CLINICAL STUDY

# Metabolic encephalopathy in Egyptian children

Hindawy A[1], Gouda A[2], El-Ayyadi A[1], Megahed H[3], Bazaraa H[2]

*Pediatric Department, Cairo University, Egypt.* **amr gouda@yahoo.com**

**Abstract**

**Fatty Acid Oxidation disorders represent an expanding group of inborn errors of metabolism. Clinical manifestations include episodic encephalopathy, hypoketotic hypoglycemia, Reye like episodes, hepatic, muscular, cardiac affection and sudden death. Analysis of urinary organic acids and plasma fatty acids of 44 clinically suspected patients by Gas Chromatography Mass spectrometry revealed 4 cases of Medium chain acyl-CoA dehydrogenase deficiency (MCADD), 3 cases of Very long chain acyl-CoA dehydrogenase deficiency, 9 cases of multiple defects of acyl-CoA dehydrogenation in addition to 3 patients with other metabolic disorders. Timely detection of these disorders including screening for MCADD can have a favorable impact on the outcome of these patients *(Tab. 11, Fig. 3, Ref. 24)* Full Text (Free, PDF) *www.bmj.sk*.**

**Key words: encephalopathy, fatty acid oxidation, inborn errors, metabolism, hypoketototic hypoglycemia.**

Inborn errors of fatty acid (FA) oxidation constitute a relatively large group of metabolic diseases. They are caused by autosomal recessive mutations in the genes coding for one of at least 15 different enzymes involved in mitochondrial fatty acid oxidation With the exception of MCADD, they are rare disorders (<1: 40 000 births), collectively however, they are common causes of treatable metabolic disease in infants and children ( Kiura et al, 2002).

Despite being the preferred fuels for skeletal and cardiac muscles, the oxidation of fatty acids represents a minor contribution to overall energy needs other than during fasting and stress. Therefore, defects of FA oxidation do not often manifest until the infant's first illness associated with significant fasting; when metabolic decompensation associated with failure of energy supply occurs (DeVivo, 1999).

When FAs accumulate as a result of defective B oxidation, they are shunted to auxiliary pathways; omega oxidation and hydroxylation, yielding dicarboxylic acids. Dicarboxylic aciduria is an important finding in FA oxidation disorders. When FA oxidation is disrupted, acyl glycine and acyl carnitine esters accumulate; offsetting the sequestration of CoA that occurs with accumulating acyl CoA thioesters. Depletion of serum and tissue carnitine may result; with decreased free and increased bound carnitine fractions.

Defects of FA oxidation result in underproduction of acetyl CoA and consequent impairment of hepatic ketogenesis. During fasting, impairment of Krebs' cycle activity and failure to supply energy for gluconeogenesis leads to hypoglycemia (which is characteristically hypoketotic). Decreased availability of both ketone bodies and glucose deprives the brain of its two main energy sources (Di Donato, 1997). In addition to the effects of energy deficiency, the abnormal accumulation of FAs and their intermediates may have deleterious effects on cellular function; they may be directly toxic to the nervous system and other tissues (Fig. 1).

## The metabolic changes in FA oxidation disorders

Acute or recurrent episodes of hypoketotic hypoglycemia associated with encephalopathy (with signs of progressive lethargy, vomiting and ultimately coma and seizures) is the classical presentation. Such attacks are usually triggered by fasting or infection and may be associated with acute organ (cardiac, hepatic or skeletal muscle) dysfunction, leading to manifestations such as cardiac arrhythmias, acute cardiac failure, acute hepatic failure and hypotonia.

[1]Pediatric Department, Cairo University, [2]Biochemical Genetic Department National Research Centre, Cairo, and [3]Clinical Genetics National Research Centre, Cairo

