A girl with developmental delay and a high CK

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Chief Complaint

• 4 yo Russia-born Armenian girl
  • learning disability
  • motor delay
Developmental stages

Born at full term via NSVD

@ 7-8 months, she sat up unsupported

@ 18 months, she began to walk

@ 3-4 yo, she started running
Review of Systems

• Pertinent positives:
  • learning disability
  • muscle weakness
  • hypotonia
  • frequent falls
Review of Systems

• Pertinent negatives:
  • diplopia
  • ptosis
  • vision loss
  • contracture
  • chest pain/palpitation
  • rashes or birthmarks
Previous work up in Moscow, Russia

• At age of 4
  • 3/2007: negative for Angelman Syndrome
  • 1/2007: negative examination for deletion in regions of chromosome 17, Smith-Magenis Syndrome
  • chromosome analysis: 46, XY, het 15
  • Serum examination: NO evidence of any hereditary aminoacidopathies, organic acidurias and defects of mitochondrial beta-oxidation
Previous work up

At age of 9

• 3/2011: Negative for deletion of exon 7 and 8 of the SMN gene

• 7/28/2011
  • CK: **2840**
  • Aldolase: **36.7**
  • Lactate/Pyruvate ratio: **19.27**
EEG at age of 9

- The main rhythm **does not meet the norm** for the given age group (N – 9Hz and higher).
  - Sleep is superficial
  - Marked diffuse changes of the cortex BEA.
  - Malfunction of the midline structures of the **basal-diencephalic level**
  - Complexes of sharp-slow wave type moderately above the background, diffuse (on the right and left), predominantly in the **left temporal-parietal** region are recorded.
Imaging/Studies:

• 5/3/2011 MRI Pelvis/Femur: Nonspecific mild muscular atrophy
• 5/20/2011 Echo: Normal ventricular size and function
• 5/25/2011 MRI Brain: Normal non-contrast and contrast MRI of the brain
• 6/9/2011 Left quadriceps muscle biopsy: muscular dystrophy, type undetermined
MRI brain @ 9 y.o.
MRI of proximal muscles @ 9 y.o.
Referred to UCLA...
Physical Examination

• General: Well-appearing, alert, active child. Appears smaller than stated age
• HEENT: normal
• Lungs: CTAB
• Heart: RRR, 1+/6 systolic murmur
• Abdomen: NABS
• Extremities: No cyanosis, clubbing or edema
• Skin: No birthmarks or skin lesions
Neurological examination

• MS: AAO x 3

• Language/Speech:
  • Follows command
  • Only answers simple questions in Armenian
  • Avoid eye contacts

• Cranial nerves 2-12: normal
Motor: MRC 4 BUE and MRC 3 BLE. No obvious calf hypertrophy.

Sensory: intact

Coordination: FNF intact

Reflexes: 1+ and symmetric at biceps, triceps, brachioradialis, patella; 2+ and symmetric at Achilles; toes down-going.

Gait: wide based with slight toe walking. + Gower’s sign.
Summary

9 y.o. girl
  Developmental delay
  Short stature
  Lower extremity weakness
  HyperCKemia
  Abnormal MRI pelvis.
Impression

A Muscle and Brain condition

DDx:

? DMD/Becker
? Dystroglycanopathy (LGMD 2I)
? Myotonic dystrophy
? Others
EMG

EMG

<table>
<thead>
<tr>
<th>Side</th>
<th>Muscle</th>
<th>Nerve</th>
<th>Root</th>
<th>Ins Act</th>
<th>Fibs/PSW</th>
<th>Fasc</th>
<th>Other</th>
<th>Amp</th>
<th>Dur</th>
<th>Poly</th>
<th>Recrt</th>
</tr>
</thead>
<tbody>
<tr>
<td>Right</td>
<td>AntTibialis</td>
<td>Dp Br Peron</td>
<td>L4-5</td>
<td>Nml</td>
<td>None</td>
<td>None</td>
<td>None</td>
<td>Nml</td>
<td>Nml</td>
<td>Nml</td>
<td>Nml</td>
</tr>
</tbody>
</table>

Results:
Because of patient discomfort, testing was limited to EMG of one muscle, the right anterior tibialis, which was normal.

