The epidemiology of medium chain acyl Co-A dehydrogenase deficiency

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ABSTRACT:

The impairment in the ability of human body due to a disorder in the Fatty Acid Oxidation (FAO) results in the incomplete breakdown of medium chain fatty acids into Acetyl Co-A caused by the deficiency of an enzyme MCAD. When this enzyme is deficient, fatty acids can't be broken down into acetyl Co-A rather they tend to accumulate within certain organs such as brain and liver leading to various serious disorders. MCAD deficiency is an inherited, rare metabolic disease. The diagnosis of MCAD is done by integrated interpretation of multiple analysis**,** requires the clinical status of the individual that is affected. Testing of MCADD is done by the analysis of Plasma acyl carnitine, testing of organic acid and acyl glycine in urine and then, confirmatory testing is performed. Genetic counselling must be provided to affected individuals, carriers, or the individuals that are at danger of becoming carriers.

Keywords: Acyl-CoA dehydrogenases, Acyl carnitine,Fatty acid-oxidation disorder ,MCAD deficiency, Ketogenesis, Newborn screening.

I. INTRODUCTION

"The impairment in the ability of human body due to a disorder in the "Fatty Acid Oxidation" (FAO) results in the incomplete breakdown ofmedium chain fatty acids into Acetyl Co-A. This FAO disorder is caused because of the deficiency of an enzyme known as Medium-Chain Acyl-CoA Dehydrogenase "MCAD" thus the disease is named as MCAD deficiency".MCAD belongs to the class of dehydrogenases and it catalyses a reaction for the Acyl Co-A compounds which range from 4-12 carbon atoms (Jethva*et al*., 2008). While MCAD deficiency is an inherited, rare metabolic disease which is brought on by vomiting and fasting but in severe cases, it is characterized by Hypoglycaemia followed by sudden death. Patients with MCAD deficiency have impaired ability due to the deficiency of the enzyme and they can't breakdown fats into ATP for the production of energy to be utilized for various functions by the body. The enzyme which is deficient in this case has been found

to be very active in leukocytes, connective tissues, and liver and is considered to be essential for the oxidation of medium-chain fatty acids. When this enzyme is deficient, fatty acids can't be broken down into acetyl Co-A rather they tend to accumulate within certain organs such as brain and liver leading to various serious disorders (Vishwanath, 2015).

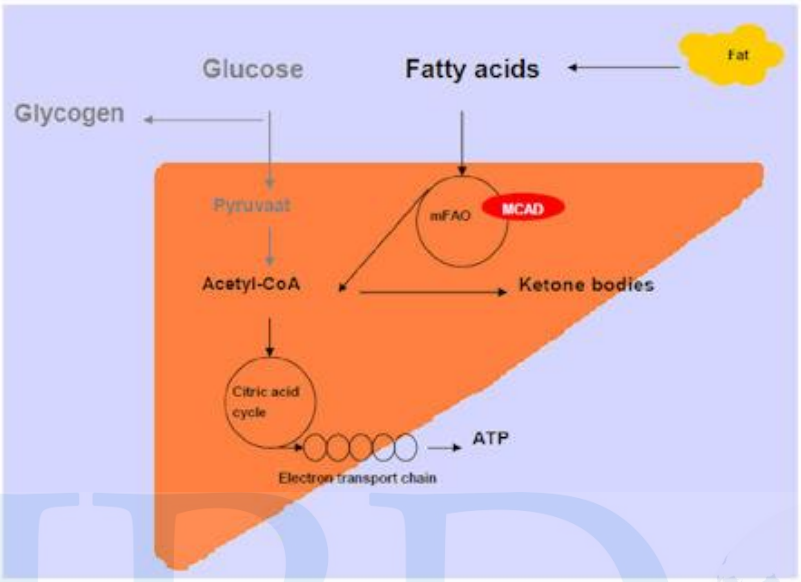

Figure 1:Fatty Acid Metabolism in MCAD Deficiency

Deficiency of MCAD enzyme also leads towards various other disorders of FAO. MCAD deficiency is found to be present since birth and various screening tests are done to diagnose this disease in the early stage (Grosse *et al.*, 2006). If it is diagnosed in the neo natal stage then it can be treated by managing the diet and lifestyle. But if is not diagnosed then it is left un-treated till the adulthood and results in severe health disorders. When MCAD enzyme is not working properly then the body cannot break down the stored fats into energy, this occurs because the pair of genes which is responsible for the proper functioning of this enzyme is either missing or not working properly. So, due to the impairment in the pair of genes, they do not code for the enzyme correctly and it becomes deficient. MCAD is a genetic metabolic disease which is inherited in "autosomal recessive" way, that is why it has an equal effect on both girls and boys(Vishwanath, 2015).The children with this disease inherit both of the genes for this enzyme which are defective and not working properly. Both of these defective genes are transferred from their parents, one from mother and one from father. Their parents are often "carriers" who have one defective gene but they do not have the disease. When both of the parents carry defective genes means they are Carriers, then for each of the child to have this disease during every pregnancy, the chances are increased up to

25% while 50% for the child to become a carrier like his parents. There are only 25% chances that the new born baby would have both the genes working correctly (Grosse *et al.*, 2006).

