Understanding the Metabolic Big Picture in MAND: A Guide for Families

IMPORTANT DISCLAIMER: These handouts are based on emerging research and mechanistic reasoning from animal models and cell studies — no MAND-specific clinical testing guidelines currently exist. The metabolic framework is hypothetical but grounded in published molecular data. Results need to be interpreted by providers familiar with both MAND and metabolic medicine.

A Guide to How MBD5 Affects Your Child's Metabolism — and Why Testing Matters

What is MAND?

MAND stands for MBD5-Associated Neurodevelopmental Disorder. It is caused by a change in the MBD5 gene — specifically, your child has only one fully working copy instead of two. This is called "haploinsufficiency." MBD5 is a gene that helps control how other genes are turned on and off. When it is only working at half capacity, several important body systems are affected — not just the brain, but also how the body makes energy, stores iron, controls blood sugar, and protects itself from damage.

This handout explains the "big picture" of how these systems connect to each other, why your child may experience fatigue or other symptoms, and why specific lab tests are being recommended.

The Four Core Problems — and How They Connect

Think of your child's metabolism like a factory with four departments that all depend on each other. When MBD5 is only half-working, all four departments are affected:

PROBLEM #1: The Energy System Is Running Too Fast AND Can't Finish the Job (Mitochondrial Dysfunction)

Every cell has tiny power plants called mitochondria. Normally, a protein called PDK1 acts like a speed governor — it controls how fast fuel (pyruvate) enters the mitochondria. Research has shown that in MAND, PDK1 is reduced, which means the speed governor is partially broken.

Fuel rushes into the mitochondria too quickly, which can overload the system.

But the problem does not stop there. Even if fuel enters the mitochondria, the cell still needs to complete the final step of energy production — passing electrons to oxygen at the very end of the energy chain. This final step is performed by an enzyme called cytochrome c oxidase (Complex IV), and it requires copper to work.

The same research that discovered the PDK1 problem also found that MBD5 haploinsufficiency reduces the expression of a gene called COX17. COX17 is the copper delivery truck — it is the chaperone protein responsible for picking up copper and delivering it specifically to Complex IV inside the mitochondria. Without enough COX17, copper cannot reach Complex IV efficiently, and the enzyme cannot do its job properly.

(Reference: Meguro-Horike M, et al. "Haploinsufficiency of MBD5 and MBD6 Impairs Mitochondrial Respiration Through Chromatin-Mediated Gene Regulation." Biochemical and Biophysical Research Communications. 2026;800:153288.)

Think of it this way: the factory is being flooded with raw materials (because PDK1 is low), but the final machine on the assembly line is broken (because COX17 is low and copper cannot reach Complex IV). The result is a massive traffic jam inside the mitochondria — fuel is coming in too fast, but the system cannot convert it into usable energy (ATP) at the end.

This traffic jam has serious consequences:

- Electrons that cannot be passed to oxygen at Complex IV back up along the energy chain, creating what scientists call "reductive stress" — too many electrons with nowhere to go
- These backed-up electrons leak out and react with oxygen to form harmful molecules called reactive oxygen species (ROS), which damage cells
- The cell cannot make enough ATP (energy), leading to fatigue

- The cell is forced to shift toward less efficient energy production (glycolysis), which produces less energy per unit of fuel

Research has confirmed that when COX17 is knocked down in human cells, cytochrome c oxidase activity drops, the enzyme cannot assemble properly, and the respiratory chain supercomplexes — the organized structures that make energy production efficient — fall apart.

(Reference: Oswald C, et al. "Knockdown of Human COX17 Affects Assembly and Supramolecular Organization of Cytochrome C Oxidase." Journal of Molecular Biology. 2009;389(3):470-9.)

In animal models, complete loss of COX17 is lethal — embryos die early in development because they cannot make enough energy. In MAND, where COX17 is reduced but not absent, the effect is more subtle but still significant: the mitochondria work, but they work poorly.

(Reference: Takahashi Y, et al. "Mammalian Copper Chaperone Cox17p Has an Essential Role in Activation of Cytochrome C Oxidase and Embryonic Development." Molecular and Cellular Biology. 2002;22(21): 7614-21.)

Additional research has shown that when copper cannot reach Complex IV, the consequences extend beyond just energy production. Copper-deficient mitochondria show decreased glutathione levels, reduced activity of the antioxidant enzyme GPX4, and increased vulnerability to a type of cell damage called ferroptosis — which is directly linked to iron-mediated damage.

(Reference: Li F, et al. "Copper Depletion Strongly Enhances Ferroptosis via Mitochondrial Perturbation and Reduction in Antioxidative Mechanisms." Antioxidants. 2022;11(11):2084.)

So in MAND, the energy problem is actually a double hit:

1. Too much fuel coming in (because PDK1 is low)
2. The final step cannot be completed (because COX17 is low and copper cannot reach Complex IV)

This creates a perfect storm for fatigue, oxidative damage, and metabolic stress.

