35 YO F ADMITTED WITH PRETERM PREMATURE RUPTURE OF MEMBRANES

Anila Bindal, MD
December 3, 2015
• G5P0403 at 22w2d by Fetal US

• Initially presented to Indiana after “large gush of fluid”

• Admitted for expectant management
  • Received antibiotics
  • Started on 17-hydroxyprogesterone

• Transferred to UCMC because nearing variability
  • Confirmed leakage of fluid, +nitrazine, +ferning, good fetal movement
  • Absent vaginal bleeding, contractions
PMH:
- Preterm delivery x 4
- 1 neonatal demise at 22 wks

PSH: none

FH: + Diabetes

NKDA

Meds: PNV

SH:
- Works as a waitress, has not been working during pregnancy
- No tobacco, ETOH, or illicits
- Has 3 sons
ROS

• GEN: denies fevers, chills, night sweats; +5lb weight loss a few weeks ago

• HEENT: denies vision problems; +new BL hearing loss 3-4 years ago (uses bilateral hearing aids), underdeveloped phonation

• RESP: denies SOB

• CV: denies CP, orthopnea

• GI: denies nausea, emesis, constipation, diarrhea; normal appetite

• DERM: denies rashes

• MSK: denies weakness, edema, neuropathy

• PSYCH: denies depression
Physical Exam

Temp: 36.5 (97.7)    BP: 97/55    HR: 91    RR: 18    SaO2: 100% RA
Ht: 149.9cm (4’11”)    Wt 39kg (86lb)    BMI 17.4

GEN: Thin, Caucasian, NAD
HEENT: EOMI, no scleral icterus, PERRLA, MMM, no thyromegaly
CV: RRR, nml S1/S2
PULM: CTA B
ABD: NT, +gravid
EXT: 2+ DP/radial pulses, no edema
DERM: no acanthosis nigricans
NEURO: alert, oriented, no tremor
PSYCH: normal affect, pleasant
Labs

+ketones

128 91 15 394
4.9 12 0.5 Ca 10.6

6.9 6.7 226

5.5 3.1
0.2
13 7
56
• No h/o diabetes (including GDM)
• Received prenatal care throughout pregnancy
• Had not seen a doctor since last pregnancy (12 years ago)
• Eats one full meal (dinner); otherwise snacks throughout the day
  • Diet includes meats, potatoes, vegetables

Diabetes on maternal side:
• Mother (Type I, diagnosed age 26, uses bilateral hearing aids)
• MGM (unknown type, diagnosed ?18 years ago)
• MGGM (unknown type)
Does she possibly have MIDD?

What is MIDD?
What is MIDD?

Maternally Inherited Diabetes and Deafness

- Mitochondrial disease
- Diabetes accompanied by hearing loss
- Usually develops in mid-adulthood

Figure 1. Organs potentially affected by m.3243A>G mutation

Murphy et al, Diabetic Medicine 2008
Other names for MIDD

- Ballinger-Wallace syndrome
- Type II DM with deafness
- Maternally-transmitted diabetes-deafness syndrome
- Mitochondrial inherited diabetes and deafness
- NIDDM with deafness
Other Labs/Studies?

HbA1c 8.5%
BG 185
Ketones: 5.34
C-peptide 0.19

GAD65 Ab neg
Insulin Ab neg
ZnT8 neg
IAT2 neg

Cortisol (@0811): 25.4
TSH 0.25 → 0.67

TTE WNL (LVEF 60%)
Facts about MIDD

- First described in 1992
- ~1% of all diabetes cases (esp Japanese but found worldwide)
- Egg cells (but not sperm cells) contribute Mitochondrial DNA to developing embryo → both M/F affected but only F pass it on
- Mutations in MT-TL1 (leucine), MT-TK (lysine), MT-TE genes (glutamic acid)
- Most commonly A → G at 3243 in tRNA Leucine gene

Donovan et al, JCEM 2006
• Same mutation m.3243A>G linked to MELAS (myopathy, encephalopathy, lactic acidosis, strokelike episodes), which has a more severe phenotype and worse prognosis