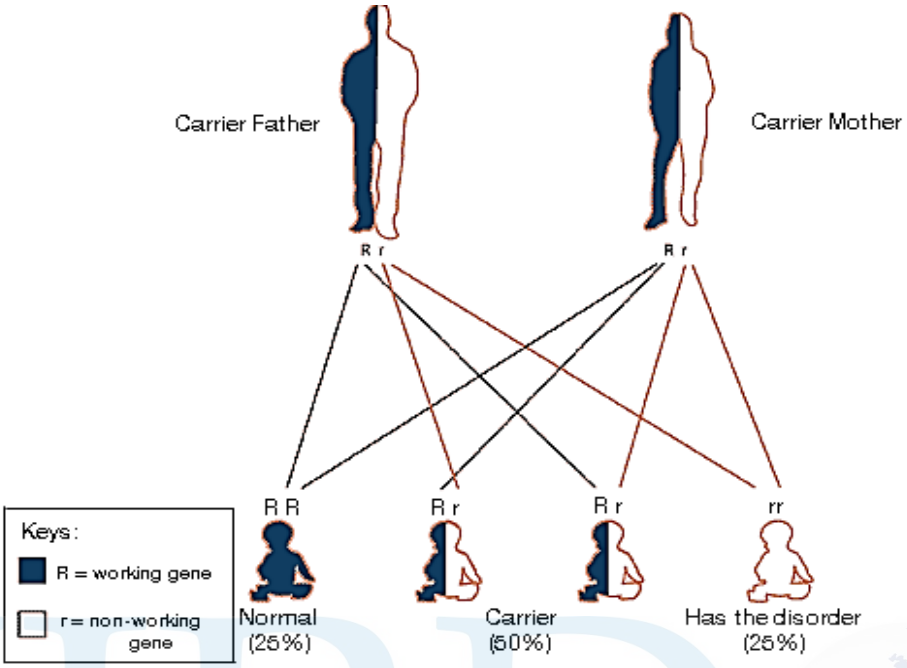

Figure 2: Inheritance Pattern of MCADD

When the glucose level becomes low in the blood then the body relies on fats for the energy especially when we are in starving or fasting condition and during sleep. So, when this MCAD enzyme is deficient then the fats cannot be broken down and cannot produce the energy. The body then has only glucose as its energy source. Though, Glucose is a good reservoir of energy but its amount is very limited in our blood, and if the body is totally dependent on glucose then the level of glucose in the blood falls below the normal level and the body suffers from a condition known as Hypoglycemia as well as also results in the accumulation of various toxic substances within the blood. MCAD deficiency belongs to the disorders which are caused due to the impairment of fatty acid oxidation within the mitochondria. Failure in the oxidation of fatty acids result in the low blood sugar level, chronic muscle cramps, seizures and death but it can be avoided if the glycogen storage is not depleted in the body then glycogen will be utilized as an energy source. The first patients with MCAD deficiency were recognized in 18th century from 1982-1984(Wang *et al.*, 1999). After then about 200 such cases were reported and when the root cause was identified, it was found to be a recessive disorder whose abnormal genes reside on autosomal chromosomes which code for abnormal product and subsequently the enzyme activity to oxidize the fatty

acids to acetyl Co-A is also in-efficient leading MCADD (Medium chain Acyl Co-A Dehydrogenase Deficiency).

Children who have defective MCAD enzyme are often normal at the time of birth and in the early childhood But when they are exposed to stress conditions such as periods of fasting and vomiting, the infection is activated in them. The symptoms appear in the early 2 years and are followed by low blood sugar levels, gastroenteritis, infections of upper respiratory tract and in chronic condition also results in the failure of organs such as liver which eventually leads towards death. As it has been explained earlier, the deficiency in the enzyme activity is due to the mutation of the genes. In MCAD deficiency, mutation is most commonly found in the ACADM (Acyl Co-A Dehydrogenase Medium-chain) gene which is found to be reside on the autosomal chromosome.