What makes MAND different from other mitochondrial conditions: In most mitochondrial diseases, a waste product called lactate builds up in the blood. In MAND, lactate may look NORMAL because the problem is not a simple blockage — it is a mismatch between input and output. Standard screening tests may miss the problem entirely.

Better markers to look for: Isocitric acid (a molecule in the energy cycle) may be elevated because the cycle is being overloaded. Alanine (an amino acid made from pyruvate) may be LOW because pyruvate is being consumed before it can be converted to alanine.

PROBLEM #2: The Protective Shield Is Weakened (Glutathione and Oxidative Stress)

When the energy system runs inefficiently, it produces harmful byproducts called "reactive oxygen species" (ROS) — think of these as sparks flying off a malfunctioning engine. The body's main fire extinguisher is a molecule called glutathione.

Research on MBD5 has found changes in the genes that control glutathione metabolism, suggesting the body may not be making or recycling glutathione efficiently. At the same time, the overloaded mitochondria are producing more sparks than usual — and the COX17/ copper problem at Complex IV makes this even worse, because backed-up electrons are a major source of these sparks.

(Reference: Bjørklund G, et al. "The Role of Glutathione Redox Imbalance in Autism Spectrum Disorder: A Review." Free Radical Biology and Medicine. 2020;160:149-162.)

This creates a dangerous mismatch: more damage being produced, less protection available.

When glutathione runs low, the body tries to compensate by pulling amino acids (protein building blocks) from other uses to make more glutathione. This is why amino acid levels may look unusual on blood tests — the body is robbing Peter to pay Paul.

Important caution about NAC: N-acetylcysteine (NAC) is often recommended to boost glutathione. However, NAC is also a potent biofilm disruptor — it can break apart the protective shields that gut bacteria build around themselves. When these biofilms are disrupted, the immune system may suddenly react to bacteria it was previously ignoring, causing

increased inflammation in the gut. This inflammation can paradoxically increase oxidative stress — the very problem NAC was meant to fix. If NAC is being considered, it should be started at a very low dose with careful monitoring, and alternative glutathione support strategies (such as liposomal glutathione or glycine supplementation) may be safer starting points.

(Reference: Dinicola S, et al. "N-Acetylcysteine as Powerful Molecule to Destroy Bacterial Biofilms. A Systematic Review." European Review for Medical and Pharmacological Sciences. 2014;18(19):2942-8.)

PROBLEM #3: Iron Is in the Wrong Place (Iron Maldistribution)

MBD5 directly controls a gene called Fth1, which makes ferritin H — the protein that safely locks iron away inside cells. With only one working copy of MBD5, the body may not make enough ferritin H. This means iron enters cells normally but cannot be safely stored.

(Reference: Tao Y, et al. "MBD5 Regulates Iron Metabolism via Methylation-Independent Genomic Targeting of Fth1 Through KAT2A in Mice." British Journal of Haematology. 2014;166(2):279-91.)

The result is a paradox: blood tests may show LOW ferritin (because less ferritin protein is being made), but iron may actually be accumulating inside cells in a dangerous, "loose" form called labile iron. This loose iron acts like gasoline on the fire — it reacts with the sparks from the malfunctioning mitochondria and makes the oxidative damage much worse.

This connects directly to the COX17/copper problem: research has shown that when copper is depleted from mitochondria, cells become much more vulnerable to iron-mediated damage (ferroptosis). So the reduced COX17 in MAND may make the iron storage problem even more dangerous — the mitochondria are already struggling with copper delivery, and now loose iron is adding fuel to the fire.

(Reference: Darshan D, et al. "Conditional Deletion of Ferritin H in Mice Induces Loss of Iron Storage and Liver Damage." Hepatology. 2009;50(3): 852-60.)

This is why iron supplementation in MAND must be approached very carefully. If the problem is iron STORAGE (not iron INTAKE), adding

more iron could make things worse. A full iron panel — not just ferritin — is essential to tell the difference.

(Reference: Pasricha SR, et al. "Iron Deficiency." Lancet. 2021;397(10270):233-248.)

PROBLEM #4: Blood Sugar and Growth May Be Affected (Glucose and Growth Hormone)

Research in animal models has shown that MBD5 also plays a role in controlling blood sugar and growth. Animals missing MBD5 had enhanced insulin sensitivity (the body responds too strongly to insulin), episodes of low blood sugar, and reduced growth hormone and IGF-1.

(Reference: Du Y, et al. "The Essential Role of Mbd5 in the Regulation of Somatic Growth and Glucose Homeostasis in Mice." PLoS One. 2012;7(10):e47358.)

Low blood sugar episodes can cause fatigue, irritability, difficulty concentrating, and behavioral changes. If growth hormone is also low, it can affect growth and contribute to low energy.