• Enhanced degradation of mitochondrial DNA-encoded proteins
  → Reduction of functional respiratory enzyme complexes and reduced ATP generation
  → Altered ATP:ADP may result in impaired insulin secretion and beta-cell apoptosis
Features of MIDD

- **Hearing loss**
  - Bilateral, progressive
  - Sensorineural, higher frequency
  - Usually age 20-30, mean age onset 33-34 yo
  - Often before DM onset

- **Diabetes**
  - Insulin sensitivity intact but β-cell dysfunction, loss of β-cell mass → insulinopenia
  - Mean age onset mid to late-30’s
  - Likely associated with progressive reduction of oxidative phosphorylation and implicating glucose-sensing mechanism of β-cells

- **Thin (BMI < 20)**
  - Especially those requiring insulin early on

- **Short stature**
  - Due to GHRH deficiency

Donovan et al, JCEM 2006
Features of MIDD

• CV disease
  • Especially cardiac conduction abnormalities (WPW, Afib)
  • Can also have cardiomyopathy/CHF
  • LVH in absence of HTN seen 4x more
  • Cardiac autonomic neuropathy

• Advanced microvascular complications:
  • Renal disease:
    • Proteinuria, especially FSGS
    • Often misdiagnosed as Alport syndrome
  • Neuropathy

Murphy et al, Diabetic Medicine 2008
Guillaumeau et al, Annal Int Med, 2001
Donovan et al, JCEM 2006
Other Features of MIDD

• **Weakness** in proximal muscles: cramps or weakness, esp during exercise
  • Muscle biopsy shows ragged-red fibers typical of mitochondrial myopathy
  • Higher lactate levels post-exercise

• **GI symptoms**
  • Especially constipation or pseudo-obstruction

• **Neuropsychiatric symptoms**
  • Depression, schizophrenia, phobias

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Fig 3. A: Gomori trichrome stain demonstrating ragged red fiber; B: Cytochrome oxidase stain negative fiber / no ragged red fiber. Picture from Carvalho et al, Archives of Neuropsychiatry, 2004.
Characteristic Macular Retinal Dystrophy: usually without vision problems

Pigment builds up in the cells of the macula

Less Diabetic Retinopathy than seen in T2DM

Ogun et al, Neurology 2012
Phenotype of MIDD

- Wide variety in phenotypic expression
- Heteroplasmy: A mix of wild-type and mutant DNA in the same cell
- Severity of MIDD features associated with percentage of mutated mitochondrial DNA
  - Blood may show negative result despite presence of mutation in other tissues because leukocytes have lowest level of heteroplasmy
  - Consider checking urine and/or buccal samples
- Symptoms often more severe in men
- Penetrance of diabetes in offspring is 85% by 70 yo
Treatment of MIDD

• Metformin discouraged as more likely to cause lactic acidosis
• First-line includes secretagogues (i.e. glyburide)
• Mean duration of DM before insulin dependence: 2-4 years
  • Continue taking carbs when ill (stroke-like symptoms when lacked carbs)
• Coenzyme Q10
• ?Avoid statins due to reduced CoQ10 levels
• Hearing aids or cochlear implants for hearing loss

Murphy et al, Diabetic Medicine 2008
Donovan et al, JCEM 2006
CoQ10 is an electron carrier in the respiratory chain used in mitochondrial oxidative phosphorylation which in turn synthesizes ATP.

- High amounts of CoQ10 in tissues with high energy requirements.
- Also acts as antioxidant.
- Mutant mitochondria show enhanced release of free radicals and impairment of mitochondrial respiratory chain.

**Figure 1:** The role of Co-enzyme Q10 as a crucial cofactor in adenosine triphosphate production.
CoQ10 Repletion?

- Few studies done: small, open label, not subject to double-blinding or randomization
- Some suggest delayed hearing loss, enhanced insulin secretion, reduced lactate levels post-exercise
- Some suggest improved myopathy symptoms, improved painful neuropathy and/or CHF
- Others report no difference

In a Cochrane review of the treatment of mitochondrial disorders, the lack of large RCTs meant that use of CoQ10 in mitochondrial disorders could not be supported. The Cochrane group has concluded that more trials with clinically relevant end-points are needed to identify effective novel therapy in mitochondrial disorders.