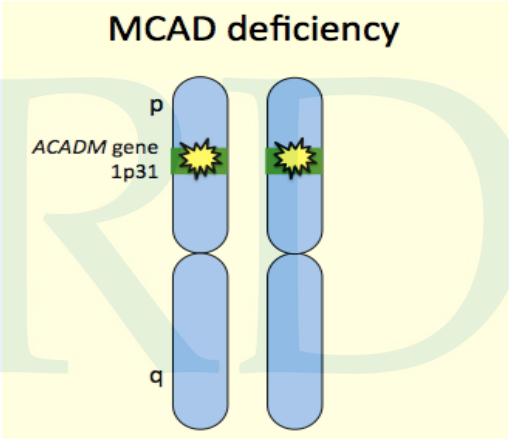

Figure 3: Location of ACADM Gene on Chromosome

Approximately 340 mutations have been recognized in this gene but the mutation which is prevailed results due to the nucleotide substitutions when a single nucleotide is substituted at 985 position. In this substitution reaction, Adenine is replaced with Guanine due to which amino acid Lysine gets replaced with Glutamic acid i.e., K329E(Coates & Tanaka, 1992). As a result of this mutation, carboxyl terminal of the enzyme is altered from its α-helical configuration. Besides such type of single nucleotide substitutions, mutations in the MCADD also results from deletions or insertions. All types of mutations are responsible for changing the structure of the enzyme and thus reduce or abolish the activity of the enzyme as well as due to deletions, enzymes become unstable and they lose their function. When these enzymes do not work properly, medium chain fatty acids are not oxidized. As a result,

fats do not convert into energy and a condition known as Hypoglycemia prevails. Also the level of in-oxidized fatty acids begins to rise and they get accumulated in various tissues, leading towards serious health problems (Wang *et al*., 1999).

II. NOMENCLATURE

MCAD deficiency was initially identified within the individuals who presenteda Reye like syndrome and their Urine organic acid analysis revealed the over-excretion of hexanoylglycine as well as Medium chain fatty acids because a significant process "ketosis" was found absent in them. As MCAD deficiency has not been identified yet, so the accumulation of medium chain fatty acids was misdiagnosed as Reye-syndrome (Kølvraa*et al*., 1982).

In the cells, the oxidation of fatty acids is carried out in the mitochondria and Acyl Co-A dehydrogenases are the enzymes which are responsible for the catalysis of fatty acids. The action of the enzymes introduces a double bond between C-2 and C-3 of Acyl Co-A thioester (substrate) at Trans position. Also in addition to the active site which is present within the enzyme in glutamate residue, FAD is required as a co-factor for the proper functioning of the enzyme. These enzymes are categorized into three specific groups on the basis of their specificity to catalyse short, medium and long chain fatty acids. As these enzymes differ only with respect to the chain length of the substrates they catalyse, so they tend to be mechanistically identical. Differences arise in the enzyme only if the location of the active site of the substrates is different. Acyl Co-A dehydrogenases is the class of enzymes which play an important role in the mammalian cells because they are involved in the oxidation of fatty acids. ACADM or MCAD catalyse the first step in fatty acid oxidation resulting in the breakdown of medium chain fatty acids into Acetyl Co-A molecules. If this enzyme gets deficient then metabolic disorders arise due to the incomplete breakdown of fatty acids. There are nine major categories of ACADs in the eukaryotic cells. Among them, five are involved in the oxidation of fatty acids which are VLCAD2, VLCAD, LCAD, MCAD and SCAD) while the other four are involved in the metabolism of branched-chain amino-acids (Coates & Tanaka, 1992). The enzyme MCAD is involved in the oxidation of medium-chain fatty acids thus the associated metabolic disorder due to its deficiency is named as MCAD deficiency.

III. PREVELANCE

MCAD deficiency mostly prevails in the individuals who belong to Northern areas (Feuchtbaum*et al.*,2012). This disease is also found to be prevalent in California and Portugal. The cause of mutation is different in individuals belonging to different areas such as in European population, the mutant is nucleotide substitution which results in the mutation (Lys304Glu) but it has not been detected in the affected population of Asia. Due to the recently developed neo-natal screening programmes, the number of new born babies identified with MCAD deficiency has been exceeded than was expected. On the basis of this neo-natal screening, prevalence of MCAD deficiency was determined in:

England: 1: 10,700 live births(Oerton*et al*., 2011).

Saudi Arabia: 1: 18000 live births(Al-Hassnan*et al*.,2010).

Japan: 1: 51,000 live births(Shigematsu*et al*., 2002).

