I will give these results to Dr. Balistreri for review.

His genetic studies are still pending.

As far as his CPK is concerned—that would need to be evaluated by a neuromuscular physician as CPK comes from muscle not liver.

If you want—when you return to see Dr. Balistreri we can try and arrange a visit with Dr. Wong or one of her colleagues who specializes in this.

Dr. B suggested we wait to schedule his return appointment when the testing is done.

Just let me know if you want to schedule the Neurosurgery appt as well.

I will be out on medical leave starting Monday 3/23 for 8 weeks unfortunately.

My nurse colleague Nicki Roedersheimer will be covering for me—I have updated her to your potential return visit.

nicole.roedersheimer@cchmc.org or 513 803 1491.
To: Mitchell, Joanne  
Subject: Blood Chemistry related to Acylcarnitine Profile

Dear Ms. Mitchell,

I have Jianhua’s blood chemistry data attached in the pdf file. During last visit, we explained to Dr. Balistreri that we didn’t think an almost normal acylcarnitine profile done 2-year ago should be used to exclude fatty acid oxidation disorders because Jianhua’s glucose level varied from 30 to almost 300 then and the sample was taken when his glucose was normal.

Since most of Jianhua’s labs are out, could we meet Dr. Balistreri again to work on his elevated CK, which may solve the etiology of his liver cirrhosis? Also, we have not discussed his pathology report and biopsy plan yet.

Dr. Eroglu of OHSU is happy to help us to have Jianhua’s liver transplant care transferred to Cincinnati Children, including GI follow-up and surgery if necessary. Could we set all these appointment together so that we can have all done in one trip? We think we also need to meet surgeon and other doctors as well, do we have to do this to get his case fully transferred over?

Thanks

Yong
Deficiency, resulting in severe early onset multisystemic Disorders of lipid metabolism can present with a profound enzyme Clinical Presentation

muscle weakness.

Muscle is not the only tissue affected in these disorders; brain, heart, liver, and skin can also be involved. In children, myopathy is often overshadowed by encephalopathy or cardiomyopathy, but in adults muscle problems are usually the primary manifestation. At present, nine different enzyme defects are known to affect lipid metabolism of muscle (Table 22-2). Some of these have been described in only a few patients, whereas others are more common. However, data about the frequency of myopathies due to disorders of lipid metabolism is not available. CPT II deficiency seems to be the most frequent form.

Clinical Presentation

Disorders of lipid metabolism can present with a profound enzyme deficiency, resulting in severe early onset multisystemic disease. Typically, episodes of hypoketotic hypoglycemia and liver failure (Reye-like disease) occur. These children present with encephalopathy leading to lethargy and coma, muscle weakness, and cardiac arrhythmias. Milder phenotypes are restricted to muscle with onset not only in childhood, but also in adulthood. These show higher residual enzyme activities in regard to muscle involvement. Two clinical presentations can be distinguished. Some manifest with recurrent attacks of rhabdomyolysis triggered by long-lasting exercise, fasting, infections, or cold. Other disorders present with permanent muscle weakness.

Recurrent attacks of rhabdomyolysis occur in CPT II deficiency. The enzymes CPT I and II are part of the carnitine transporter system located in the outer (CPT I) and inner (CPT II) mitochondrial membranes to incorporate long-chain fatty acids from the cytosol into the mitochondrial matrix (Fig. 22-8). In the most common form of CPT II deficiency, symptoms are restricted to muscle. This form is a common cause of hereditary rhabdomyolysis and is also called the “adult” form of CPT II deficiency. Despite the common adult onset, first attacks can occur in early childhood. In contrast to McArdle disease (GSD V)—another rather frequent metabolic myopathy that causes rhabdomyolysis—patients with CPT II deficiency do not suffer from muscle cramps. In addition to the muscle form of CPT II deficiency, a multisystemic form is seen in infants, affecting the liver and heart and sometimes associated with muscle weakness. This type manifests mainly with lethargy and encephalopathy as consequences of hypoketotic hypoglycemia. Finally, there is a neonatal lethal form with congenital anomalies. However, these forms are much less common than the muscle form.

