6 years old male with PKU. He is the 1st off spring of consanguineous parents (1st cousins), and presented with severe mental retardation, convulsions, hyperactivity, and convulsions since birth. EEG detected multiple epileptogenic activities with tendency for secondary generalization.

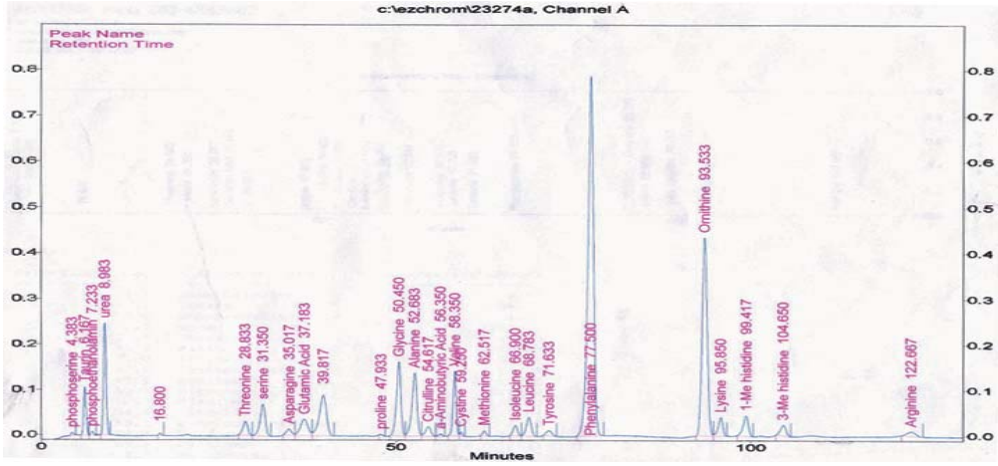

Fig. 12b: Curve of plasma amino acids separation by amino acid analyzer of case no. 9. The plasma phenylalanine level was 1673.24 mmol/L (Normal: 41–86 µmol/L).

DISCUSSION

Inborn errors of metabolism should be considered in severely ill neonates with lethargy, poor feeding, convulsions, coma and death in the neonatal period especially if there is positive sib death or consanguineous marriage. Also, inborn errors of metabolism should be suspected in children with unexplained

mental retardation, developmental delay or convulsions.[7]

There are two main problems in detecting inborn errors of metabolism:

1. Symptoms are nonspecific and often similar to those of sick neonates, therefore, only a small number of these diseases will be diagnosed from typical clinical picture alone and we can rarely target the specific investigation required for diagnosis of the offending disease.
2. Investigations are complex and expensive.[8]

In our study, out of 1343 cases attending the outpatient clinics, 50 cases were suspected to have metabolic disease, 20 cases of them (40%) proved to have amino-acido-pathies (Representing 1.5% of the total). Out of the 20 cases of amino-acido-pathies identified, 15 cases (30%) had PKU, one case (2%) had hyperglycinemia, one case (2%) had MSUD, one case (2%) had alkaptonuria, one case (2%) had citrullinemia and one case (2%) had trimethylaminuria (Fish odor syndrome).

On the other hand, a greater percentage (10%) of cases with amino acid defects were recorded by another genetic study done in Egypt on 100 mental retarded patients by Abdel-Meguid.[9] Also Temtamy et al. recorded disturbances of amino acid metabolism in 4.2% of mentally retarded cases in Egyptian children.[10]

Shawky et al. reported that 51 cases out of 450 studied mental retarded cases (11.32%) have confirmed positive inborn errors of amino acid metabolism. Forty cases (78%) have PKU, four cases (7.84%) had generalized non-specific amino aciduria, two cases (3.92%) had NKH, two cases (3.92%) had hyperprolinemia, two cases (3.92%) had histidinemia and one case (1.96%) had homocystinuria.[11]

El-Sobky and El-Sayed studied 231 cases (44 neonate and 187 children) with different symptoms suggesting inborn errors of metabolism. Abnormal results were found in 26 cases (31.3%) which included 13 cases (10.4%) with amino-acido-pathies, two cases (4.55%) with fatty acid oxidation defects, 8 cases (14.7%) with organic acidemia and three cases (1.6%) with cystic fibrosis, congenital adrenal hyperplasia and congenital hypothyroidism.[8]

