Neurodevelopmental
Precision Medicine
Europe

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Name: Albana Qemali
DOB: 11/13/2013
Sex: Female
Interview with Parents and patient
Follow-UP
Today: May 6 2025

Interim
Not taking B12/folinic acid because of availability. Without more anxiety.
Worse the week before menses
Muscle pain after being on jumper for a long time, relieved by masage, no different with B12.
Understands more and more. Socially behaving better. Wants to learn other language. Limited ability to expressive with sentences. Short phrases. Little progress with expressive speech.

EnergyNeeds and Ubiquinol – Limited intake because of reflux

Labs Oct 17 2024
Increased Esterified to free carnitine
High normal Alanine, A/L 2.9
Low CoQ10, Vit D
CBC, CMP ok
Pyruvate low
MTHFR 1298 Hetero
UOA normal

Labs April 16 2025
Low Zinc and High Copper – zinc deficiency
Ceruloplasmin Low
Esterified to free carnitine now normal - good
CoQ10 now high - good
Alanine high and A/L now 3.5 - ongoing mitochondrial dysfunction
Homocysteine 6.7 - good
Ferritin 22 - good
Vit D 47 – normal now - good
Pyruvate increased – ongoing mitochondrial dysfunction

Last Visit: September 30, 2024
Ran out of B12/FA without any change.
For anything oral she has stomach discomfort

FOLLOW UP ON LINE CONSULTATION

Antibiotics for illnesses has caused behavior and language regression
Stopped Bumex and Memantine

Previous Labs
Q10 high
Pyruvate normal
Lysosomal oligosaccharides normal
S100B 0.14 (<0.1.05)

Mito Swab
CS 177%
C4 25%
C1 15%
C2 68%

Previous Recommendations

Workup for possible CONGENITAL DISORDER OF DEGLYCOSYLATION 1
- Urine oligosaccharides
- Blood alpha-fetoprotein

Workup for possible COQ4 deficiency
- CoQ10 level after one week without supplementation.

Possible ACAD9 – Complex I Deficiency
- Avoid Aspirin
- Consider Riboflavin Supplementation
- Mito-Swab to look for complex I deficiency

Fasting before breakfast
- Ammonia – slightly elevated 51 (17-50) / Normal 45
- Complete Metabolic Panel (CMP) – normal
- lactic acid – 3,8 (H)
- Acylcarnitine profile – summary normal
  Carnitine slightly elevated free on supplementation
- Pyruvate – not done
- homocysteine – normal 6.1
- Amino acids analysis, Plasma(Quantitative) – A/L 2.8 (H)
- Urine Organic Acids – Succinic high, 2-oxogluteraric low, hydroxybutyric high
- Urinary orotic acid
  NSE 16 – normal x 2
  S-100 0.242 (<0.105)
  CRP 0.2 (<5)
  IL-1B <5
  IL-8 normal
  CH-50 normal
  Vit D 57
  TSH ok

FOLLOW UP ON LINE CONSULTATION

Repeat after a large protein meal (protein shake: Premier Protein Shake 30g protein)

- Ammonia – 68 (18-72)
- Complete Metabolic Panel (CMP)
- lactic acid – 3.4 (H)
- Acylcarnitine profile – not calculated
- Pyruvate
- homocysteine
- Amino acids analysis, Plasma(Quantitative) – Alanine 1034, A/L 4.4, Citrulline 62 (1-46) and Arginine 269 (10-140)
- Urine Organic Acids – hydroxybutyric, Fumaric, 3-methylcrotonylglycine, Tiglyglycine high
- Urinary orotic acid

Genetics Workup:

- Whole Genome Sequencing Trio
  - CLPB – VUS – 3-methylglutaconic aciduria. Produces stop, No examples in ClinVar but no found in the general population. Very severe disease. No 3-methylglutaconic aciduria in the urine
  - BSCL2 – heterozygous -- ENCEPHALOPATHY, PROGRESSIVE, WITH OR WITHOUT LIPODYSTROPHY – inconsistent with patient phenotype
  - CSGALNACT1 -- SKELETAL DYSPLASIA, MILD, WITH JOINT LAXITY AND ADVANCED BONE AGE – inconsistent with patient phenotype
  - DHTKD1 -- DEHYDROGENASE E1 AND TRANSKETOLASE DOMAINS-CONTAINING PROTEIN 1 – inconsistent with patient phenotype, no elevation in adipic acid
  - NGLY1 – Manifestations below