Among the populations of Europe, almost every 1 child in 10,000 is expected to have MCADD but this frequency is far less in non-European population. As far as the population of Korea is considered, no cases of MCADD has yet been reported among their new born babies while 2 cases of MCADD were detected among102,000 new born babies in Japan. So, MCADD prevails in different geographical regions with different frequencies and it can be screened through various neo-natal screening programmes. Through such screening programmes it is possible to record the frequency data of different countries for comparison and thus it can be analysed that in which geographical region MCADD is prevailing the most and the signs and symptoms of the disease can be identified. But it should be noted that number of patients when diagnosed based on the symptoms of disease were half than when they were tested through neo-natal screening (Grosse *et al.*, 2006).

IV. PATHOPHYSIOLOGY

MCADD is because of a disorder in the β- oxidation of fatty acids inside the mitochondria due to which medium chain fatty acids cannot be oxidized to acetyl Co-A. When the glycogen storage is depleted in the body during starving or fasting conditions and when there is higher demands for energy then another major pathway ketogenesis serves as significant source to provide energy and it is derived by the oxidation of fatty acids. This process is carried out in the liver and fuels the peripheral tissues. β- Oxidation of fatty acids

is consisted upon 4 reactions that are linked sequentially and their catalysis is carried out by two sets of enzymes which are specified according to the chain length of the fatty acids which are being catalysed (Jethva*et al*., 2008). At the end of each cycle one molecule of acetyl Co-A and one molecule of acyl Co-A is generated.

Medium Chain Acyl Co-A Dehydrogenase enzyme is involved in the dehydrogenation of those fatty acids whose chain length is varied from 4-12 C-atoms. When this enzyme is deficient then oxidation can't be carried out and thus failure to derive the ketogenesis pathway increase the dependency on glucose and ultimately the blood glucose level is lowered leading to hypoglycemia.Also due to failure in the oxidation of fatty acids metabolites such as medium chain fatty acids start accumulating in the urine, blood, bile and other body fluids which can cause serious damage to the health **(**Derks*et al*., 1982).

When the chain length of fatty acids exceeds beyond 12 C-atoms MCAD can't oxidize them, thus the body becomes unable to breakdown fats for energy, inhibiting Gluconeogenesis. In such conditions body is again dependent on glucose leading to severe hypoglycemia as well as with prolonged hypoketonuria. So to oxidize fats of different chain lengths different enzymes are required such as LCAD to oxidize long chain fatty acids and MCAD to oxidize medium chain fatty acids. If these enzymes are depleted or not working correctly then bouts of illness arise associated with the metabolic disorders. MCADD is most often detected in the early childhood within the age period of 3 months to 3 years. But the symptoms of the disease usually observed when the child is exposed to some stress conditions or when he ingest such food that can't be metabolized by his body. Usually this metabolic disease is categorized with prolonged starvation, lethargies and infections.