As regards the age and sex distribution of the suspected index cases fulfilling the inclusion criteria; their ages ranged from 5 days to 11 years with a mean of (53.58+45.28 months). Their maximum age incidence was early childhood representing 25 cases, 50%, similarly the maximum age incidence was early childhood in confirmed cases representing (12 cases, 60%). Both sexes were equally distributed in both suspected and confirmed cases. Most inborn errors of metabolism are inherited in an autosomal recessive manner. Both sexes are affected equally in autosomal recessive conditions.[12]

In the present study, the age of onset of amino acid disorders was variable. Alkaptonuria and MSUD presented at birth, trimethylaminuria in early childhood citrullinemia PKU in early infancy, while non-ketotic hyperglycinemia (NKH) presented in late infancy.

Disorders of amino acid metabolism can present at any age but are not usually symptomatic at birth or in the first day of life. Disorders with acute presentation often presents at time of protein catabolism e.g. in the neonatal period (Metabolic transition, delayed food in-take), late infancy (Change to protein rich meals with greater intervals; common infections with fever, vomiting and reduced food in-take) or puberty (Change in growth rate, psychosocial factors).[13] Ozand and Gascon revealed that different phenotypic expression with different ages was observed in inborn errors of metabolism even among members of the same family, however, the neonatal onset is invariably lethal.[14]

In the present study, Lower Egypt had the highest incidence as parental birth origin (69.5%). This epidemiologic information allows appropriate screening and counseling. The same result was also reported in a study done by Shawky et al.[11]

The overall recorded consanguinity rate among the suspected cases in our study was 69.56% of which 56.52% was first cousins while second cousins consanguinity represented 13.04%. On the other hand, consanguinity among the confirmed cases in our study was 65% of which 50% was first cousins.

Consanguinity rate may reach up to 28% in Egypt which helps to accumulate deleterious genes in families.[15] Also, Abdel-Salam et al. found a consanguinity rate of 36.2% in rural areas and of 20.37% in urban areas in Egypt.[16] Consanguinity is of special importance in genetic counseling of autosomal recessive disorders.

Shawky et al. reported that consanguinity rate of mentally retarded patients of the selective screening program for mentally retarded cases were 74.5% and 52.9% had first cousins consanguinity.[11]

The family history of similarly affected cases with suspected metabolic disorder in our study was recorded in 43.5% of our index families of which 32.6% had an-other sibling affected and 10.9% had an aunt or uncle affected. While the family history of confirmed cases was 30%, of which 25% had other sibs affected.

Shawky et al. reported that family history of mental subnormality of similar disorders among the selective screening program was 37 %.[11]

In this study, one index case (2% of the 50 index cases suspected to have metabolic disease, and 0.07% of the 1343 cases attending the clinic during the period of the study) had trimethylaminuria, resulting in fishy smell of urine, sweat and breath as noticed by the mother at the age of 4 years. Family history was positive for her mother and two affected sibs.

Extended metabolic screen showed no abnormalities in amino acids or organic acids in this syndrome. Mitchell and Smith reported that over 200 cases of the disease have been described on a world wide basis.[17] Lee et al. found that the condition could affect infants, children and adults and it was confirmed to be associated with the excretion of excessive amount of trim ethylamine[18], while Chalmers showed that the disorder was present from birth but became apparent as foods containing high amounts of choline or

trimethylamine N oxide from marine (Sea or salt water) fish were introduced into the diet.[19] The cause of the disease is a lack of the trimethylamine oxidase enzyme in liver.

Normally this enzyme oxidizes trimethylamine to trimethylamine oxide which is odorless and is excreted in urine. This metabolic defect ca-uses massive excretion of trimethylamine in urine.[20] Phillips et al. found that the flavin mono-oxygenase (FMO) family of enzymes was responsible for trimethyl-amine oxidation.[21] The final diagnosis should be made by detection of urinary trimethylamine greater than 18 µmol/mmol creatinine by gas chromatography.[22]