Another disorder of the carnitine carrier system that involves muscle is primary carnitine deficiency, which results from a defect of the carnitine transporter. These patients excrete the filtered carnitine in the urine. There are two clinical manifestations of primary carnitine deficiency: systemic primary carnitine deficiency, which presents as a multisystemic infantile disease with metabolic crises, and primary muscle carnitine deficiency, with late-onset and permanent muscle weakness. Secondary forms of carnitine deficiency are observed in several other muscle disorders, including acyl-CoA

<table>
<thead>
<tr>
<th>Biochemical Defect</th>
<th>Affected Gene(s)</th>
<th>Typical Muscle Phenotype</th>
<th>Characteristic Changes of Acyll-carnitine Spectrum in Blood</th>
<th>Muscle Histology</th>
</tr>
</thead>
<tbody>
<tr>
<td>Carnitine palmitoyl-transferase II deficiency</td>
<td>CPT II</td>
<td>Attacks with myoglobinuria</td>
<td>C16:0 and C18:1 carnitine elevated</td>
<td>Often normal interictally</td>
</tr>
<tr>
<td>Multiple acyl-CoA dehydrogenase deficiency (glutaric aciduria type 2)</td>
<td>ETFDH, ETFA, or ETFB</td>
<td>Permanent muscle weakness</td>
<td>Multiple acyl-carnitines (C4–C18:1) elevated</td>
<td>Lipid storage</td>
</tr>
<tr>
<td>Medium-chain acyl-CoA dehydrogenase deficiency</td>
<td>MCAD</td>
<td>Attacks with myoglobinuria; permanent muscle weakness</td>
<td>C8 carnitine elevated</td>
<td>Lipid storage</td>
</tr>
<tr>
<td>Very long chain acyl-CoA dehydrogenase deficiency</td>
<td>ACADVL</td>
<td>Attacks with myoglobinuria</td>
<td>C14:1 carnitine elevated</td>
<td>Often normal interictally</td>
</tr>
<tr>
<td>Primary muscle carnitine deficiency</td>
<td>Unknown</td>
<td>Permanent muscle weakness</td>
<td>Carnitine rarely reduced</td>
<td>Lipid storage</td>
</tr>
<tr>
<td>Primary systemic carnitine deficiency (carnitine transporter defect)</td>
<td>SLC22A5, OCTN2, HADHA, HADHB</td>
<td>Hypotonia, cardiomyopathy</td>
<td>Carnitine reduced</td>
<td>Lipid storage</td>
</tr>
<tr>
<td>Trifunctional protein deficiency of long-chain 3-hydroxyacyl-CoA dehydrogenase, long-chain 2-enoyl-CoA hydratase, and long-chain 3-ketoacyl-CoA thiolase</td>
<td>HADHA and HADHB</td>
<td>Attacks with myoglobinuria</td>
<td>3-hydroxy C16 and C18 acyl-carnitine elevated (can be normal interictally)</td>
<td>Often normal interictally</td>
</tr>
<tr>
<td>Short-chain acyl-CoA dehydrogenase deficiency</td>
<td>ACADS</td>
<td>Hypotonia</td>
<td>C4 carnitine elevated</td>
<td>Sometimes lipid storage</td>
</tr>
<tr>
<td>Neutral lipid storage disease with ichthyosis</td>
<td>ABHD5, GC1S8</td>
<td>Permanent muscle weakness</td>
<td>Normal</td>
<td>Abundant lipid storage</td>
</tr>
<tr>
<td>Neutral lipid storage disease without ichthyosis</td>
<td>PNPLA2, ATGL</td>
<td>Permanent muscle weakness</td>
<td>Normal</td>
<td>Abundant lipid storage</td>
</tr>
</tbody>
</table>

Thus, the term myopathies of lipid metabolism is more appropriate for this group of metabolic myopathies. All known enzyme defects of lipid metabolism follow an autosomal recessive mode of inheritance. Muscle is not the only tissue affected in these disorders; brain, heart, liver, and skin can also be involved. In children, myopathy is often overshadowed by encephalopathy or cardiomyopathy, but in adults muscle problems are usually the primary manifestation. At present, nine different enzyme defects are known to affect lipid metabolism of muscle (Table 22-2). Some of these have been described in only a few patients, whereas others are more common. However, data about the frequency of myopathies due to disorders of lipid metabolism is not available. CPT II deficiency seems to be the most frequent form.

