TWO CASES WITH GAIT DIFFICULTY AND STIFFNESS

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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

	Case 1	Case 2
Motor examination	HF4, HABD 4	RKF 4+, RHE 4, BL TE 4+
Sensory examination	PP : decreased below the knees Vibration :absent at the toes	Intact LT, PP and proprioception. Vibration : 7 seconds at the toes
Reflexes	Brisk with clonus at the ankles	Brisk with clonus at the ankles
Plantar responses	Extensor	Extensor
Gait	Spatic Needs assistance to walk	Spastic Using cane

? DIAGNOSIS AND WHAT TESTS?

DIAGNOSTIC TESTING

	CASE #1	CASE #2
VITAMIN B12	206	1430
COOPER	84	1.50
HIV	NEG	NEG
SYPHILIS Ab		NEG
HTLV I/II		NEG

NCS/EMG

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

Case #2: Sensory-motor demyelinating polyneuropathy, mild

DIAGNOSTIC TESTING

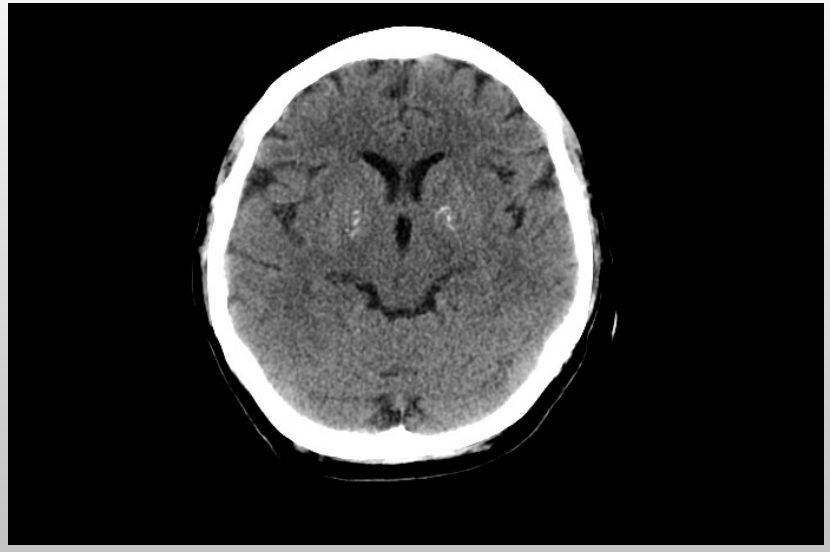
IMAGING

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, ADRENOMYELONEUROPATHY
  - 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

ADRENOMYELONEUROPATHY

- PRESENTS IN ADULTS MALES BETWEEN 20 AND 40 YEARS OF AGE (AVERAGE 28 YEARS)
- SYMPTOMS AND SIGNS:
  - SPINAL CORD DYSFUNCTION (SPASTIC PARAPARESIS)
  - ABNORMAL SPHINCTER CONTROL,
  - SEXUAL AND GONADAL DYSFUNCTION 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
  - MILDER 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!!!**