Identifying common elements in late-diagnosed late-onset MADD patients by using graphs

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Abstract  Multiple acyl-CoA dehydrogenation deficiency (MADD), or commonly referred to as glutaric acidemia type 2 (GA2), is a genetic metabolic disorder affecting amino acid, fatty acid, and choline mechanisms. It is passed on in an autosomal-recessive manner. While most cases present themselves at birth or at an early age, it is also quite possible to get a diagnosis well into adulthood. For these late-onset patients, the road to diagnosis is often long, painful, and frustrating. In addition, due to late diagnosis they can also suffer from long-lasting effects of their worsening symptoms. The goal of this work is to identify the common symptoms among patients who are diagnosed very late after the onset of their symptoms. We take a graphical approach and present a new way to look at data with the hope that, in the future, this might help to detect any patterns and facilitate early diagnosis. Data related to age at the onset of symptoms, age at diagnosis, gender, and various common symptoms are studied.

Keywords  glutaric acidemia type 2 · late diagnosis · muscle weakness · vomiting · hypoglycemia · data analysis

Mathematics Subject Classification (2000) 92C50 · 92D10 · 65S05

1 Introduction

Multiple acyl-CoA dehydrogenation deficiency (MADD), or glutaric acidemia type 2 (GA2), is a very rare genetic metabolic disorder affecting amino acid, fatty acid, and choline mechanisms. It is an autosomal-recessive disorder, which means that when both parents carry a defective gene and both parents pass a copy of the defective gene, a child is born with MADD. Most forms of MADD are due to a deficiency of two enzymes: electron transfer flavoprotein (ETF, encoded by ETFA and ETFB) or an electron transfer flavoprotein dehydrogenase (ETFDH). Both of these enzymes play an important role in body’s ability to break down fats and proteins and turn them into energy. Without these enzymes, body’s only source of energy are sugar and carbohydrates. In the case that the patient with MADD does not get enough sugar or carbohydrate to supplement for its energy needs, then the body can go into a metabolic crisis leading to loss of ability to eat, speak, walk, breath, or even death. Therefore in its most severe forms, early detection is very crucial and most infants who show severe symptoms shortly after birth do not survive. While most cases present themselves at birth or at an early age, it is also quite possible to get a diagnosis well into adulthood. In addition, while some patients show the symptoms suddenly and severely, some patients also present with symptoms that worsen slowly over the years.

The focus of this work is to study the common symptoms of the late-onset patients who first developed their symptoms in childhood or adulthood. For these late-onset patients, the road to diagnosis is often long, painful, and frustrating. In addition, due to late diagnosis they can also suffer from long-lasting effects of their worsening symptoms. Therefore, the goal is to identify the most common symptoms in patients diag-
nosed 10 or more years after the initial onset of their symptoms. This work presents a graphical look at the data regarding the 103 late-onset cases studied in literature to date. MATLAB is used to obtain variety of color-coded plots using data related to age at the onset of symptoms, age at diagnosis, gender, gene type, and some of the most common symptoms. The goal is to present a new way to look at the data, in addition to a classical statistical approach. Such approach is widely used in other data-related fields. Looking at carefully obtained plots may present different kinds of findings and patterns that is difficult to observe otherwise. The hope is that such graphical approach will also prove useful in medical research and help detect any patterns and facilitate early diagnosis.

The paper is organized as follows: In section 2, we describe the methods used to obtain and analyze the data. In section 3, we look at the data from different perspectives. We consider an over all look at the gender of the patients included in the study, in addition to the genes they carry. Results of the analysis of the most common symptoms is also given. In section 4, conclusions of our findings are presented.

## 2 Methods

Recently, all the findings related to 350 late-onset MADD patients studied in the literature between 1979 and January 2014 were compiled [1]. A detailed table with crucial information about patients and references is also presented. Due to the focus of our work, we only have complete data for 103 of these patients. Here this medical data related to 103 patients is turned into a numerical data set and presented in terms of color-coded plots produced by using MATLAB. Most plots are done as age at onset versus age at diagnosis. A third variable is plotted in a color-coded fashion, $y = x$ line drawn in the middle to help observe the patients diagnosed at the time of the onset of their symptoms, or diagnosed via newborn screening before they presented with any symptoms. It also makes is easier to observe the time difference between the two events. Further away a marker is from the $y = x$ line vertically, the longer it must have taken for that particular patient to get diagnosed. Most of the plots are color-coded with respect to gender, blue representing males and red representing females. Only the gene analysis is done by color-coding the data with respect to gene type.

## 3 Results

The following analysis is done for 103 patients, including 50 males and 53 females. All plots are color-coded according to the gender, except for the gene analysis, in which color-coding is done with respect to the effected genes, as described on the plot.