Important: A low IGF-1 level alone cannot diagnose growth hormone deficiency. Studies have shown IGF-1 has poor accuracy as a standalone test — in one large study, it had only 68.5% sensitivity and 41.7% specificity. If IGF-1 is low, a pediatric endocrinologist should perform stimulation testing before any conclusions are drawn.

(Reference: Iwayama H, et al. "Insulin-Like Growth Factor-1 Level Is a Poor Diagnostic Indicator of Growth Hormone Deficiency." Scientific Reports. 2021;11(1):16159.)

How These Four Problems Create a Vicious Cycle

These four problems do not exist in isolation — they feed into each other:

1. Fuel floods into the mitochondria too fast (because PDK1 is low)
2. The mitochondria cannot finish processing the fuel (because COX17 is low and copper cannot reach Complex IV)
3. Backed-up electrons leak out and create reactive oxygen species (oxidative damage)

4. The weakened glutathione shield (Problem #2) cannot neutralize the damage
5. Loose iron from impaired ferritin storage (Problem #3) amplifies the damage further
6. Low blood sugar (Problem #4) deprives the brain and muscles of fuel
7. The oxidative damage from steps 3–5 further damages the mitochondria, making Problem #1 worse
8. The body pulls amino acids and nutrients from other functions to try to repair the damage, potentially affecting growth, immune function, and brain chemistry

This is why fatigue in MAND is likely not caused by any single deficiency — it is the result of multiple systems being stressed simultaneously. And this is why testing needs to look at all four areas together, not just one at a time.

Why Standard Tests May Miss the Problem

Many of the standard screening tests that doctors use were designed for more common conditions and may be misleading in MAND:

- Normal lactate does NOT mean the mitochondria are fine (the problem is a mismatch between fuel input and Complex IV output, not a simple blockage)
- Low ferritin does NOT necessarily mean iron deficiency (it may mean the body cannot make enough ferritin protein)
- Normal glutathione on a basic panel does NOT mean there is no oxidative stress (the GSH:GSSG ratio is more informative than total glutathione)
- A low IGF-1 does NOT diagnose growth hormone deficiency (stimulation testing is required)
- Normal serum copper does NOT mean copper is reaching the mitochondria (the problem may be in the COX17 delivery system, not total body copper)

This is why specialized testing — urinary organic acids, comprehensive amino acid profiles, full iron panels, and glutathione redox panels — may be helpful.

What the Lab Tests Are Looking For — A Summary

Energy System Tests (Handout #1): Checking whether the mitochondria are overloaded and whether the energy chain is backed up. Key markers include urinary isocitric acid, Krebs cycle intermediates, plasma alanine, and newer markers like FGF21 and GDF15.

Amino Acid Tests (Handout #2): Checking whether the body is consuming amino acids faster than normal to compensate for energy and antioxidant problems. Key patterns include low alanine, low glutamate, low lysine, low histidine, and elevated cystathionine.

Glutathione and Oxidative Stress Tests (Handout #3): Checking whether the body's antioxidant defenses are overwhelmed. Key markers include the GSH:GSSG ratio, 8-OHdG (DNA damage marker), and pyroglutamic acid.

Iron Studies (Handout #4): Checking whether iron is being stored safely or accumulating in a dangerous form. The full panel (ferritin, serum iron, TIBC, transferrin saturation, soluble transferrin receptor) is needed — ferritin alone is not enough.

Glucose and Growth Hormone Tests (Handout #5): Checking whether blood sugar is dropping too low and whether the growth hormone system is working properly. Fasting glucose, insulin, IGF-1, and HbA1c are key tests.

Nutritional Cofactor Tests (Handout #6): Checking whether the vitamins and minerals that support all of the above systems are at adequate levels. Key cofactors include CoQ10, carnitine, B vitamins, selenium, zinc, copper, and magnesium. Copper and ceruloplasmin testing is particularly important in MAND given the COX17 connection — the goal is to understand whether copper is available in the body AND whether it is reaching the mitochondria.

What This Means for Your Child

Understanding this big picture helps explain why:

- Your child may be fatigued even when basic blood work looks "normal"
- Iron supplements may not be helping (or could potentially be making things worse)
- Multiple systems need to be evaluated together, not in isolation
- Nutritional support needs to be targeted and carefully monitored, not one-size-fits-all
- A team approach — involving genetics, metabolic medicine, nutrition, and endocrinology — may be most effective

The goal of testing is to identify which of these four interconnected problems is most active in YOUR child, so that interventions can be targeted appropriately. Every child with MAND is different, and the balance between these four problems may vary from person to person.

Summary of Key References:

- Meguro-Horike M, et al. "Haploinsufficiency of MBD5 and MBD6 Impairs Mitochondrial Respiration Through Chromatin-Mediated Gene Regulation." Biochemical and Biophysical Research Communications. 2026;800:153288.
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