Impression:
This is a normal study. There is no electrodiagnostic evidence of muscle membrane instability in the right anterior tibialis muscle.
Laboratory studies

- CK 2840, 2343
- Aldolase 36.7
- Myotonic dystrophy 1 and 2 – negative
- Lactic acid 2.12
- Pyruvic acid 0.11
Impression

A disease of muscle and brain

DDx:

? DMD/Becker
? Dystroglycanopathy (LGMD 2I)
? Myotonic dystrophy
? Others
Targeted Genetic Testing

Variance of unknown significance

<table>
<thead>
<tr>
<th>Exon</th>
<th>DNA Sequence Variation</th>
<th>Effect</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>10</td>
<td>c.1698 C&gt;T, Heterozygous</td>
<td>p.His566His</td>
<td>rs4641</td>
</tr>
</tbody>
</table>
Muscle biopsy requested for review at UCLA
Trichrome
NADH
Dystrophin staining
Selected immunohistochemistry

• Alpha Sarcoglycan Positive
• Beta Sarcoglycan Positive
• Gamma Sarcoglycan Positive
• Alpha Dystroglycan Positive
Differential Diagnosis

- DMD/Becker
- Dystroglycanopathy (LGMD 2I)
- Myotonic dystrophy
- Others
Others ...

- Bethlem congenital muscular dystrophy
- congenital muscular dystrophy type 1A (MDC1A; merosin-deficient CMD)
- congenital muscular dystrophy type 1B (MDC1B)
- congenital muscular dystrophy type 1C (MDC1C)
- congenital muscular dystrophy type 1D (MDC1D)
- congenital muscular dystrophy with integrin deficiency
- Fukuyama congenital muscular dystrophy
- LMNA-related disorders
- muscle-eye-brain disease
- rigid spine muscular dystrophy (RSMD1)
- SEPN1-related disorders
- SYNE1-related disorder
- Ullrich congenital muscular dystrophy
- Walker-Warburg syndrome

And OTHERS ...
Summary

9 y.o. girl with

- development delay
- proximal muscle weakness
- eccentrically located giant granules with central pallor
- mitochondrial involvement

Suspicious for Mitochondrial myopathy
To confirm our suspicion

- Requested EM which was done in Children’s hospital
- Sent out Whole exome sequencing
Whole Exome Sequencing

• Three heterozygous variants were identified in CHKB gene
  • c.151C>T
  • c.847G>A
  • c.902C>T
Choline Kinase Beta (CHKB)

c.151C>T
Premature termination mutation

c.847G>A (AR)
c.902C>T ? pathogenic
Trio Next Generation Sequencing

Father c.847G>A
Mother c.151C>T
Choline Kinase Beta Muscular Dystrophy

• First described In 1964 and 1966
  • Shy and Gonatas and Shy et al described children with myopathy and giant mitochondria and dubbed this condition “megaconial myopathy.”
• AR, loss of function mutation
• Found on Cx 22
• CK elevated
Choline Kinase Beta Muscular Dystrophy

• Most characteristic phenotypic features
  • intellectually delay (delay of speech and language and autism spectrum disorder)
  • progressive proximal muscle weakness,
  • approximately 50% of reported patients have cardiac involvement
Unique Histological Features

- Gigantic mitochondria
  - Megaconial
- Peripheral placement
- Central devoid of organelles
Genetic confirmation

Nishino et al group published first genetic mutation responsible for this unique megacononial muscular dystrophy

• The similarities of these clinical and morphological features with those of a spontaneous mutant mouse harboring a loss-of-function mutation in the choline kinase beta gene (Chkb)
Choline kinase beta Muscular Dystrophy

• They found deleterious mutations in all patients and defined the molecular basis of this congenital megaconial muscular dystrophy