**Address for correspondence:** Dr. Amr Sobhi Gouda, National Research Center, Tahrir st, Dokki, Cairo, Egypt.

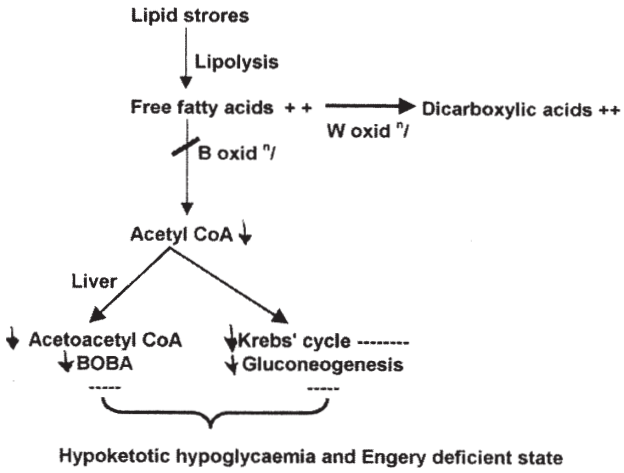


**Fig. 1. Hypoketotic hypoglycaemia and energy deficient state.**

Such episodes bear resemblance to Reye syndrome and are often described as "Reye-like" disorders. In fact, it is now clear that most patients who appear to have Reye syndrome have an IEM; most commonly MCADD and ornithine transcarbomylase deficiency. The mortality of the first such episodes has been quoted to be as high as 59 % (Wilson et al, 1999). Because birth is a time when prolonged fasting can also occur, some patients will develop a neonatal encephalopathy; but more often not, and will be evaluated as sepsis rather than an IEM.

The other common type of presentation reflects chronic disruption of muscle function with manifestations relevant to myopathy or cardiomyopathy. Examples include muscle weakness, hypotonia, exercise associated myoglobinuria, congestive heart failure and cardiac arrhythmias. Other presentations include recurrent vomiting, failure to thrive and (in some defects) hepatic affection; with fatty infiltration, cirrhosis or chronic hepatic failure. Although being healthy between acute episodes is the usual case, some patients with the fore mentioned chronic conditions may not be diagnosed until they develop an acute crisis as a complication of fasting (Nyhan and Ozand, 1998).

Blood ammonia is often mildly elevated (up to 2 folds) but higher levels were sometimes observed. Hepatomegaly with elevated transaminases is common during acute illness and liver biopsy reveals abundant deposits of lipid. These findings have often led to the diagnosis of Reye syndrome (Keppen et al, 1999).

For the majority of FA oxidation disorders, urine contains a diagnostic pattern of abnormal FA by-products (largely dicarboxylic acids and glycine conjugates of FFAs) when examined by gas chromatography – mass spectrometry (GC-MS). In MCADD for example, a diagnostic pattern of medium chain dicarboxylic acids, hexanoyl-glycine and suberyl-glycine is present.

Analysis of plasma for abnormal levels of specific FFA or acyl-carnitine species can also be diagnostic for many of the B oxidation defects (Kelley, 1998). An approach that can be used both during remission and during acute illness is to examine the urine or blood for specific carnitine esters (such as octanoyl-carnitine for MCADD) by fast atom bombardment-mass spectrometry or tandem mass spectrometry (MS-MS) (Ioulianas et al, 2000).

These disorders carry a definite risk of mortality (acute episodes, cardiac or hepatic failure or sudden death) and neurological sequalae (related to delay in proper intervention) as opposed to normal healthy life free of episodes of illness in most of the disorders when recognized and treated by relatively simple means (diet, avoidance of fasting, ensuring continuous carbohydrate supply, sometimes L-carnitine & riboflavin) (Tojo et al, 2000).

Because these disorders have diverse clinical presentations and because they are considered to be under diagnosed, even in the developed world, this study aims to evaluate patients clinically suspected of having FAox disorders to identify the characteristics of these disorders among our patients and to study the need for screening for them in certain patients groups.

## Patients and methods

44 cases were selected from patients attending the Cairo University Pediatric Hospital between October, 2000 and December, 2001 including:

– 30 patients with suspected acute metabolic crisis; presenting with otherwise unexplained encephalopathic manifestations (abnormal consciousness and/or convulsions) of acute onset (sometimes following minor or moderate respiratory or gastrointestinal infection), especially in association with hypoglycemia, hepatomegaly, elevated hepatic transaminases, marked hypotonia, or family history of unexplained deaths.

– 12 patients without existing acute illness; who were included because of different combinations of failure to thrive, episodic recurrent vomiting, recurrent encephalopathy, hepatic affection, myopathy or cardiomyopathy, and suggestive family history.

– Two asymptomatic infants who had positive consanguinity and multiple sibling deaths during late infancy the death reported to be following acute deterioration after minor illness.