Clinical Presentation

Disorders of lipid metabolism can present with a profound enzyme deficiency, resulting in severe early onset multisystemic disease. Typically, episodes of hypoketotic hypoglycemia and liver failure (Reye-like disease) occur. These children present with encephalopathy leading to lethargy and coma, muscle weakness, and cardiac arrhythmias. Milder phenotypes are restricted to muscle with onset not only in childhood, but also in adulthood. These show higher residual enzyme activities in regard to muscle involvement. Two clinical presentations can be distinguished. Some manifest with recurrent attacks of rhabdomyolysis triggered by long-lasting exercise, fasting, infections, or cold. Other disorders present with permanent muscle weakness.
dehydrogenase deficiencies. Moreover, drugs such as valproate and zidovudine can also cause a secondary carnitine deficiency.

Different enzymes are necessary for beta-oxidation of fatty acids within the mitochondria depending on the length of the fatty acids that are metabolized (short, medium, long, and very long chain acyl-CoA). The different defects can result in late-onset metabolic myopathies or in infantile multisystemic diseases, including muscular hypotonia.

Clinical presentation of the late-onset myopathic form of very long chain acyl-CoA dehydrogenase (VLCAD) deficiency is similar to that of muscle CPT II deficiency. Patients present with attacks of rhabdomyolysis after long-lasting exercise or fasting. In patients with infantile hepatic manifestations of VLCAD deficiency, the myopathic phenotype can present in later life. Attacks of rhabdomyolysis are also observed in the late-onset form of trifunctional protein deficiency, frequently associated with peripheral neuropathy. However, in contrast to VLCAD and CPT II deficiencies, these were observed only in childhood.

Multiple acyl-CoA dehydrogenase deficiency (MADD) is caused by defects in flavoproteins that are responsible for transfer of electrons from flavin adenine dinucleotide to the respiratory chain: electron transfer flavoprotein (ETF), encoded by two genes—ETFb (subunit A) and ETFa (subunit B), and electron transfer flavoprotein ubiquinone oxidoreductase (ETF-QO), encoded by the ETFDH gene. MADD affects not only multiple acyl-CoA dehydrogenases, but also the metabolism of amino acids and choline. The defect of amino acid metabolism results in glutaric aciduria; MADD is also called glutaric aciduria type II. MADD can manifest as a severe neonatal disorder, but later-onset cases are seen in children and adults, affecting muscle only and resulting in permanent weakness. Some patients with later onset can also have episodes of encephalopathy generally precipitated by an infection. Children typically suffer from recurrent episodes of vomiting.

Medium-chain acyl-CoA dehydrogenase (MCAD) deficiency is a common disorder of fatty acid metabolism resulting in infantile metabolic decompensation, including hypotonia or rhabdomyolysis. Late-onset disease with predominant muscle involvement is rare. Short-chain dehydrogenase deficiency typically manifests in childhood. Muscle weakness is seen in some patients as a manifestation of a mild multisystemic presentation in which developmental delay is the leading feature. A juvenile late-onset form with muscle weakness is observed rarely.

Finally, there are disorders affecting the utilization of stored triglycerides due to a defect of the triglyceride lipase. These are called neutral lipid storage diseases. Two different forms of neutral lipid storage disease are associated with different gene defects: neutral lipid storage disease with ichthyosis, also known as Chanarin-Dorfman syndrome (ABHD5 gene), which manifests an ichthyosiform non-bullous erythroderma, and neutral lipid storage disease without ichthyosis (PNPLA2 gene). The latter form can present not only with proximal, but also with distal muscle weakness.

**Diagnosis and Evaluation**

Analysis of the acyl-carnitine profile and carnitine level in blood by tandem mass spectrometry can provide insights about the underlying enzyme deficiency of lipid metabolism. This is a useful screening test in patients with unknown myopathy and can be performed before a muscle biopsy. It can also be used in newborn screening and can be done not only on serum samples, but also on dried blood spots (Guthrie card). In enzyme defects of lipid metabolism there is accumulation of certain fatty acids in blood. For example, in CPT II deficiency the long-chain fatty acids C16 and C18:1 are increased. Typical profiles of different disorders of muscle lipid metabolism are listed in Table 22-2. The diagnostic yield is maximized if the specimens are obtained during a metabolic crisis or after fasting overnight. A normal acyl-carnitine spectrum does not exclude a myopathy of lipid metabolism because the acyl-carnitine profile can be normal between attacks.

