TWO CASES WITH GAIT DIFFICULTY AND STIFFNESS

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CARRELL KRUSEN SYMPOSIUM

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CASE # 1

• 68 YEAR OLD MALE PATIENT WHO PRESENTS WITH 10 YEAR HISTORY
  • GAIT DIFFICULTY
  • STIFFNESS
  • LEGS WEAKNESS
  • MUSCLE SPASMS
  • NUMBNESS IN THE FEET

• PMH: ADDISON DISEASE, HEPATITIS

• GRADUALLY PROGRESSED, STARTED USING CANE IN 2007 AND WHEELCHAIR IN 2014
CASE # 2

• 64-YEAR-OLD FEMALE WHO PRESENTS WITH 8 YEAR HISTORY
  • GAIT DIFFICULTY WITH MULTIPLE FALLS
  • STIFFNESS

2 MONTH HISTORY
  • MUSCLE SPASMS
  • INCONTINENCE

SHE STARTED USING A CANE 2 YEARS PRIOR TO COMING TO OUR CLINIC
## NEURO EXAM

<table>
<thead>
<tr>
<th></th>
<th>Case 1</th>
<th>Case 2</th>
</tr>
</thead>
<tbody>
<tr>
<td>Motor examination</td>
<td>HF4, HABD 4</td>
<td>RKF 4+, RHE 4, BL TE 4+</td>
</tr>
<tr>
<td>Sensory examination</td>
<td>PP : decreased below the knees</td>
<td>Intact LT, PP and proprioception. Vibration : 7 seconds at the toes</td>
</tr>
<tr>
<td></td>
<td>Vibration : absent at the toes</td>
<td></td>
</tr>
<tr>
<td>Reflexes</td>
<td>Brisk with clonus at the ankles</td>
<td>Brisk with clonus at the ankles</td>
</tr>
<tr>
<td>Plantar responses</td>
<td>Extensor</td>
<td>Extensor</td>
</tr>
<tr>
<td>Gait</td>
<td>Spastic Needs assistance to walk</td>
<td>Spastic Using cane</td>
</tr>
</tbody>
</table>
? DIAGNOSIS AND WHAT TESTS?
## Diagnostic Testing

<table>
<thead>
<tr>
<th></th>
<th>Case #1</th>
<th>Case #2</th>
</tr>
</thead>
<tbody>
<tr>
<td>Vitamin B12</td>
<td>206</td>
<td>1430</td>
</tr>
<tr>
<td>COOPER</td>
<td>84</td>
<td>1.50</td>
</tr>
<tr>
<td>HIV</td>
<td>NEG</td>
<td>NEG</td>
</tr>
<tr>
<td>Syphilis Ab</td>
<td></td>
<td>NEG</td>
</tr>
<tr>
<td>HTLV I/II</td>
<td></td>
<td>NEG</td>
</tr>
</tbody>
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**NCS/EMG**

**Case #1:** Sensory-motor demyelinating polyneuropathy, moderate to severe

**Case #2:** Sensory-motor demyelinating polyneuropathy, mild
DIAGNOSTIC TESTING

IMAGING

CASE #1
- MRI OF THE BRAIN: NORMAL
- MRI C-SPINE: UNREMARKABLE

CASE #2
- MRI OF THE BRAIN: MINERALIZATION WITHIN THE GLOBUS PALLIDUS BILATERALLY AS SEEN IN THE CT FINDINGS
- CT C-SPINE: UNREMARKABLE
DIFFERENTIAL DIAGNOSIS

PROGRESSIVE SPASTIC PARAPARESIS WITH SENSORY SYMPTOMS

- MYELOPATHY VS MYELONEUROPATHY
  - MULTIPLE SCLEROSIS
  - VITAMIN B12 AND COOPER DEFICIENCY
  - INFECTIOUS (HIV, HTLVI/II, NEUROSYPHILIS, NEUROBORRELIOSIS)
  - SPINAL CORD STRUCTURAL LESIONS SUCH AS TUMORS
  - VASCULAR LESION OF THE CORD, AV FISTULA
  - ADRENOLEUKODYSTROPHY, ADRENOHYELOONEUROPATHY
  - HEREDITARY SPASTIC PARAPARESIS (SCA, FRIEDREICH ATAXIA, AUTOSOMAL RECESSIVE SPASTIC ATAXIA)
  - PLS (SENSORY SYMPTOMS WOULD BE LESS LIKELY)
DIAGNOSTIC TESTING

VLCFA

• **CASE #1:** RATIOS OF C24/22 AND C26/22, HIGHER THAN NORMAL. CONSISTENT WITH A DEFECT IN PEROXISOMAL FATTY ACID OXIDATION, SUCH AS X-LINKED ALD OR AMN

• **CASE#2:** THE CONCENTRATIONS OF C26:0, C22:0 AND THE C26/C22 RATIOS WERE ABNORMAL. INDICATIVE OF POSSIBLE HETEROZYGOSITY FOR X-LINKED ALD