• Stereotypic phenotypes
  • Language
  • ? Autism
  • proximal muscle weakness
| Table 1 | Characteristics of the patients with CHKB gene mutations |
|---|---|---|---|---|---|---|---|---|
| Patients | 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8 |
| Age at presentation | 4 years 1 month | 14 months | 6 years 2 months | 38 days | 12 months | 17 years | 3 years | 4 years |
| Gender | M | M | M | F | M | F | F | F |
| Current age | 12 years 6 months | Died at age 2 years 1 month | Died at age 7 years 4 months | 8 years 2 months | 18 years 10 months | 23 years 8 months | 23 years 3 months | 9 years 2 months |
| Presenting symptom | Ichthyosis, ID (Birth) | Motor developmental delay (14 months) | Proximal weakness ID | Foot deformity, intracardiac cardiac defect (PDA) | ID, proximal weakness | Developmental delay, hyperactivity, delay in language, hand biting (2 years) | Delay in walking | Delay in language and walking |
| Age at independent walking | 2 years 1 month | Not able to walk | 3 years | Not able to walk at age 21 months | 24 months | 3 years | 3 years | Not able to walk at age 6 years 6 months |
| Language skills | No words at age 4 years 6 months | Single words at age 15 months, no increase in number of words by 21 months of age | No words at age 14 months | Single words: 3–4 years, mild ID at age 12 years | Single words: 3 years | Single words: 5 years | Simple 2-word sentences: 6 years 6 months |
| Consanguinity/family history | 2nd degree/N | 1st degree/ Y | 1st degree/ Y | 1st degree/ N | 1st degree/ N | Y (3.5 years, generalized tonic seizure) | N | N |
| Seizures | N | N | N | Y (generalized tonic seizures with an onset at 9 years of age) | N |
| Autistic features/behavioral problems | Severe, aggressive, anxious behaviors, stereotypical hand movements, head banging, self mutilation | N | Hyperactivity | N | Severe behavioral problems, stereotypical hand biting, short eye contact | N | Stereotypical head movements, echolalia, autistic features, aggressive behavior, crying attacks, sleep disorder |
| Skin findings/age at recognition | Ichthyosis, exfoliative desquamative, diffuse lesions, Skin biopsy: Ichthyosis congenita/Birth | Ichthyosis/4 years | Ichthyosis (face and genital region)/8 months | Diffuse ichthyosis (forehead, face, body)/17 years | Ichthyosis (neck and trunk desquamation)/11 years | ICHTHYOSIS (at birth, became prominent at age 12 months, recognized at the age of 4 years), diffuse, around umbilical region desquamation and xerosis | N |
| Dysmorphic features | Atypical face, prominent nasal bridge and ears, distal laxity | N | N | High arched palate, facial hypomimia, distal laxity | N | N | N | Hyperelorism, low set ears, long face |
| ID Serum CK level (U/L) | Severe ID 3X | NA | Moderate ID Normal | NA | Mildly elevated | Severe ID 9X | Severe ID N-3X | Moderate ID Mildly elevated |
| Normal:≤300 U/L | ECHO normal (6 years), decreased left | ECHO: dilated CMP (21 months) | ECHO normal (6 years 2 months) | Fetal and neonatal | ECHO: normal (14 years) | ECHO: normal (17 years) | ECHO: normal (17 years) | ECHO: normal (7 years) |

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Background

• Choline kinase (CK) was discovered in 1953.

• Two genes encode choline kinase, *Chka* and *Chkb*, and 3 isoforms of the enzyme have been identified — CKα-1, CKα-2, and CKβ — and the active form of CK is a hetero- or homo-dimer.
Choline kinase beta function

• Defect in choline kinase beta activity in muscle, and different distribution of choline kinase isoforms in muscle and brain describe varying degrees of phenotype in the mouse model and patients (Wu et al 2010; Mitsuhashi et al 2011a, b)

• In addition, mitochondrial dysfunction in muscle is described both in mutant mice and patients with CHKB mutations (Mitsuhashi et al 2011a, b; Gutierrez Rios et al 2012; Castro-Gago et al 2014)
Proposed pathogenesis

• The relationship between phospholipid abnormality and mitochondrial dysfunction could be explained by
  • Upregulation of a second alternative pathway
  • MAM dysfunction leading to altered mitochondrial dynamics, resulting in increased size and intracellular displacement of mitochondria
Proposed pathogenesis

• Defect in choline kinase beta activity in muscle, and different distribution of choline kinase isoforms in muscle and brain describe varying degrees of phenotype in the mouse model and patients.