Serum CK is often normal between attacks in muscle disorders of lipid metabolism that are characterized by episodes of rhabdomyolysis. A mild or moderate elevation of CK is typically observed in patients with permanent weakness. Creatinine levels should always be obtained to detect renal failure in patients with rhabdomyolysis. Myoglobin and ketones should be measured in blood and urine. In children with Reye-like symptoms mild hyperammonemia and elevated liver enzymes can be present. Analysis of organic acid profile in urine is important, especially to detect glutaric aciduria in MADD.
Histologic studies typically reveal clear lipid accumulation only in those with permanent weakness. In patients with attacks of myoglobinuria, muscle biopsies done during the acute phase can show only necrotic fibers, but these are frequently normal interictally, and these forms may demonstrate little or no lipid accumulation. Muscle biopsies should not be taken during the phase of rhabdomyolysis, but several weeks later because necrosis can mask the characteristic features of metabolic myopathies. Lipid accumulation is frequently more pronounced in the oxidative type I fibers than in type II fibers, because normal muscle also contains more lipid in type I fibers. The most pronounced lipid accumulation is seen in neutral lipid storage disease. Lipid droplets can be stained by Oil Red O (Fig. 22-9) or by Sudan Black. VLCAD deficiency can be detected by immunohistochemistry. In neutral lipid storage diseases peripheral blood smears typically show neutral lipid vacuoles in leukocytes (Jordan’s anomaly).

Further investigations of the enzyme molecular genetic defect are necessary to confirm the diagnosis of lipid myopathies. In late-onset cases, there is often considerable residual enzyme activity that makes diagnosis difficult. For example, in patients with muscle CPT II deficiency, there is normal activity of CPT under optimal assay conditions. However, abnormal regulation of the enzyme can be seen by abnormal inhibition by malonyl CoA. Biochemical analysis of enzyme deficiencies in lipid metabolism of muscle is difficult, and these studies are performed only in specialized laboratories. Fibroblasts and lymphocytes are also tissues in which the enzymes can be measured. Fatty acid oxidation rates can be measured in fibroblasts by incubating cells with radiolabeled fatty acids of different chain length. This method can differentiate short-, medium-, or long-chain defects. Carnitine levels can be measured not only in blood, but also in muscle, bearing in mind that secondary carnitine deficiency is quite common. Secondary coenzyme Q (CoQ) deficiency in muscle can be measured in MADD due to a defect of ETF-QO.

Molecular genetic testing is relatively simple for CPT II and MCAD deficiencies. Although more than 40 mutations are known in the CPT2 gene, a missense mutation S113L in patients with muscle CPT II deficiency is found in approximately 60% of mutant alleles. More than 90% of the patients carry this mutation on at least one allele. In patients with MCAD deficiency, there is a common point mutation 985A>G with similar frequency compared to the CPT II mutation S113L. Such common mutations are not present in other genes affected in myopathies of lipid metabolism, and molecular genetic testing requires primary sequencing of the gene.

**Treatment**

Treatment strategies for myopathies caused by defects of lipid metabolism include avoidance of exacerbating factors, dietary regimens containing high amounts of carbohydrate, supplementation with fatty acids that bypass the enzyme defect, riboflavin or carnitine, and IV glucose.

Avoidance of exacerbating factors still plays a large role in the management of patients with attacks of rhabdomyolysis or metabolic crises. In children, fasting and infections are the major causes of metabolic decompensation and rhabdomyolysis. Thus, regular feedings are essential in children. In adults, exercise and cold temperatures are the major precipitants of rhabdomyolysis. Thus, avoidance of intense or prolonged exercise and protection from cold is necessary. Certain drugs, such as valproate, diazepam, and ibuprofen, can trigger attacks in patients with CPT II deficiency.