    - **NEUROLOGIC**
    - *Central Nervous System*
      - Global developmental delay - yes
      - Hypotonia - yes
      - Involuntary movements - no
      - Myoclonic jerks – no
      - Epilepsy, multifocal, intractable - no
      - Regression of motor development - no
      - Prominent perivascular spaces with surrounding gliosis in periatrial white matter - no
      - Delayed myelination, mild - no
    - *Peripheral Nervous System*
      - Hyporeflexia
      - Peripheral neuropathy
    - **METABOLIC FEATURES**
      - Abnormal urine oligosaccharides (keratan sulfate, heparan sulfate, and chondroitin sulfate)

- Normal transferrin isoelectric focusing test
- Normal N-glycan analysis

- **ENDOCRINE FEATURES**
  - Adrenal insufficiency
- **LABORATORY ABNORMALITIES**
  - Increased blood lactate (in some patients)
  - Elevated alpha-fetoprotein (in some patients)

- CPS1 – AR disorder but one defect perhaps causes milder disease, can explain mild increase in ammonia but citrulline and arginine are usually low and in this case they are elevated
- COQ4 – coQ biosynthesis pathway deficiency
- ACAD9 -- MITOCHONDRIAL COMPLEX I DEFICIENCY, NUCLEAR TYPE 20 – VUS thought to be benign

- **CARDIOVASCULAR**
- *Heart*
  - Cardiomyopathy, dilated
  - Cardiomyopathy, hypertrophic
  - Congestive heart failure

- **ABDOMEN**
- *Liver*
  - Liver failure
  - Microvesicular steatosis
  - Decreased mitochondrial complex I activity

- **MUSCLE, SOFT TISSUES**
  - Muscle weakness
  - Hypotonia
  - Exercise intolerance
  - Decreased mitochondrial complex I activity

- **NEUROLOGIC**

  Central Nervous System
  - Encephalopathy
  - Cerebellar stroke
  - Cerebral edema

- **METABOLIC FEATURES**
  - Reye-like episode
  - Hypoglycemia
  - Lactic acidosis

- **HEMATOLOGY**

- - Thrombocytopenia

- **LABORATORY ABNORMALITIES**
- - Hypoglycemia
  - Elevated plasma ammonia
  - Elevated liver transaminases
  - Elevated serum lactate
  - Elevated lactate dehydrogenase
  - Elevated prothrombin time
  - Hypoketotic dicarboxylic aciduria (in some patients)
  - Elevated long-chain acylcarnitine species (in some patients)

- **MISCELLANEOUS**
- - Onset usually in infancy
  - Clinical presentation varies
  - Onset may be precipitated by viral infection, Reye-like episode following ingestion of aspirin
  - Favorable response to treatment with riboflavin

Aim for Original Visit: Verbal communication is lacking. Previous treatments did not completely improve communication. Dx with Autoimmune encephalitis and mitochondrial dysfunction.

Medical Hx: see albana.spa.mk

Overview:
Pregnancy history:
Problems during pregnancy: Migraines and Fever / Infection without abx
Supplements: Folate, MVI
Pregnancy length: Full Term.
Type of delivery: FTP after induction -> c/s with Loose cord.
Problems after delivery in child: Jaundice.
Birth Exam: patent foramen ovale which closed spontaneously. Lipoma on back at 2 days of age.

Early Life:
Breastfeeding: First 9 months almost exclusively for first 6 months.
Switch to solids: 6 months started
Sleep: not good. Needed to be soothed to sleep.
Ear Infections: Multiple with recurrent abx
Reported reactions to vaccine with falling asleep / lethargy without fever or rash. AT 6 months developed strabismus after DTP

Developmental history:
Mama / dada said specifically at 36 months.
Walked at 20 months.

Pointed at 44 months.
Neurodevelopmental Regression: None
Developmental problem first suspected at: 2 years of age.
Diagnosis of autism made at 3 years of age months.
Other Developmental Diagnoses Include: Speech, motor and global delay at 2 years
Therapies started included ABA.