All patients were between 1 month and 3 years old, the following patients were excluded from selection:

– Those with evidence of ketosis by dipstick testing of urine.

– Those with acute neurological manifestations adequately explained by either: Documented CNS infection, Documented intracranial haemorrhage, Marked hypernatraemia in patients presenting with encephalopathy following gastroenteritis.

10 apparently healthy children of matching age were also included for comparison as controls.

All patients were subjected to:

1) Complete history taking and physical examination.

2) Initial laboratory tests; including blood glucose level, urinary ketones and transaminases (SGOT and SGPT).

3) Other investigations according to the clinical condition including:

– CSF examination for cells, glucose and proteins in all patients.

– Blood gases in all patients with acute critical conditions.

– Plasma ammonia.

– Neuroimaging studies.

**Tab. 1. Sibling deaths among the study group.**

| | No of pts | Percentage |
|---|---|---|
| No sibling deaths | 31 | 70.5 |
| One sibling death | 6 | 13.6 |
| Two sibling deaths | 3 | 6.8 |
| Three sibling deaths | 3 | 6.8 |
| Four sibling deaths | 1 | 2.3 |
| Total | 44 | 100 |

**Tab. 2. Age distribution of different patient groups.**

| Group | Mean age (months) | Range | Difference from study group |
|---|---|---|---|
| Study group | 10.1±8.3 | 1–36 | |
| FA disorders | 7.75±8.52 | 1–36 | NS (p>0.10) |
| MCADD | 7.5±3.78 | 2–10 | NS (p>0.10) |
| VLCADD | 7.3±4.51 | 3–12 | NS (p>0.10) |
| Multiple defects | 8±11.2 | 1–36 | NS (p>0.10) |
| Other metabolic disorders | 14±8.71 | 8–24 | NS (p>0.10) |

Fa disorders – all patients diagnosed with disorders of fatty acid oxidation, multiple defects – patients with multiple acyl-CoA dehydrogenation defects, NS – not significant

4) Analysis of urinary organic acids by GC-MS: Organic acids are extracted from acidified, salt saturated urine. The extracts are evaporated to dryness under nitrogen and trimethylsily (TMS) derivatives formed using BSTFA and pyridine. TMS derivatives are identified using gas chromatography-mass spectrometry (GC-MC) electron impact (Chalmers and Lawson, 1982).

5) Analysis of plasma fatty acids: Venous blood samples obtained from the patients and mixed with an anticoagulant (heparin sodium) were centrifuged at 2000 rpm for 10 minutes. The plasma was separated and frozen at -20 °C. For analysis of total (free and esterified) fatty acids in plasma (Onkenhout et al, 1995).

6) Samples have been, as much as possible, obtained early in acute critical patients; however, it was not always feasible to obtain samples before starting treatment.

## Results

*The study group*

44 patients were included; their age ranged between 1 and 36 months with a mean of 10.1±8.3 months, while controls had a mean age of 11.6±6.0 months (no significant difference; p>0.10), with a range of 3–24 months. Patients included 28 males (64 %) and 16 females (36 %), while controls were 6 males and 4 females. The male preponderance in the study group was not statistically significant (p>0.10). The parents of 20 patients (45.5 %) were consanguineous compared to 4 controls (40 %) with no significant difference (p>0.10). 13 patients (29.6 %) had positive family history of sibling deaths (Tab. 1).

Patients have been classified according to their clinical presentation into 9 categories. They are shown in Table 6. Of the 30 patients with acute presentations, the acute illness was preceded with acute gastroenteritis in 8 patients, respiratory tract infection in 3 patients, vomiting and/or poor feeding in 3 others and undifferentiated fever in one patient; however, 50 % (15 cases) did not report any preceding illness.

Neurological manifestations were present in 36 patients (81.8 %), hepatomegaly in 27 patients (61.4 %) and cardiac manifestations in 12 patients (27.3 %) ;mostly acute cardiac failure or cardiogenic shock in association with acute illness (8 cases). 3 had chronic heart failure of whom echocardiography revealed asymmetrical hypertrophy in one and dilated heart with impaired contractility in the other two.