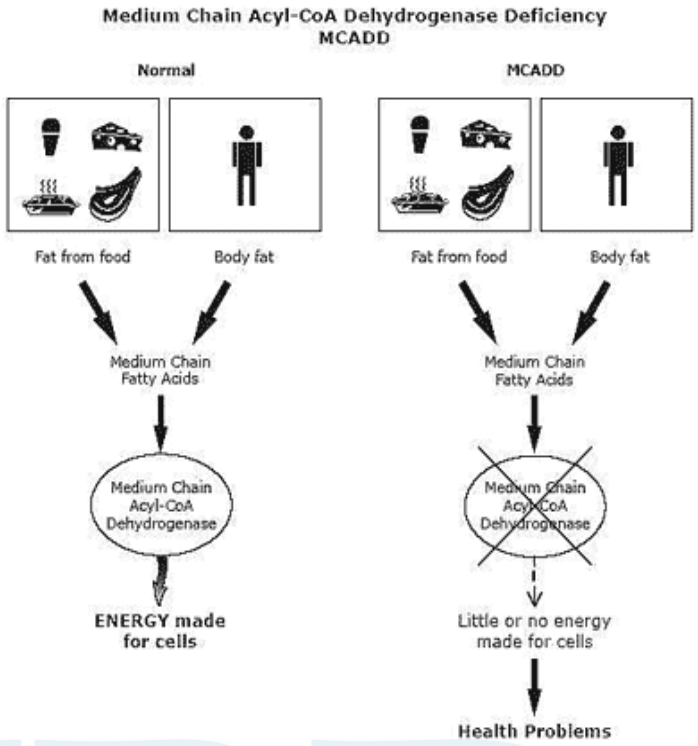

Figure 4: New-born Screening of MCADD

V. SIGNS AND SYMPTOMS

The onset of MCAD deficiency is usually during early childhood within the duration from 3 months to 3 years or during the infancy stage. As it has been mentioned earlier the symptoms of the disease appear only when the child is exposed to stress conditions like prolonged fasting, starving and illness or when such food is ingested which can't be metabolised by the bod of the child (Grosse *et al.*, 2006).The first symptoms which are detectable during this metabolic disorder are behavioural change, loss of appetite, changes in mood swings, extreme sleepiness and lethargies. The associated symptoms with this disorder can be categorized as vomiting, diarrhoea, hypoglycaemia and fever. If the disease is prolonged and is left untreated then severe problems can arise as seizures, infections of upper respiratory tract leading to breathing problems and coma which can lead to death. Patients who have MCADD remain healthy instead of their metabolic crisis. But if this condition is left un-checked then permanent damage of brain and liver can occur due to which intellectual and learning disabilities can arise. It has also been reported that some children who have MCADD have only mild symptoms or even not at all.

VI. CLINICAL CHARACTERISTICS

It was thought that symptoms of MCADD appear only in the early childhood but now it has been reported that its symptoms may also appear in the adulthood. Clinically their symptoms are same as prolonged starving, breathing problems and requirements for energy also gets increased especially in the fever conditions. Due to such metabolic crisis tiredness and vomiting are also accompanied (Wang *et al*., 1999). This type of MCADD has the symptoms as explained above but in certain circumstances unexplained and sudden death can also occur if this disease is not diagnosed in the early stages. According to a recorded data, 18% of the patients experienced death during their early metabolic crisis(Iafolla*et al*., 1994). In acute conditions, hypoglycaemia, hyperuricemia and hypoketotic can also be categorized. Individuals who have classic MCADD lose their developmental abilities and also suffer from a disorder of attention deficit both of which are considered as secondary to the brain injury. Besides, 18% of the individuals have also suffered from acute weakness of muscles (Iafolla*et al*., 1994).

When MCADD was thoroughly studied it was identified that patients also lose tolerance to strenuous exercise and heavy muscular activity. If this disease is diagnosed in the early stages through neo-natal screening then it can be treated and children can be saved from severe metabolic crisis. It has also been shown that in some infants MCAD deficiency make the screening results impossible due to which clinical manifestation can't be done. But if the disorder is diagnosed then excellent prognosis can be made and sudden deaths can be avoided. Those pregnant women who have MCAD deficiency they suffer from various complications like Hemolysis, Elevated liver enzymes, Low Platelets which are symptoms of HELLP syndrome. And when the foetus also suffers from the same disease like his mother then AFLP (Acute Fatty Liver of Pregnancy) becomes frequency(Derks*et al*., 2006).During the recent decades the neo-natal screening has been expanded due to the Mass Spectrometry which has led a great advancement to identify those infants who present abnormalities in their metabolic system. Only those children are thought to be suffering from MCADD and metabolic disorders who have mild biochemical phenotype. Though these individuals are capable of high enzyme activity for MCAD but these are at high risk that they can develop clinical manifestations. So, their treatment should be initiated without any delay (Zschocke*et al*., 2001).

VII. DIAGNOSIS/TESTING

The diagnosis of MCAD is done by integrated interpretation of multiple analysis**,** requires the clinical status of the individual that is affected. Affected individual may be symptomatic or asymptomatic (Vishwanath, 2015)**.** Fatty acid β-oxidation is necessary because it provides energy for the hepatic ketogenesis which serves as a major energy source during the periods of high energy demands and fasting conditions. It fulfils the energy requirements when there is glycogen storage in our body. For diagnosis, two types of testing are performed (Grosse *et al.*, 2006). One is initial and the other is confirmatory testing. After initial testing, confirmatory testing is done by identification of bi-allelic variants that are pathogenic.The flux of Fatty acid β-oxidation measurement or determination of tissue enzyme activity of MCAD is included in biochemical testing and testing of molecular genetics. Some individuals with the deficiency of MCAD are asymptomatic for all their life span but most of them are asymptomatic for a long-life span. (Matern&Rinaldo, 2000).We should conduct such diagnostic methods that are sensitive enough so that we could identify the individual affected by fatty acid beta-oxidation.Age of diagnosis is related with the age of child. Older the child greater will be the risk for MCAD deficiency. Moreover, it will cause the muscle weakness in the child. The severity of disease increases if there is delay between clinical onset and diagnosis .so the age is the major factor in causing the severity (Wang *et al*., 1999)

7.1 Types of testing

7.1.1 Initial testing

Initial testing is done by the analysis of Plasma acyl carnitine, testing of organic acid and acyl glycine in urine(Jethva*et al.*, 2008).Analysis of plasma acyl carnitine is done by characterizing the accumulation of C_6 to C_{10} species along with the octenyl-carnitine level in individual affected with MCAD deficiency.Plasma acyl carnitine analysis is not reliable. The major problem that is faced during the analysis is that significant elevation of C_6-C_{10}acylcarnitine cannot be highlighted in persons having low secondary carnitine level. The profile of such individuals contains low level of free carnitine and acetyl carnitine. Though these findings are not reliable, but indicate the possible metabolic disorder. So, plasma acylcarnitine analysis is not the only analysis to diagnose the MCAD deficiency. We can use urine organic acids or urine acyl glycine to achieve a good biochemical diagnosis. (Matern&Rinaldo, 2000).