Current Therapies:
Mitochondrial Protocol improvements in putting words together.

Medical Issues:

Drug Allergies: NKDA

Previous Therapies:
Namecheck protocol with minor improvements.
Ukraine treatment with IVIG 2g/kg combined with immunosuppression Aug 2021 -> Jan 2022, improved sleep and social interactions. Now on Oral IgG.
TRS nasal spray resolved strabismus.

Current Medications
1. Risperidone 1mg/ml Oral Solution, take 0.5ml once a day at 20:00.
2. Carbamazepine retard 200mg 2 times a day (200mg in morning at 200mg at night).
3. Cromoglycic acid (or sodium cromoglicate - Allergoval) 200mg 3 times a day before the
main meals.
4. Leukovorin tablets 15 mg twice a day.

Supplements at original visit

Immunoglobulins IgG, IgM, IgA for oral intake
Mitochondrial cocktail" - metabolic supplements for regular use
1. Vitamin D 5000 IU daily.
2. Ubiquinol 200mg 3 times a day.
3. Acetyl-L-carnitine 750mg 3 times a day before meals.
4. Ascorbic acid 50mg a day.
5. Alfa lipoic acid 150mg / day.
6. Vitamin E 100 IU daily.
7. Citrulline malate take 2 grams at morning and evening.
8. Glutathione take 100mg in morning and evening.
9. Resveratrol 500-600mg daily.
10.Niacinamide 500mg daily in morning.
11.Inosine take 500mg 3 tablets a day.

Neurologic
MRI: Left temporal arachnoid cyst.
EEG: Low amplitude.

Metabolic:
Homocysteine normal
MTHFR Homozygous for 1298
MTRR meter for 66 A>G
Ammonia elevated
Lactate and L/P elevated
Amino Acids overall low.
FRAT double negative
Self Restricts meat

Nutritional:
Vit D: low normal

Endocrine:
Total T4 ok

Immune abnormalities:
NSE and S100B were elevated initially but improved.
ANA normal
C3c, C4 ok
IgG ok
EST ok
Neutrophil myeloperoxidase activity low initially but then improved with therapy
Cunningham Panel: Elevated D1 and Anti-Tubulin. CamKinase II 170.

Genetic Workup:
Mito Nuclear Panel: Several VUS, particular carbamoylphosphate synthetase I gene

Social Hx: Lives with Biological Mother, Father.

Family history:
Mother late talker.
No family history of autism.
No family history of seizure or other neurological disorders
No family history of mitochondrial disease
Mom dx Sjogren's syndrome, otherwise no other family history of lupus, rheumatoid arthritis, Crohn's disease, ulcerative colitis, or celiac disease
Diabetes on mom's side

Examination
Wt: 45kg, Ht 146cm

Upset crying
Large subcutaneous lipoma on right lower back which is stable by ultrasounds.

IMPRESSION:

FOLLOW UP ON LINE CONSULTATION

The following problems seems to be:
Mitochondrial Dysfunction given biomarkers, motor delays. Mitochondrial dysfunction can compromise transport of folate into the nervous system.

PLAN:

GI
- Doctors Data Comprehensive Stool Analysis
- GI Consultation for Reflex as it may be a source of pain

Mitochondrial Support
- Continue Ubiquinol 100mg twice a day (Morning and Afternoon)
- Continue EnergyNeeds by Neuroneeds (Morning and Afternoon)(https://www.neuroneeds.com/product/energyneeds/) 3 capsules twice a day
- Add L-Carnitine 500mg twice a day
- Add Creatine Monohydrate 500mg twice a day

Central Folate Leucovorin
- Liquid L-Leucovorin (25mg/ml) 1ml twice a day (Morning and Afternoon)
- Start at ½ ml twice a day for two weeks and then increase to full dose

Follow-Up: 3 months zoom

Time: 1hr face to face

Diagnostic Codes
Encephalopathy [G93.40 (348.30)]
Mixed receptive and expressive developmental Language Disorder [F80.2]
Sleep disorder [G47.9 (780.50)]

Coding
99214 – Level 5 Follow-Up, 60 minutes

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