GENETICS

• **CASE #1:** PATHOGENIC GENE IDENTIFIED IN THE POSITION NT907A, TYR174CYS. DETECTED IN 93% OF ABCD1 MUTATIONS

• **CASE #2:** PATHOGENIC VARIANT IDENTIFIED IN ABCD1, C1998C.A (P.TYR666*) HETEROZYGOUS, ASSOCIATED WITH X-LINKED ALD, A CARRIER FOR ALD

DIAGNOSIS: ADRENOMYELONEUROPATHY
DISCUSSION

ADRENOLEUKODYSTROPHY (ALD):

- PEROXISOMAL DISORDER OF BETA-OXIDATION
- ACCUMULATION OF VERY LONG CHAIN FATTY ACIDS IN ALL TISSUES
- FREQUENCY: 1 IN 21,000 FOR HEMIZYGOTES; 1 IN 16,800 FOR HEMIZYGOTES PLUS HETEROZYGOTES
- X-LINKED DISORDER
- IT IS CAUSED BY MUTATIONS IN THE (ATP)-BINDING CASSETTE (ABC), SUBFAMILY D, MEMBER 1 GENE (ACD1 GENE), LOCATED AT XQ28, THAT ENCODES AN ABC TRANSPORTER
- PRIMARILY AFFECT THE (CNS), ADRENAL CORTEX, AND LEYDIG CELLS IN THE TESTES
- PRESENTS AS RAPIDLY PROGRESSIVE CHILDHOOD CEREBRAL DISORDER

- ALD CONSISTS OF A SPECTRUM OF PHENOTYPES INCLUDING ADRENOMYELONEUROPATHY (AMN)
- THESE CONDITIONS ARE KNOWN AS THE ALD/AMN COMPLEX
ADRENOAMYELONEUROPATHY

• PRESENTS IN ADULTS MALES BETWEEN 20 AND 40 YEARS OF AGE (AVERAGE 28 YEARS)

• SYMPTOMS AND SIGNS:
  • SPINAL CORD DYSPFUNCTION (SPASTIC PARAPARESIS)
  • ABNORMAL SPHINCTER CONTROL,
  • SEXUAL AND GONADAL DYSPFUNCTION MAY PRECEDE MOTOR ABNORMALITIES
  • ADRENAL INSUFFICIENCY
  • CEREBRAL INVOLVEMENT IS RARE, OCCURRING IN 6% OF THE PATIENTS
  • PROGRESSIVE CEREBELLAR DISORDER

• FEMALE CARRIERS DEVELOP MYELOPATHY SYMPTOMS IN ADULTHOOD
  • ONSET >35 YEARS OLD
  • MILD SYMPTOMS

• LONG-TERM FOLLOW-UP STUDIES REPORT BRAIN INVOLVEMENT IN 20%-60%
DIAGNOSIS

• PLASMA CONCENTRATION OF VLCFAs ELEVATED IN NEARLY ALL MALES WITH THE ALD/AMN COMPLEX

• GENETIC TESTING IS CONFIRMATORY

• ADRENAL FUNCTION TESTING SHOULD BE PERFORMED AT THE TIME OF DIAGNOSIS AND RE-EVALUATED YEARLY

• ALL CONFIRMED ALD/AMN COMPLEX WILL NEED (MRI) OF THE BRAIN.
TREATMENT

• CHILDHOOD CEREBRAL ALD
SUPPORTIVE CARE
ALLOGENIC HEMATOPOIETIC CELL TRANSPLANTATION (HCT)
INVESTIGATIONAL: GENE THERAPY FOR BOYS WITH EARLY CEREBRAL ALD WHO DO NOT HAVE A MATCHED RELATED DONOR FOR ALLOGENIC HCT

• ADRENOMYELONEUROPATHY
SUPPORTIVE
NO BENEFIT REPORTED WITH HEMATOPOIETIC STEM CELL TRANSPLANTATION

• ADRENAL INSUFFICIENCY
LIFELONG CORTICOSTEROID REPLACEMENT THERAPY

DIETARY MODIFICATIONS (INCLUDING LORENZO’S OIL) OR STATIN MEDICATIONS TO LOWER VLFCA HAVE NOT DEMONSTRATED CLINICAL EFFICACY
CONCLUSION

• ADRENOMYELONEUROPATHY SHOULD BE CONSIDERED IN THE DIFFERENTIAL OF PATIENTS WITH PROGRESSIVE SPASTIC PARAPARESIS
• FEMALE CARRIERS MAY HAVE SIMILAR SYMPTOMS AS MALE PATIENTS WITH THIS CONDITION
• ADRENAL FUNCTION SHOULD BE MONITORED CLOSELY
• TREATMENT IS MOSTLY SUPPORTIVE FOR ADRENOMYELONEUROPATHY
• QUESTIONS??

• THANKS!!!