Blood glucose levels were done to all patients and levels below 45 mg/dL were found in 9 patients all of then had no tested urinary ketones bodies. The mean blood glucose was 59±26 mg/dL, significantly less than that of the control group which was 75.3±12.7 mg/dL (p<0.01). Concerning the hepatic transaminases, 15 patients had normal ALT and AST, 7 patients had one of both enzymes elevated while 22 patients (50 %) had elevation of both As regards outcome; of the 30 patients presenting acutely, and 21 of them died (70 %).

**Tab. 3. Clinical categoties of studied patients with FA oxidation disorders.**

| Clinical presentation | Total number (%) | FA oxidation disorders | | | |
|---|---|---|---|---|---|
| | | total | MCADD | VLCAD | multiple |
| Acute conditions | 30 (68.2) | 14 (87.5) | 4 (100) | 3 (100) | 7 (78) |
| 1) acute encephalopathy | 23 (52.3) | 9 (56) | 3 (75) | 2 (67) | 4 (45) |
| 2) acute encephalopathy with cardio-respiratory failure | 5 (11.4) | 3 (19) | 0 | 1 (33) | 2 (22) |
| 3) sepsis-like illness | 2 (4.5) | 2 (12.5) | 1 (25) | 0 | 1 (11) |
| Chronic conditions | 12 (27.3) | 2 (12.5) | 0 | 0 | 2 (22) |
| Family histofy alone | 2 (4.5) | 0 | 0 | 0 | 0 |
| Total | 44 (100) | 16 (100) | 4 (100) | 3 (100) | 9 (100) |

**Tab. 4. Presence of a precipitating illness in patients with FA disorders according to age.**

| Age group | No of cases | No of cases with a precipitating illness | % |
|---|---|---|---|
| ≤3 months | 6 | 1 | 17 |
| >3–12 months | 8 | 4 | 50 |
| >12 months | 2 | 2 | 100 |

**Tab. 5. Neurological manifestations.**

| Group | Present | Absent | Difference from study group |
|---|---|---|---|
| Study group | 56 (78%) | 8 | |
| FA disorders | 16 | 0 | S ($p<0.05$) |
| MCADD | 4 | 0 | |
| VLCADD | 3 | 0 | |
| Multiple defects | 9 | 0 | |
| Other metabolic disorders | 3 | 0 | NS ($p>0.10$) |

**Tab. 6. Types of neurological manifestations in patients diagnosed with FA oxidation disorders.**

| Manifestation | MCADD | VLCADD | Multiple defects | Total | % |
|---|---|---|---|---|---|
| impaired consciousness | 3 | 2 | 5 | 10 | 62.5 |
| convulsions (acute) | 2 | 1 | 1 | 4 | 25 |
| convulsions (recurrent) | 0 | 0 | 2 | 2 | 12.5 |
| hypotonia | 2 | 0 | 4 | 4 | 25 |
| developmental delay | 0 | 0 | 1 | 1 | 6 |
| apnea/shallow respiration | 0 | 1 | 1 | 2 | 12.5 |

Total >100 % as many had more than one manifestations

**Tab. 7. Hepatomegaly.**

| Group | Present | Absent | Difference from study group |
|---|---|---|---|
| Study group | 27 (61%) | 17 | |
| FA disorders | 10 (63%) | 6 | NS ($p<0.10$) |
| MCADD | 2 (50%) | 2 | |
| VLCADD | 2 (50%) | 1 | |
| Multiple defects | 6 (67%) | 3 | |
| Other metabolic disorders | 2 (67%) | 1 | NS ($p>0.10$) |

***Urinary Organic Acids And plasma fatty acids***

Four patients had moderate increase in urinary adipic and suberic acids on organic acid analysis. Plasma fatty acid profile showed large peaks of C8, C10 and C10: 1W6; diagnostic of medium chain acyl-CoA dehydrogenase deficiency (9.1 %).