Discussion
There is not enough robust clinical evidence to support the routine use of CoQ10 supplementation in clinical practice in any form of diabetes. Although evidence for use of CoQ10 supplementation is lacking, it is readily available without prescription and appears to have few major reported adverse effects, and therefore its use is likely to continue. In MIDD the rarity of the condition makes robust clinical studies of CoQ10 less likely to be forthcoming and, as there are no effective treatments, it is likely that some patients will continue to use CoQ10 supplementation.
### Table 3. Recommendations for care of patients with MIDD

<table>
<thead>
<tr>
<th>Procedure</th>
<th>At diagnosis</th>
<th>Follow-up</th>
<th>Intervention</th>
</tr>
</thead>
<tbody>
<tr>
<td>Neurological and cardiovascular</td>
<td>Yes</td>
<td>Yearly or as per findings</td>
<td>Sulfonylurea or insulin</td>
</tr>
<tr>
<td>examination</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Diabetes screening if not known</td>
<td>Yes (fasting blood glucose)</td>
<td>Biannually from age 12 years, then yearly once adult</td>
<td>Hearing aids or cochlear implant</td>
</tr>
<tr>
<td>to have diabetes</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hearing test</td>
<td>Yes</td>
<td>Yearly or as per findings</td>
<td></td>
</tr>
<tr>
<td>Ophtalmological examination</td>
<td>Yes</td>
<td>Yearly or as per findings</td>
<td>ACE-I, statins</td>
</tr>
<tr>
<td>Echocardiogram</td>
<td>At 35 years of age or earlier</td>
<td>Three to five yearly or earlier based on clinical findings and family</td>
<td></td>
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<tr>
<td></td>
<td>if evidence of heart failure</td>
<td>history</td>
<td></td>
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<tr>
<td></td>
<td>or arrhythmias</td>
<td></td>
<td></td>
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<tr>
<td>Renal assessment</td>
<td>Yes (urinary protein)</td>
<td>Yearly</td>
<td>ACE-I, optimize BP control</td>
</tr>
<tr>
<td>Brain MRI</td>
<td>No</td>
<td>Low threshold for investigating central neurological symptoms</td>
<td>ACE-I (aspirin and statins if</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>traditional risk factors present)</td>
</tr>
</tbody>
</table>
Other medication considerations in MIDD:

- Tetracyclines
- Chloramphenicol
- Phenytoin
- Valproate
- HMG CoA Reductase Inhibitors
- Antiretrovirals
MIDD During Pregnancy

- Placenta accreta
- Preterm labor
- PPROM
- Higher miscarriage rate
- Magnesium sulfate should be avoided!
  - Competes with calcium in mitochondrial membranes and may exacerbate muscle damage

Donovan et al, JCEM 2006
I met with the mother to discuss the care of 22+4 week premature infant, mm had ruptured 2 weeks back. Our discussion revolved around the medical management as well as concerns for the best interests of the infant. I had discussed with mom that if baby delivers now, baby in all likelihood will not survive due to lung immaturity and she has the option of not going for resuscitation. I also emphasized that if by any chance the baby survives with intervention there will be very high likelihood of neurological sequelae including severe IVH. Mom is hearing impaired but communicates well. She was treated for DKA.

**mortality is high (@50%)**

**Ethics:** Importantly, I discussed the overall outcomes for a about 23 weeker, including that mortality is high (@50%) and that long-term morbidity remains a significant problem though estimates of probability are hard to provide especially with the inherent uncertainty in actual gestational age. I also discussed issues revolving around redirection of care in the event of the babies sustaining significant insults to their brain. I discussed the possibility that resuscitative efforts could be ineffective in sustaining a 23 weeker’s life and that mortality could ensue even after initial stabilization of the infant. I expressed that we as the medical team would offer our expertise and help guide the parents in decisions regarding the best interests of the child and this would be an evolving process.
Back to our patient...