In general, the recommended dietary regimen for patients with disorders of lipid metabolism is a high-carbohydrate, low-fat diet with frequent and regularly scheduled meals. Slow-release carbohydrate intake should be increased during intercurrent illness or sustained exercise.

In patients with muscle CPT II deficiency it has been shown that ingestion of polysaccharides can improve exercise intolerance, whereas oral glucose ingestion does not. This study also demonstrated that intravenous (IV) glucose infusions improve exercise intolerance in patients with CPT II deficiency (Box 22-2). IV glucose can be recommended in crises of infantile CPT II deficiency (including insulin that reduces mobilization of the stored lipids), but is not generally given in patients with other disorders of lipid metabolism. A study in patients with VLCAD deficiency did not show a benefit of IV glucose (Box 22-2).

Supplementation with medium-chain triglycerides (MCT) could be beneficial in disorders with long-chain fatty acid oxidation defects because medium-chain acyl-CoA esters can bypass the long-chain oxidation enzymes. Anecdotal evidence suggests that MCT is effective in cases of trifunctional protein deficiency, VLCAD, and CPT II deficiency. However, no effect of oral medium-chain triglycerides was observed in a study on patients with VLCAD deficiency. MCT supplements are contraindicated in patients with medium- or short-chain beta-oxidation defects or MADD.

Oral intake of the triglyceride triheptanoin, which contains the odd-chain (C7) fatty acid hepanoate, can provide an alternative source to fill the citric cycle. This so-called anaplerotic diet was investigated for patients with VLCAD deficiency and muscle CPT II deficiency. In children with VLCAD deficiency, cardiomyopathy, hepatomegaly, and muscle weakness were improved.

### Box 22-2 Treatment Options in Carnitine Palmitoyltransferase II Deficiency

<table>
<thead>
<tr>
<th>Option</th>
</tr>
</thead>
<tbody>
<tr>
<td>High-carbohydrate and low-fat diet with frequent and regularly scheduled meals</td>
</tr>
<tr>
<td>Increased intake of polysaccharides during sustained exercise</td>
</tr>
<tr>
<td>IV glucose in crisis</td>
</tr>
<tr>
<td>Supplementation with medium-chain triglycerides (MCT)</td>
</tr>
<tr>
<td>Oral intake of the triglyceride triheptanoin</td>
</tr>
<tr>
<td>Bezafibrate</td>
</tr>
</tbody>
</table>

![Figure 22-9 Oil Red O staining showing lipid droplets.](image-url)
In patients with CPT II deficiency, triheptanoin intake reduced muscle pain after exercise and might prevent attacks of rhabdomyolysis. L-Carnitine substitution (100–400 mg/kg/day in children and 2–4 g/day in adults) is unequivocally beneficial in cases of primary carnitine deficiency. The role of carnitine supplementation in other fatty acid oxidation disorders remains controversial. Secondary carnitine deficiency is common, caused either by acylcarnitine wastage or inhibition of the plasma membrane carnitine transporter by accumulating acylcarnitines.

Riboflavin (vitamin B2) is the cofactor shared by ETF, ETFDH, and all acyl-CoA dehydrogenases. Many of the patients with MADD presenting with myopathy improve with riboflavin supplementation (100–400 mg/day). It has been shown that riboflavin-responsive myopathy with MADD is frequently caused by ETFDH mutations. A secondary CoQ deficiency was observed in one study, arguing that additional CoQ supplementation should be considered.

A future therapeutic option might consist of bezafibrate, which can induce up-regulation of different genes involved in lipid metabolism by activating the peroxisome proliferator-activated receptor α. In fibroblasts and myoblasts from patients with muscle CPT II deficiency and in fibroblasts of patients with VLCAD deficiency, bezafibrate improved the biochemical defect.

Recently it was shown that administration of bezafibrate (600 mg/day for 6 months) in six patients with muscle CPT II deficiency resulted in an increased rate of palmitoylcarnitine oxidation in muscle mitochondria. In this study, a self-assessment score for general health improved. Frequency of attacks with rhabdomyolysis and maximal CK levels were lower during treatment compared to a 6-month period before, but it was not shown that there was a statistically significant decrease. No adverse effects were reported, an important finding because rhabdomyolysis is a potential side effect of bezafibrate. However, as long as no placebo-controlled, double-blind study has proven its efficacy, bezafibrate cannot be recommended, in general, for treatment of patients with muscle CPT II deficiency.