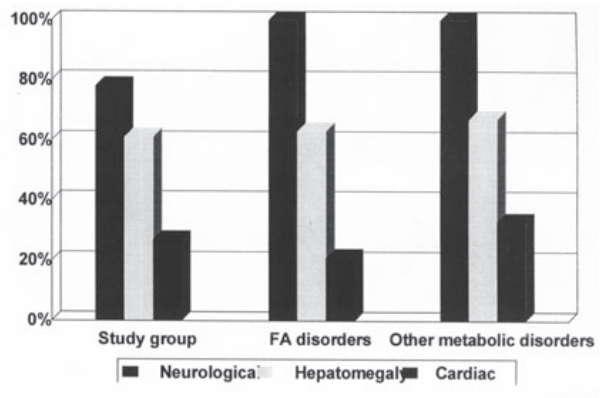


**Fig. 2. Neurological, hepatic and cardiac manifestations in different patient groups.**

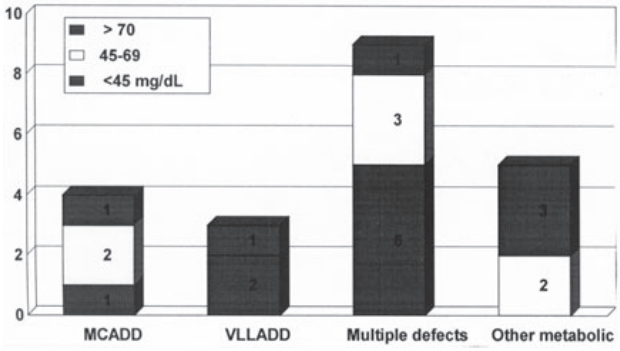


**Fig. 3. Blood glucose levels in different patient groups.**

Three patients had moderate increase in adipic, suberic and sebacic acids on urinary organic acid analysis, together with moderate amounts of 4 hydroxyphenylacetic acid. Plasma fatty acid profile showed large peaks of C12:1W7 and C14:2 W6; characteristic of very-long-chain acyl CoA dehydrogenase deficiency (6.8 %).

Nine patients showed marked urinary excretion of ethylmalonate with increased methyl succinate and prominent acylglycine excretion including hexanoyl-, isobutyryl-, butyryl-, isovaleryl- and suberyl-glycine. This profile is highly suggestive of multiple acyl-CoA dehydrogenation defects (20.5 %).

Two patients showed greatly increased urinary excretion of isovaleryl glycine with moderate increase in 3 hydroxyisovalerate, a profile consistent with isovaleric acidaemia due to isovaleryl CoA dehydrogenase deficiency (4.5 %). One patient had marked orotic aciduria suggesting a urea cycle defect (2.3 %).

*Acid Oxidation Disorders*

There were 16 patients diagnosed with fatty acid oxidation disorders; four with MCADD, 3 with VLCADD and 9 with multiple defects of acyl-CoA dehydrogenation, in addition to 3 patients with other metabolic disorders. There was no significant difference in age, sex or consanguinity between each of these

**Tab. 8. Liver enzymes.**

| | Controls | Study group | MCADD | VLCADD | Multiple defects | Other metabolic disorders |
|---|---|---|---|---|---|---|
| Both normal | 9 | 15 | 2 | | 2 | 3 |
| One elevated | 1 | | | 1 | 1 | |
| Both elevated: ALT | | | | | | |
| <2X | 0 | 11 | | | 3 | |
| 2-4X | 0 | 6 | 2 | | 1 | |
| 4-10X | 0 | 3 | | 1 | 1 | |
| >10X | 0 | 2 | | 1 | 1 | |
| Mean ALT (U/L) | 26.8±8.9 | 132±355 | 78.5±60.9 | 907±1262 | 126±160 | 25.7±15.3 |
| Difference from study group | | | NS | NS | NS | S p<0.05 |

**Tab. 9. Outcome according to diagnosis.**

| Group | No of cases | No of cases | Mortality | |
|---|---|---|---|---|
| | | | % acute cases | % all cases |
| Study group | 44 | 21 | 70 | 48 |
| FA disorders | 16 | 11 | 79 | 69 |
| MCADD | 4 | 3 | 75 | 75 |
| VLCADD | 3 | 2 | 67 | 67 |
| Multiple defects | 9 | 6 | 86 | 67 |
| Other metabolic disorders | 3 | 3 | 100 | 100 |

**Tab. 10. Mortality predictors in acute presentations*.**

| Factor | Relative risk | Mortality rate |
|---|---|---|
| age ≤3 months | 1.75 | 100 |
| blood glucose <45 mg/dL | 1.69 | 100 |
| cardiac affection | 1.64 | 100 |
| >10 fold ++ in GPT | 1.47 | 100 |
| prior sibling deaths | 1.31 | 86 |
| >2 fold ++ in GPT | 1.10 | 75 |
| blood glucose <70 mg/dL | 1.00 | 70 |
| MCADD | 1.08 | 75 |
| VLCADD | 0.95 | 67 |
| Multiple defects | 0.93 | 67 |

*Arranged according to relative risk compared to study group, except diagnosis-related factors.
Factors with relative risk less than one include: age below 1 y (0.90), hepatomegaly (0.96), precipitating illness (0.75 %), and elevation of one or both transaminases (0.65).