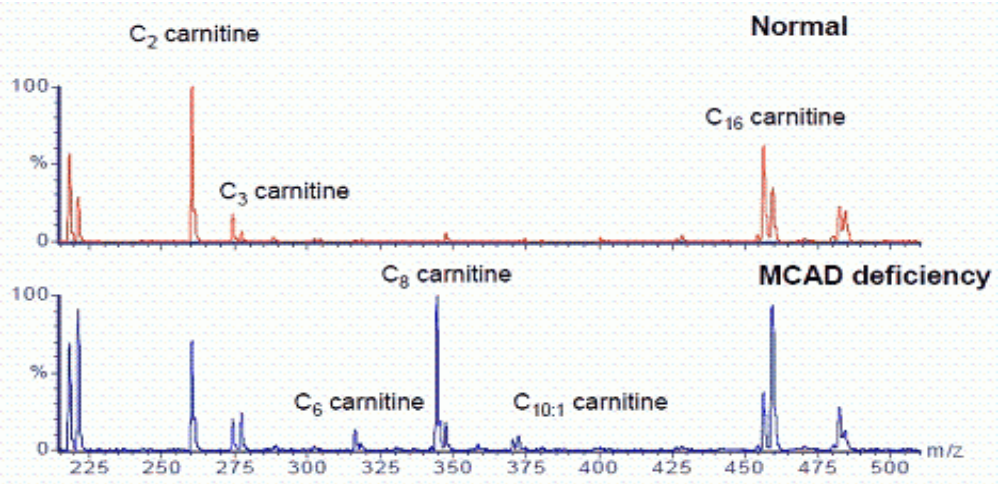

Figure 5: Graphical Representation of Carnitine levels in Normal & MCADD

Testing of organic acid in urine characterized the increased pattern of medium chain dicarboxylic acids. They occur in a particular pattern that is (C_6>C_8>C_{10}). Ketones level is less in symptomatic individuals. There are some additional markers of MCAD deficiency that includes 5-hydroxy hexanoic acid, hexanoyl glycine, phenyl-propionyl glycine and suberylglycine. But these additional biomarkers are prominent during acute conditions.During acute conditions, ketone production in the body remains normal. So, it is not advisable to detect ketonuria level for the diagnosis of MCAD deficiency.Urine organic acid analysis is not preferable in the individuals having deficiency of MCAD but they still maintain stability and do not fast. Because during these conditions, the excretion level cannot be detected by organic acid analysis. Urine acyl glycine analysis is done by the isotope analysis of urinary n-hexanoyl glycine, 3-phenyl propionyl glycine and suberglycine(Matern&Rinaldo, 2000). Under acute conditions, excess of hexanoyl glycine and suberglycine are excreted which can be analysed by testing organic acid. For this provocative tests are not required. This test is effective only after birth. And preferred test in asymptomatic individuals.

Carnitine Concentrations in Plasma and Urine

	Plasma*			Urine†		
	Case 1	Case 2	Normal Range	Case 1	Case 2	Normal Range
Total carnitine	2.8	22.0	26.0-66.0	61.9	7.4	0.0-31.0
Free carnitine	0.3	14.4	21.0-53.0	12.0	0.6	0.0-15.0
Carnitine esters	2.5	7.6	0.0-22.0	49.9	6.8	0.0-17.0
Esterified carnitine–free carnitine ratio	8.3	0.53	0.0-0.54	4.2	11.3	0.0-3.0

Figure 6: Concentrations of Carnitine in Plasma & Urine

7.1.2 Confirmatory testing

After initial testing, confirmatory testing is performed. The aim of confirmatory testing is to detect the β oxidation flux in fibroblasts' fatty acid. Moreover, it is done to determine the MCAD enzyme activity in different tissues (Wang *et al*., 1999). Molecular Genetic Testing is done by analyzing the substrate for the disease-causing varieties of microorganisms and by analyzing single gene (Jethva*et al*., 2008). It involves the Lys304Glu (985>G) and p. Tyr42His (199 C > T). The targeted analysis is considered for these two variants irrespective of the sequence analysis. The diagnosis is based on the identification of the both pathogenic variants (Wang *et al*., 1999) If the variants are available, then this diagnosis is confirmed. But if one of the two variants is missing and not identified then sequence analysis is considered (Matern&Rinaldo, 2000). Perform single gene analysis if one or no variant is detected. Perform sequence analysis first and then perform deletion/duplication analysis (Grosse *et al*., 2006).