In conclusion, treatment of myopathies of lipid metabolism remains inadequate. Bezafibrate treatment offers promising results. However, dietary advice is the only therapeutic option as long as there are no therapeutic effects of specific drugs. Because many disorders of lipid metabolism are rare, clinical studies are difficult to perform. In the future, gene therapy might correct the metabolic defect.

Outcome
The outcome is usually much better in patients with myopathies of lipid metabolism that manifest late in life only with muscular symptoms than in those with infantile multisystemic manifestations. The most favorable disease course is seen in patients presenting with attacks of rhabdomyolysis, such as the muscle form of CPT II deficiency. At rest and except for episodes of myoglobinuria, muscle strength is normal. Patients usually have an excellent long-term prognosis. In many cases, attacks can be effectively prevented after the diagnosis is made by avoiding situations that can provoke rhabdomyolysis and by increasing carbohydrate intake during prolonged exercise or other situations that provoke attacks. Acute tubular necrosis as a result of massive myoglobinuria is the only life-threatening complication. Although renal failure has been documented in approximately 25% of patients, if it is promptly recognized and appropriately treated, a complete recovery should be expected in virtually all cases. Cardiac arrest can occur very rarely during an attack in the muscle form of CPT II deficiency. Only one case with a fatal outcome has been reported, and respiratory failure from muscle weakness was reported in another patient.

In patients with muscle disorders of lipid metabolism with persistent weakness, the disease is usually slowly progressive but can lead to significant disability over years. Typically, proximal weakness is present, but involvement of facial, bulbar, or respiratory muscles is rare. Cardiomyopathy can result in heart failure or in cerebral cardiac embolism. Children with metabolic crises can progress into coma if they are not treated promptly with IV glucose. These children have a high risk of sudden death due to cardiac arrhythmia.

Mitochondrial Myopathies
The term mitochondrial myopathy is generally used only for defects of the respiratory chain. Myopathies with defects located elsewhere in the metabolic pathways within the mitochondria are generally not classified as mitochondrial myopathies (e.g., myopathies due to defects in the beta-oxidation of fatty acids are classified as myopathies of lipid metabolism). Mitochondrial disorders are frequently multisystemic diseases; the term mitochondrial myopathy is used for those with predominant muscle involvement.

From the genetic point of view, mitochondrial disorders are unique because mitochondria have their own genome, enabling intramitochondrial protein synthesis. However, only a very small proportion of mitochondrial proteins are encoded by the mitochondrial DNA. The majority are encoded by nuclear DNA, and these proteins are imported into the mitochondria. Therefore, mitochondrial disorders can follow both mendelian and maternal traits of inheritance. Mitochondrial genetics differ from mendelian genetics in several aspects. Due to the polyploid nature of the mitochondrial genome, with several thousand copies per cell, a mixture of mutant and normal mtDNA is frequently observed. Called heteroplasmmy, this has implications for molecular diagnostics because the mutant mtDNA may be absent or present only in very low levels in certain tissues. Moreover, the level of heteroplasmmy influences the phenotype: a threshold of mutant mtDNA has to be reached before biochemical effects and phenotypical abnormalities occur.

Clinical Presentation
Chronic progressive external ophthalmoplegia (CPEO) is the most common form of mitochondrial myopathy; it can present as an isolated disorder or as the leading manifestation of a multisystemic syndrome. Prolonged exercise may exacerbate the disease. Some patients seek medical attention only when ptosis covers a specific eye and leads to visual disturbance. Patients with CPEO use their frontalis muscles to lift their eyelids and show compensatory chin elevation. Together with the ptosis this is called Hutchinson’s triad. Ophthalmoplegia is often symmetric and may not lead to complaints because patients simply turn their heads to compensate. Only a minority of patients suffer from diplopia. Muscle weakness is often not restricted to the extraocular muscles, and severe weakness of the facial muscles can present with the facies myopathic. Many patients also suffer from exercise intolerance. In most cases, neurologic examination shows limb weakness, most prominent in the proximal muscles of the lower extremities.