**Tab. 11. Predictors of diagnosis of FA disorders in our study group.**

| Factor | Relative risk | Sensitivity % | Specificity % |
|---|---|---|---|
| age <6 months | 1.05 | 37.5 | 37.5 |
| 6–12 months | 1.44 | 50 | 44.5 |
| >12 months | 0.49 | 12.5 | 20 |
| consanguinity | 1.2 | 50 | 40 |
| acute presentation | 3.27* | 87.5* | 46.5 |
| coma | 1.40 | 56 | 43 |
| cardiac affection | 0.89 | 25 | 33.5 |
| hepatomegaly | 1.05 | 62.5 | 37 |
| precipitating illness | 0.78 | 4 | 32 |
| glucose <70 | 3.29* | 81* | 52 |
| glucose <45 | 3.89* | 50 | 89* |
| at least one of the liver enzyme | 1.55 | 75* | 41 |
| incr. both,GPT 2x | 2.33* | 44 | 63.5 |
| GPT4X | 2.6* | 25 | 80* |

patient groups and the study group, taken as a whole. The others results of organic acids and fatty acids analysis is VLCADD 6.8 %, MCADD 9.1 % and normal 56.8 %.

Of the 14 patients with acute presentations, 7 patients (50 %) had evidence of a preceding illness that could have been the precipitating factor; acute GE in all but two patients with MCADD; one had vomiting and poor feeding while the other had fever and salicylate intake. Table 4 shows that younger patients were more likely not to have an evident precipitating illness.

The following Tables and Figures show the clinical and basic laboratory features of different patient groups (Tabs 2–11) (Figs 2 and 3).

## Discussion

In the recent years, a growing number of genetically distinct inborn errors of mitochondrial fatty acid oxidation defect have been described and the number of individual diseases is currently over a dozen. Most of these disorders present in infancy with acute life-threatening episodes of hypoketotic hypoglycemic attacks and coma induced by fasting or stress.

Manifestations consequent upon muscular, cardiac or hepatic affection also occur. They have been retrospectively diagnosed in many cases of Sudden Infant Death Syndrome. Some cases present with failure to thrive, while others remain permanently

asymptomatic (Kelley, 1998). The very variable clinical presentation is also reflected on the age of onset which can vary from one day to 14 years. This may be due to the fact that flux in ß-oxidation is usually negligible under non-fasting conditions, so patients may first present following metabolic decompensation consequent upon prolonged fasting or intercurrent infection (Costa et al, 1998). The diagnosis of mitochondrial fatty acid oxidation defects requires a high level of suspicion in the appropriate clinical setting and a selective screening.

Most of these disorders can be controlled by dietary interventions, based on ensuring a constant carbohydrate supply, avoidance of fasting and early intervention during intercurrent illness, sometimes supplemented with drug (eg. L-carnitine and Riboflavin) therapy (Nyhan and Ozand, 1998).

We subjected 44 patients clinically suspected of having fatty acid oxidation disorders to urinary organic acid and plasma fatty acid assay. Four patients had moderate increase in urinary adipic and suberic acids and large plasma peaks of C 8:0, C10:0 and C10:1δ-6. Adipic and suberic acids are characteristic for MCADD. Kiura restated the previously known fact that increased C10:1 w-6 is diagnostic of MCADD, increased C14:1 occurs in VLCADD, and both may be elevated in multiple acyl-CoA dehydrogenase deficiency (Kiura et al, 2002).

Clinically, 3 of these patients were 8–10 months old, consistent with the usual age of onset (6–24 months) mentioned by Costa et al, 1998. Two of them deteriorated following acute GE; with coma and seizures. One of them was profoundly hypoglycemic (11 mg/dL); the other two could not be assessed being on I.V. glucose. Two of them died. Although classically patients are expected to be free between attacks (Surtee and Leonard, 1989), one of our patients had failure to thrive with no previous acute episodes. Failure to thrive is one of the several possible „chronic" manifestations of MCADD mentioned by Wang et al (2001). The fourth patient presented at 2 months of age with lethargy, hypotonia, poor feeding and hepatomegaly and was initially diagnosed as having sepsis. This is not unusual if we consider that Atta et al (1998) reported several cases with neonatal onset and frequently fatal outcome; this patient also died.