7.1.3 Biochemical testing

To analyze the oxidationof fatty acid in cultured fibroblasts, we must analyze the acyl carnitine level culture media and disintegrated cells (Jethva*et al*., 2008). Then incubate the culture by labelled or un-labelled palmitic acid and un-labelled carnitine. Moreover, the C_6-C_{10} accumulation confirms the diagnosis (Wang *et al*., 1999).Measurement of enzyme activity reveals that the persons having the MCAD deficiency suffer below 10% of normal functioning of the MCAD enzyme in fibroblasts or in leukocytes, liver, heart, skeletal muscles or amniocytes (Matern&Rinaldo, 2000).

Gene	Continent	Variant Detection Frequency by Test Method	Sequence analysis and deletion/duplication analysis
ACADM	Asia	0%	100%
	Australia	67%	97%
	Europe	50%	100%
	N. America	68%	96%

VIII. TREATMENT OF MANIFESTATIONS

The treatment of manifestations involves the treatment of symptomatic patients by reversing the catabolism and maintaining the anabolism. Tablets of glucose or sweet drinks can be taken so that carbohydrates should be taken in by MCAD patients or injections can be injected in those patients who are unable to take carbs by mouth. Such injections are intravenous i.e. injected in veins. The glucose is taken by intravenous with 2mL/kg bolus of dextrose, which is then followed by the ion dextrose to maintain the blood glucose level. To treat the MCAD deficiency, fasting is the main thing that should be avoided. Treatment for symptomatic and asymptomatic individuals is different. There is no need to avoid fasting for asymptomatic individuals (Grosse *et al.*, 2006). The time recommended during which fasting can be done is, in new born having their ages ranging from 6 to 12 months: 8 hours, in adults: 10 hours and in children after the age of two years: 12 hours. For avoiding the fasting, there should be frequent feedings for infants and for toddlers, a low-fat diet is preferable that is <30%

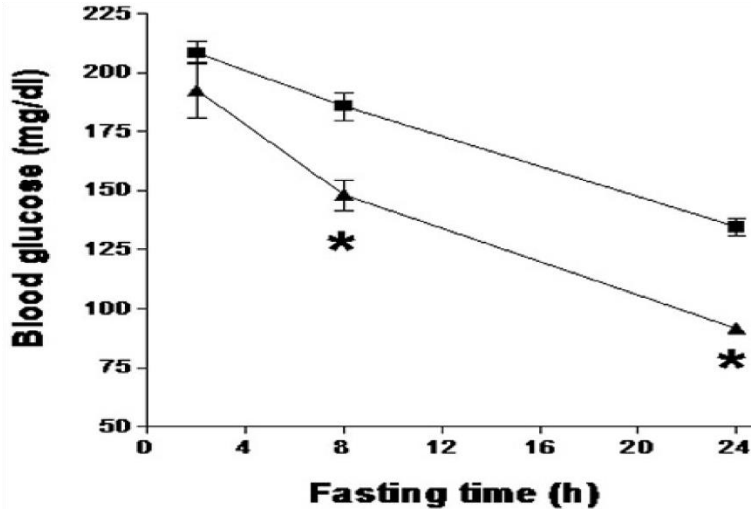

Figure 7: Relationship between Fasting time & Blood Glucose Levels

The patient's MCAD enzyme activity also help in treatment. There are also two possibilities. If MCAD enzyme's remaining activity is greater than 10% than there is no need to avoid fasting and no treatment is needed (Matern&Rinaldo, 2000). If residual MCAD enzyme activity is less than 30% then treatment is needed. So, the different enzyme activity essays are important in treatment of MCAD deficiency. It was revealed through the long-term outcomes that when the persons affected with MCAD are treated, they become susceptible to gain more weight. So, to avoid this condition, regular diet plan should be recommended and physical awareness is suggested.Surveillance involves to consult the specialist when there is a condition involving the fever and poor calorie intake or uptake. At the initial stages of the disease, the patient should visit the consultant frequently with family to ensure that the family understands and is comfortable with the treatment. Moreover, proper diet plan should be followed. The routinely visits of the patients should be based on the comfort level of patient, family and consultants.