### 3.1 Gender Analysis

We first look at the gender distribution of the patients in the study according their age when they initially developed symptoms. From the location of red and blue dots in figure 1(a), we observe that until about late teen years, females had a big gap between onset of their symptoms and their diagnosis with MADD. Males on the other hand, seem to have issues with late diagnosis if the onset of their symptoms occur after their late teen years. In addition, women seem to be more likely to have an onset beyond childhood years than men. Zooming in to see the patients who had onset of their symptoms before age 5, we see in figure 1(b) that significantly more males had their onset early on during their childhood compared to females. In addition, majority of the patients having onset before age 5 were diagnosed rather quickly, each having a diagnosis shortly after birth, at the time of their onset, or most often by age 5. We also see that 5 patients were diagnosed with MADD via newborn screening, but did not develop symptoms immediately. Four of them developed symptoms by age 1 and one of them at age 8. Since the newborn screening for MADD is rather new, these numbers might change in the future.

### 3.2 Gene Analysis

Here we would like to see the distribution of the 3 genes, ETFDH, ETFA, and ETBA, that lead to MADD among the patients in this study. Although there are 103 patients in this study, we have gene information for only 64 of them. Figure 1(c) is the plot of the defected genes that patients are carrying where ETFDH is represented in blue, ETFA is represented in green, and ETFB is represented in red. As widely documented in literature, we also observe that mutations in ETFDH are the most common cause of MADD. In addition, some patients having ETFDH mutations had their onset well into their adulthood, even in their 50’s. We see that only 5 patients carry mutations of ETFA or ETFB gene. Also, we see in figure 1(d) that four patients with ETFA or ETFB mutations had the onset of their condition early in their childhood years, and the
fifth one had onset at age 14. All 5 of them were diagnosed very quickly following their onset. One reason for these patients being diagnosed very quickly is that patients carrying ETFA or ETFB mutations present with more sudden and severe symptoms that require an urgent and detailed attention, especially since these patients are also infants or very young children.

3.3 Symptom Analysis

The main goal of this work is to identify common symptoms in patients who are diagnosed very late. For this purpose, we identified 8 commonly observed symptoms in patients in this study. We find that 69 patients had muscle weakness, making it the most common symptom at any age of onset. Muscle weakness was also present in 23 of the 25 patients presented with exercise intolerance and in 13 of the 17 patients presented with fatigue. However, only 6 patients experienced all three symptoms altogether. In addition, 17 of the 28 patients who experienced hypoglycemia and 12 of the 23 patients who experienced vomiting also had muscle weakness. Among the less common symptoms were respiratory failure with 14 patients, 10 of them also having muscle weakness, lipid storage myopathy and heart failure with 9 patients each, and seizures with 6 patients. Only 18 patients had muscle weakness as their only symptom. Hence, we can say that although muscle weakness is the most common symptom in late-onset MADD patients, it often accompanies other symptoms. It is most likely those symptoms coupled with the patient’s age at onset that changes the course of diagno-

Fig. 1 Gender and Mutation Data: (a) shows all patients in this study; (b) shows the patients less than 5 years of age; (c) shows all patients with ETFDH, ETFA, or ETFB mutations (n=64); (d) shows the same information for patients less than 5 years of age.
sis process, making it much longer than usual in some cases.

We will now focus on patients experiencing muscle weakness. As seen in figure 2(a), muscle weakness occurs in 69 (34 m, 35 f) patients, which is about 67% percent of the patients in the study. We also observe that 39 (15 m, 24 f) patients have been diagnosed 3 or more years after the onset of their symptoms and 29 (12 m, 17 f) of these patients, or 74%, experienced muscle weakness. 20 (9 m, 11 f) patients have been diagnosed 10 or more years after the onset of their symptoms and 16 (7 m, 9 f) of these patients, or 80%, experienced muscle weakness. That is, 80% of the patients diagnosed 10 or more years after the initial onset of their symptoms experienced muscle weakness. We note that there is a pretty even distribution of the number of male and female patients in each of these groups. However, looking at figure 2(b), we observe that among the patients diagnosed 10 or more years after their onset, there is an interesting and distinct separation between male and female patients. All females in this group had the onset of their symptoms before their twenties whereas all males had their onset after their late teens. Therefore it makes sense to consider MADD during the diagnostic work-up for patients experiencing muscle problems for a considerable amount of time along the lines of this age/gender pattern.