In the present study, one index case (2% of the 50 index cases suspected to have metabolic disease, and 0.07% of the 1343 cases attending the clinic during the period of the study), had citrullinemia presenting with convulsions, drowsiness, mental retardation and a similar family history of an affected sister. He had a plasma ammonia concentration of 320 mmg/L (Normal: 80-110 µmol/L) with elevated citrulline 730 µmol/L by ex-tended metabolic screen. This was consistent with the reported gradual onset of clinical symptoms of this disorder, in the form of mental retardation, attacks of drowsiness and tonic clonic convulsions at the age of two years, when the diagnosis was missed in infancy.[23]

Van-Buggenhout et al. reported that among 306 patients screened for metabolic disorder, two cases (0.6%) were proved to have citrullinemia.[24]

In our study, one female patient of consanguineous parents (2% of the 50 index cases suspected to have metabolic disease, and 0.07% of the 1343 cases attending the clinic during the period of the study), with a percentage of 0.07% of the 1343 attending cases during the period of the study, had MSUD disease. She presented with poor suckling, convulsions, difficulty in respiration, episodes of cyanosis and died at the age of 15 days.

Sobky and El-Sayed reported that among 231 cases with different symptoms suggesting in born errors of metabolism, 2 cases (0.9%) with MSUD were detected.[8]

In our study, one index male patient (2% of the 50 index cases suspected to have metabolic disease, and 0.07% of the 1343 cases attending the clinic during the period of the study) with a percentage of 0.07% of the 1343 attending cases during the period of study, had alkaptonuria. The child was 4 years old of consanguineous parents. His mother noticed darkening of the urine to almost black since birth when exposed to air, stationary in course. Amino acid profiles were normal as detected by amino acid analyzer. Ozalp et al. reported that alkaptonuria represents 0.11% of the total selective cases in Turkey.[25] While Kaur et al. showed that Alkaptonuria represents 0.51% of the selective cases in North India 3. In the literature, more than 126 patients with alkaptonuria have been reported from Czechoslovakia, 108 from Germany and 90 from United States. In countries of Middle East, the disease was first reported from Lebanon in 1958 and from

Sudan in 1965, two adult patients from Saudi Arabia and one from Yemen.[26]

In our study, one female patient (2% of the 50 index cases suspected to have metabolic disease, and 0.07% of the 1343 cases attending the clinic during the period of the study %) was diagnosed as NKH. The patient was 3.2/12years old, of consanguineous parents. She had been well with normal development up to one year of age, and then there was rapid deterioration in mental and motor milestones of development, and convulsions not responding to anticonvulsant drugs. On referral she was found to have lower limb spasticity with hypertonia and hyperreflexia. MRI showed periventricular leukomalacia with left temporal arachnoid cyst. Amino acid concentrations determined by amino acid analyzer showed raised level of plasma glycine (709.73 μmol/L; normal range: 1–15 μmol/L).

Shawky et al. reported that among 450 cases of mentally retarded patients two cases (0.4%) of NKH were detected.[11] Wraith et al. reported that infantile NKH has been described in several children who had normal growth and development until at least six months of age, then developed lethargy, refusal to feed, profound hypotonia, seizures and moderate mental retardation.[27] This is in accordance with our case as regards the age of onset, moderate mental retardation, seizures, while hypertonia was a constant feature of our reported case.

PKU was the most common in-born error of amino acid metabolism among our cases (30%), with a percentage of 1.1% of the 1343 attending cases during the period of study. The blood phenylalanine level ranged from 810-1673. 29 μmol/L. Shawky et al. reported that PKU was the most common inborn error of amino acid metabolism, it represented 78% of disturbances of amino acid and 8.9% of the 450 studied mentally retarded cases.[11]

In the present study, PKU cases were classified into classic type (73.3%) with blood phenylalanine>1200 μmol/L and atypical type (26.7%) with blood phenylalanine<1200 μmol/l. Shawky et al. reported that PKU cases can be classified into: classic type (90%), atypical type (7.5%) and malignant type (2.5%) 11. The main clinical finding among our PKU cases included hypopigmentation (86.7%), mental retardation (100%), seizures (33.33%), hyper-activity (53.33%) and micro-cephaly (13.33%). Shawky et al. (2001) showed that the main clinical finding included hypopigmentation (100%), microcephaly (37.5%), hyperactivity (90%), seizures (25%) and abnormal EEG (42.5%).[11]

RECOMMENDATIONS

The remaining cases with unexplained mental retardation need further follow up and further investigations in order to reach a specific diagnosis to guide their families in prenatal diagnosis.

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