Three other patients had large peaks of C12:1δ7 and C14:2δ6 on plasma fatty acid analysis. Increased C14 species is characteristic of VLCADD (Kiura et al, 2002). Our patients had no elevation of C16 species and clinically, they presented with coma; two of them had hypoglycemia (20 and 23 mg/dl) and marked elevation of the transaminases and died. Two patients had previous sibling sibling deaths. The youngest patient was 3 months old and developed refractory cardiogenic shock and cardiac arrest. This patient might have had the early onset form with cardiac affection.

It is to be noted; however, that these clinical presentations are also compatible with LCADD. Although most patients with LCADD have multiple hypoglycemic episodes and some present as late as 8 years or even later with muscle pains and myoglobinuria , early episodes with cardiac arrest (as our younger case) are also reported, even as early as 36 hours of age (Nyhan and Ozand, 1998). On biochemical basis, the accumulation of C14 species does not distinguish VLLADD from LCADD. Bonafe et al, 2000 stated that patients with the early severe cardiac form of VLCADD accumulate longer chain intermediates (mainly C14 and C16) than those with the "less severe" hypoglycemic form, which is the likely form in at least two of our cases, who accumulate C12 more.

This would bring us back to the conclusion of Aoyama et al (1993); that immunoblot analysis or testing for enzyme activity in fibroblasts using palmitoyl CoA and anti-LCAD or anti-VLCAD antibodies is the sure way of distinction. Treatment of both conditions is similar.

We also had nine patients with marked urinary excretion of multiple organic acids, suggesting a multiple defect in acyl-CoA dehydrogenation (MADD). Two patients with early onset disease (first month) had profound hypoglycemia (undetectable in one and 15 mg/dL in the other) together with encephalopathy. Both of them died. This is in accordance with the severe fatal illness described by Matern et al, 2000; however, our cases did not have dysmorphic features described by the same author to be common. The later onset form, which could occur as early as 7 weeks, involving the other 7 cases was described to be highly heterogeneous and sometimes riboflavin responsive (Nyhan and Ozand, 1998). Two of our patients were not acutely ill, they had recurrent convulsions; associated in one of them with motor delay and hepatomegaly, consistent with the picture described by Tojo et al (2000). Of the other five patients who presented acutely, four died.

In addition to 16 patients with fatty acid oxidation disorders, we diagnosed a urea cycle defect in a 10 mo old patient with coma, seizures, brain edema and hyperammonaemia who had marked orotic aciduria. Isovaleric acidaemia was found in two patients; 8 and 24 months old. Both had multiple sibling deaths and acute fatal metabolic crisis.

In this study, patients with MCADD and VLCADD were within the first year of life, agreeing with Abdenur et al (2001) who reported a series of 104 children with MCADD 68 % of whom were <12 months and 99 % <2 years of age. However, later onset has been reported in several patients diagnosed with MCADD (Shetty et al, 1999) and VLCADD (Merinero et al, 1999). Our results indicate that the age group most likely to yield patients with FA oxidation disorders is 6–12 months. This coincides with increased risk of developing initial episodes of a sufficiently prolonged fasting consequent upon infections disease. Despite that the incidence of initial episodes decreases progressively with increasing age, no age is exclusive especially that patients in the whole 1–36 months age range of our study group included positive cases.

29.5 % of studied patients had prior sibling deaths, 4 of whom (9 %) had 3 or 4 previous deaths! The presence of unexplained deaths is a feature of these disorders (Ioulianos et al, 2000) but still couples having 4 deaths due to a metabolic disorder without being diagnosed present a strong clue to the under diagnosis of these disorders.

Of our patients diagnosed with fatty acid oxidation disorders, all patients with VLCADD and MCADD and 78 % of pa-

tients with MADD had acute presentations. Only two patients had chronic/recurrent manifestations. Kelley (1998) described several chronic manifestations. A larger number of patients with chronic failure to thrive, cardiac or hepatic affection should be studied in order to determine whether FA disorders are uncommon or under diagnosed in these groups.