• In addition, mitochondrial dysfunction in muscle is described both in mutant mice and patients with CHKB mutations.
Alternative pathogenesis

*CHKB*, which is located on chromosome 22q13.33, is immediately upstream of *CPT1B* (carnitine palmitoyltransferase 1B)
- a key lipid transport enzyme located in the mitochondrial outer membrane
- Downstream effect
  - mitochondria resulting from alterations in overall fatty acid metabolism due to the effects on *CPT1B*, ultimately affecting mitochondrial respiratory chain activity.
Conclusion

• Muscle and brain disease
• Role of choline kinase beta gene is important for both brain and muscle development
• Two possible pathogenesis has been proposed including MAM pathway and CPT1B (down stream effect)
References

- Gengshu Wu, Dennis E. Vance. Choline kinase and its function. This paper is one of a selection of papers published in this special issue entitled “Second International Symposium on Recent Advances in Basic, Clinical, and Social Medicine” and has undergone the Journal’s usual peer review process.


Proposed mechanism

• It has been shown that this hindlimb muscular dystrophy is due to decreased biosynthesis of phosphatidylcholine and increased catabolism of phosphatidylcholine in the hindlimbs, but not the forelimbs, of mice.

• In the mid 1950s it was clear that choline kinase was important for the biosynthesis of phosphatidylcholine, but no one predicted a role for choline kinase in muscular dystrophy, bone deformities, or cancer.
Table 1  Characteristics of the patients with CHIKI gene mutations

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<th>3</th>
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<th>5</th>
<th>6</th>
<th>7</th>
<th>8</th>
</tr>
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<tbody>
<tr>
<td>Age at presentation</td>
<td>4 years 1 month</td>
<td>14 months</td>
<td>6 years 2 months</td>
<td>38 days</td>
<td>12 months</td>
<td>17 years</td>
<td>3 years</td>
<td>4 years</td>
</tr>
<tr>
<td>Gender</td>
<td>M</td>
<td>M</td>
<td>M</td>
<td>F</td>
<td>F</td>
<td>F</td>
<td>F</td>
<td>F</td>
</tr>
<tr>
<td>Current age</td>
<td>12 years 6 months</td>
<td>12 years 6 months</td>
<td>8 years 2 months</td>
<td>8 years 2 months</td>
<td>18 years 10 months</td>
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<td>Consanguinity/family history</td>
<td>Seizures</td>
<td>N</td>
<td>1st degree/ Y</td>
<td>1st degree/ Y</td>
<td>1st degree/ N</td>
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<td>Severe behavioral problems, stereotypical head movements, echolalia, autistic features, aggressive behavior, crying attacks, sleep disorder</td>
<td>Ichthyosis (at birth, became prominent at age 12 months, recognized at the age of 4 years), diffuse, around umbilical region desquamation and xerosis</td>
<td>N</td>
<td></td>
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<td>Autistic features/behavioral problems</td>
<td>N</td>
<td>Y</td>
<td>N</td>
<td>N</td>
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<td></td>
</tr>
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<td>Skin findings/age at recognition</td>
<td>Ichthyosis, exfoliative desquamative diffuse lesions, Skin biopsy; ichthyosis congenita/Birth</td>
<td>Ichthyosis/4 years</td>
<td>Herpetic skin lesion (gastrointestinal region)</td>
<td>8 months</td>
<td>Diffuse ichthyosis (forehead, face, body) 17 years</td>
<td>Diffuse ichthyosis (neck and trunk desquamation) 11 years</td>
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<td>N</td>
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<td>N</td>
<td>N</td>
<td>N</td>
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<td>ID Serum CK level (U/L)</td>
<td>Normal≤300 U/L</td>
<td>Severe ID 3X</td>
<td>Moderate ID Normal</td>
<td>NA</td>
<td>Mildly elevated</td>
<td>Mild ID 3X</td>
<td>Severe ID 9X</td>
<td>Severe ID N-3X</td>
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<td>Cardiac evaluation</td>
<td>ECHO normal (6 years), decreased left</td>
<td>ECHO: dilated CMP (21 months)</td>
<td>ECHO normal (6 years 2 months)</td>
<td>Fetal and neonatal ECHO: PDA</td>
<td>ECHO: normal (14 years)</td>
<td>ECHO: normal (17 years)</td>
<td>ECHO: Seudan ASD (1 years, 17 years)</td>
<td>ECHO: normal (7 years)</td>
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