The circumstances that should be refrained to prevent the MCAD deficiency are, there must not be the hypoglycemic condition so that catabolism can be avoided. For this, frequent feedings are required or it may be through IV uptake of carbohydrates. The formulas containing medium chain triglycerides as fat source must be avoided in infants to avoid MCAD deficiency. Alcohol consumption must be low to avoid MCAD deficiency. MCAD deficiency should be avoided in pregnant women so for this, catabolism is being prevented in pregnant women. This condition in pregnant women causes the carnitine deficiency, active

liver failure, and HELLP syndrome. So, to avoid the MCAD deficiency in pregnant women, catabolism must be avoided.

IX. GENETIC COUNSELLING

The provision of information about personal decisions to individuals and/or families is called genetic counselling".The deficiency of MCAD is passed on from one generation to the next as a trait which is autosomal recessive. During birth, there is a chance that the offspring of the person who is affected also show a risk of being diseased by 25% of the percentage with 50% of them being asymptomatic carriers and 25% as unaffected and non-carriers. The processes of evaluating biochemically or testing through molecular genetics or both are given to the parents who are asymptomatic as well as to their siblings as they might suffering from MCAD deficiency. The individuals living in Northern Europe have more carrier transmission potential for ACADM p.Lys304Glu disease- causing variety of microorganism, thus MCAD deficient reproductive parents should be offered by carrier testing techniques (Matern&Rinaldo, 2000).To make the genetic status of families clear, the following criterion is used to assess the genetic risk by using family history excluding all the personal, cultural, or ethical issues that an individual might face.

9.1 Inheritance mode

The inheritance of deficiency of MCAD i.e. Medium-chain acyl Co-enzyme A dehydrogenase should be done in a way that is somatic cell recessive (Coates & Tanaka, 1992). Proband, a person who is the first affected with deficiency of MCAD, is descended from the parents who are necessarily heterozygous and carriers of the disease causing variety of micro-organisms in ACADM (Wang *et al*., 1999). The transporters or carriers show no symptoms of the disease i.e. they are asymptomatic. A process of analysing biochemically or at molecular genetics level or both is carried out individuals who are themselves asymptomatic but their children have deficiency of MCAD because they have bi-allelic ACADM pathogenic variants. During birth, there is a chance that the off springs of the person who is affected are in danger that they might also get affected by a percentage of 25% with 50% of them being asymptomatic carriers and 25% as unaffected and non-carriers (Wang *et al*., 1999). Because the individuals might not show any symptoms of until late adulthood, so there exist no clear genotype-phenotype relation for MCAD deficiency. Thus, all the siblings that appear unaffected must be tested. If a sibling at risk is known to be unaffected, there is still a risk of 2/3 that it could be a carrier. The affected parent transfers an

ACADM pathogenic variant to its offspring with MCAD deficiency. There is a risk by 1/40 that parent of a person with insufficient MCAD might be a heterozygote of ACADM disease- causing variety of microorganism, So, if the child of an affected individual and an individual of Northern Europe mate, the risk of MCAD deficiency will be 1/80. The children of a parent suffering with MCAD deficiency must all be tested (Matern&Rinaldo, 2000). There is a 50% risk that the off springs of the affected parents are carriers. Carrier testing options include the following tests: getting the genetics of the molecules analyzedand the measuring the functioning of tissue MCAD enzymes. Genetics of the molecules can be analyzed only when both the pathogenic varieties are detected in the person of the family who is afflicted (Matern&Rinaldo, 2000). The functioning of MCAD enzyme accounts for overall 49% regular working. However, the biological and chemical screening inspections, that are acylcarnitine, organic acid or acyl glycine investigations, do not determine the condition of the carrier. Other related genetic counselling issues involve, finding genetic status of individual, approving that the carrier is clear and having prenatal test availability requires optimal time i.e. before pregnancy and genetic counselling must be provided to affected individuals, carriers, or the individuals that are at danger of becoming carriers. DNA banking has to be established to store DNA for future use. This DNA has been extracted from white blood cells. It is thought that testing methodologies and varieties of the alleles and disorders can be bettered. These considerations must be provided to banking DNA of individuals that are affected (Matern&Rinaldo, 2000).

CONCLUSION

Mitochondrial β-oxidation causes numerous other disorders. The occurrence of these disorders reveal the genetic errors occurring in this pathway. Moreover, deaths by the MCAD deficiency in new born children can be prevented by Newborn Screening.The information about molecular aspects of MCAD deficiency is available. Whereas, a lot of information must be discovered for the β-oxidation disorder at molecular level. The appearance of this information will provide knowledge of pathogenesis of these disorders. Moreover, this information will provide efficient diagnosis for the patients suffering with β-oxidation disorders.

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