• Treated for DKA

• Ophthalmalogy consult: eyes WNL

• Continue pregnancy or terminate?
  • Can choose to defer plan until 24 weeks at which point if she chooses to terminate, she would have to do so in another state
Specimen Type: Blood in EDTA
Submitters ID No: M125145216, 9520046975
Ordered By: Mayo Medical Lab-Sendout Testing/Superior Dr. Support Center

Date Specimen Received: 8/21/2015
Date Test(s) Started: 9/30/2015
Date of Report: 10/27/2015

Test(s) Requested: Mitochondrial Disorders / Testing for 58 Confirmed Disease-Associated mtDNA Variants and mtDNA Deletion Testing
Clinical Indications: Diabetes, concern for maternally-inherited diabetes and deafness

Result:

<table>
<thead>
<tr>
<th>Gene</th>
<th>mtDNA</th>
<th>Heteroplasmatic (%)</th>
<th>Classification</th>
</tr>
</thead>
<tbody>
<tr>
<td>MT-TL1</td>
<td>m.3243 A&gt;G</td>
<td>Approximately 28%</td>
<td>Pathogenic Variant</td>
</tr>
</tbody>
</table>

Interpretation:
This analysis of 58 confirmed mitochondrial DNA (mtDNA) point pathogenic variants (see attached list) and large mtDNA deletions identified the m.3243 A>G pathogenic variant in the MT-TL1 gene. The m.3243 A>G mutation has been associated with various phenotypes including Mitochondrial Encephalomyopathy, Lactic Acidosis, and Stroke-like episodes (MELAS) (m.3243 A>G accounts for approximately 80% of MELAS cases), Leigh syndrome, Maternally Inherited Diabetes and Deafness (MIDD) (m.3243 A>G present in approximately 2%-7% of patients with MIDD), and Hyperpolaric Cardiomyopathy (m.3243 A>G present in approximately 10% of Finnish patients) (Longo, N. 2003; Majima et al., 1998). This result is expected to be consistent with a diagnosis of mitochondrial disorder in this individual.

Recommendation:
Mitochondrial DNA disorders are maternally inherited. Genetic counseling and testing appropriate materniline relatives for this pathogenic variant are recommended.

Resources:
Patients willing to share their genetic and health data (de-identified for privacy) to advance knowledge and to connect with others with the same variant/condition can visit genomeconnect.org.

Methods:
The entire mitochondrial genome from the submitted sample was amplified and sequenced using a solid state sequencing by-synthesis process. The DNA sequence was evaluated for the presence of 58 confirmed mtDNA pathogenic variants and large mtDNA deletions. Any identified variant is confirmed by conventional dideoxy sequence analysis or other methods.
Maternally inherited diabetes and deafness
Wolfram Syndrome
RCAD Renal cysts and diabetes
Optic atrophy
Retinitis Pigmentosa
Prader Willi Syndrome
Alstrom Syndrome
Bardet-Biedl Syndrome
Leprechaunism
Rabson-Mendenhall Syndrome
Partial Lipodystrophy
Mandibular Dysplasia with Deafness and Progeroid features (MDP/POLD1) Syndrome
Hattersley et al., Diabetes Genes
Our patient...

- Fetal Echo WNL except possible PAC’s
- No signs of preterm labor
- Plan for patient to be hospitalized until delivers
Patient’s course...

- 24 days after admission, at GA 25w4d, patient went into active preterm labor
  - Spontaneous NSVD
  - Failure of attempted manual extraction of the placenta → D&C

- Baby in NICU

- Patient discharged 5 days later
Follow-up

- Patient asked to follow-up with UCMC Endo clinic at least once but reports she prefers to follow in Indiana due to insurance issues

- Tried to call several times but patient not responsive

- Geneticist called patient twice about genetic testing results and official diagnosis, but patient not responsive

- Baby still in NICU with grade IV IVH and patient has been visiting
References