Half of our patients with acute metabolic crisis had a preceding precipitating illness; mostly gastroenteritis. Abdenur et al (2001) and many others have reported the association of fasting and intercurrent infection with triggering acute metabolic decompensation in these patients. Of note is that in our positive cases, an evident precipitating factor was present in 17 % of patients up to 3 months old and 100 % of those older than one year. Early severe defects can present without a preceding illness while a severe enough illness can precipitate crisis in an older previously asymptomatic child. At least in these patients, prevention and early treatment of acute GE, still a common problem in Egyptian infants and toddlers, can reduce the mortality associated with these defects.

78 % of the study group had neurological manifestations. Significantly enough, no patient diagnosed with a fatty acid oxidation disorder did not have neurological manifestations ($p<0.05$); an energy deficiency state together with the accumulation of fatty acids and their intermediates are expected to affect neurological function.

63 % of patients with fatty acid oxidation disorders had hepatomegaly, in agreement with Atta et al (1998) who reported hepatomegaly in 61 % of their series (MCADD). 75 % had elevated one or both hepatic transaminases. Anderson et al (2001) reported that 100 % of their patients had elevated transaminases. In our study, both hepatomegaly and elevated transaminases were used for patient selection so the difference between positive cases and the study group was not statistically significant.

Acute cardiac affection, in the form of acute heart failure, circulatory shock + arrhythmias was present in 12 patients, 4 of whom were positive (MCAD, VLCAD, 2 with MAD). All 12 patients died. Cardio respiratory compromise during acute crises is well known (Wang et al, 2001) and especially in MADD. Although cardiomyopathy can be a feature of MADD and VLCADD (Andersen et al, 2001) but not MCADD (Saudubray et al, 1999) none of our positive patients had chronic cardiac affection, presumably due to the high preponderance of acute cases. Screening of a larger number of patients with cardiomyopathy is needed.

81 % of our patients had low glucose levels (<70 mg/dL) and 50 % had levels <45 mg/dL. This corresponds to a specificity of 52 % for glucose <70 mg/dL and 89 % for <45 mg/dL. Hypoglycemia <45 mg/dL was highly predictive of FA disorders in our patients. However, Wilson et al (1999) reported 84 % with hypoglycemia and 100 % with glucose <70 mg/dL. The difference may have resulted from some of our patients having received I.V. glucose prior to sampling. We believe that if all patients were sampled before starting glucose therapy, and if moderately low glucose levels (45–70 mg/dL) were also considered, hypoglycemia would be a much more sensitive indication, in addition to the high specificity.

Plasma ammonia was elevated, in the 1.5–2 fold range in all 3 positive cases for which it has been done. This agrees with Wilson et al (1999) who mentioned that level of ammonia to be "usual".

Of note is the high mortality rate of patients with acute presentation among positive cases (79 %). Bonafe et al (2000) reported a figure of (59 %). In this study, increased mortality was associated with age below 3 months, prior sibling deaths, glucose <45 mg/dL, cardiac affection and 10 fold or higher increase in ALT.

Although MCADD is classically the only common of these disorders (Nyhan and Ozand, 1998), we could diagnose nine cases with MADD. This disease is highly heterogeneous and it would be reasonable to believe that it could have been under diagnosed; Abdenur et al (2001) considered neonatal screening for this disease as "suitable".

Considering genetic diagnosis, a single mutation is present in most patients with MCADD (A985G) and LCHADD (G1528C) but not in the other disorders. MCADD screening by detection of this mutation is already in wide spread use but it may be difficult to differentiate diseased compound heterozygote from heterozygote carriers (Romppanen et al, 1998). Metabolic diagnosis, on the other hand, including organic acid and fatty acid or acylcanitine analysis could detect these disorders, and several others, irrespective of the genotype and without the need to test for a specific suspected disease. We would recommend these initial tests in clinically suspected patients. Because they are less influenced by the clinical status than organic acids, acylglycine are a useful complementary diagnostic tool (Bonafe et al, 2000). Kiura et al (2002) described a method for FFA based diagnosis of MCADD, MADD and VLCADD by GC/MS on blood spots.

Mass neonatal screening for MCADD is currently employed in some countries. It should be considered based on the incidence of sudden death, disease prevalence and effectiveness of proper management.

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