Next, we focus on patients who experienced vomiting as a symptom. 23 patients in the study experienced vomiting as a sole symptom or along with other symptoms. We notice in figure 3(a) that patients having onset of their symptoms after their thirties do not complain about vomiting. In addition, we see significantly more females with this particular symptom. In figure 3(b), we observe that 11 patients experienced muscle weakness in addition to vomiting, and 7 of these patients were diagnosed 10 or more years after the onset of their symptoms. That is, about 64% of patients experiencing vomiting and muscle weakness are diagnosed 10 or more years after their onset.

Another common symptom among the late-onset MADD patients in our study is hypoglycemia. 28 patients in the study experienced hypoglycemia as a symptom. Looking at figure 3(c), we see that not only it occurs in younger patients more commonly, but also patients are diagnosed much quicker. Similar to vomiting it is also observed more commonly in patients younger than 30. As seen in figure 3(d), 17 of these patients also experienced muscle weakness. In contrast to other symptoms, only 2 patients has been diagnosed over 10 years after the onset of their symptoms, one being post-mortem.

4 Discussion

Data related to gender, age at onset, age at diagnosis, genes involved, and some of the most common symptoms for 103 patients is analyzed by converting the verbal patient data to numerical data, and by using MATLAB plots. As has been known in the literature, our analysis also confirms that most of the late onset patients have deficiency in their ETFDH gene, while only a few have deficiency in the ETFA or ETFB gene.
Fig. 3 Vomiting and Hypoglycemia: (a) shows patients having vomiting as a symptom; (b) shows patients having both vomiting and muscle weakness as a symptom; (c) shows patients having hypoglycemia as a symptom; (d) shows patients having both hypoglycemia and muscle weakness as a symptom.

Those having mutations in one of the latter two genes presented with symptoms in their infancy or early childhood, and were diagnosed almost immediately.

We observe that patients under age 5 seem to receive diagnosis quicker than older patients. Traditionally, metabolic conditions have thought of as pediatric diagnoses. The idea of even considering a teenager or an adult to have an inborn error of metabolism is just often not in the mind of the doctor. This is the biggest factor for why the diagnosis is often not made early. In addition, if a woman that has had a “successful” pregnancy, then it is not believed that she has a defective metabolism. As a result, even though a woman presents with MADD related symptoms, this belief keeps doctor from even ordering right types of tests to look for a metabolic root of the problem in the first place. When a child presents with hallmark symptoms of MADD, like muscle weakness, hypoglycemia or vomiting, it is taken more seriously and more rigorous blood work including a metabolic workup is done to find the problem. On the other hand, when an older person complains of such symptoms, it is often explained via more trivial, common conditions appropriate to the patient’s age and activities at the time. As a result not only those patients suffer longer, their conditions get much worse by the time they receive a diagnosis. In table 1, we present the typical explanations for the commons symptoms of MADD. Instead, we suggest that the following tests be considered if an ongoing muscle problem is present in an older child or adult: H & E Histochemical staining for Light Microscopy; Electron Microscopy; and Enzyme
Table 1 The typical misdiagnoses for the common symptoms of MADD

<table>
<thead>
<tr>
<th>Symptom</th>
<th>Common explanation</th>
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<tbody>
<tr>
<td>muscle weakness</td>
<td>fatigue</td>
</tr>
<tr>
<td>vomiting</td>
<td>gastrointestinal conditions</td>
</tr>
<tr>
<td>hypoglycemia</td>
<td>insulin related disorders</td>
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More detailed analysis shows that muscle weakness was the most common symptom occurring in 67% of the patients in the study. Most important finding is that 80% of the patients with muscle weakness are diagnosed late, that is they are diagnosed more than 10 years after the onset of their symptoms. Moreover, all the females in this group had their onset before their twenties and all the males had their onset after their late teen years. Although this might be due to their biological differences, it could very well be due to gender bias in reaction to health concerns. Generally, men tend to wait longer before they seek a doctor’s advice for a problem they are experiencing. However, this pattern can still be considered as an inclusive criteria while considering diagnostic possibilities.

The analysis also shows that 64% of the patients with vomiting and muscle weakness are diagnosed late. In addition, we observe that vomiting and hypoglycemia, two of the signature symptoms of MADD, occurs in patients having their onset before their thirties. We do not see older patients having these symptoms. While hypoglycemia seems to occur in both females and males at the same frequency, vomiting is reported by significantly more females than males. These patterns can also be used as part of the differential diagnostic process.

The findings in this paper can be utilized for patients presenting especially with muscle problems. Careful consideration should be given to MADD possibility depending on the patients age, gender, and the length of the course of patients medical problems. We expect that the awareness in the medical community treating adult patients along with the patterns and patient demographics described here should improve and shorten the diagnostic process for adult patients.

References