Case Series of Neuropathy with Ophthalmoplegia and Dysarthria

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Background: Mitochondrial diseases

- Disrupt fundamental cellular energy process resulting in multisystem diseases
- Brain, nerves and muscles are frequently involved with variable severity
- Caused by mutations in nuclear or mitochondrial DNA
- Phenotypic and genotypic variability
  - MERRF, MELAS, SANDO, MNGIE, axonal CMT2 etc

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Objective

- **Describe clinical characteristic and diagnostic features of patients with sensory ataxic neuropathy, dysarthria and ophthalmoparesis (SANDO) at the KUMC**

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Method

- Retrospective chart review of patients with clinical diagnosis of SANDO at the University of Kansas Medical Center

- IRB submission and approval at the University of Kansas Medical Center with exempt status

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Results – Demographics

Participants	n = 5
Gender (M/F)	1/4
Median age at presentation (years)	40
Positive Family History	4/5 (3 siblings)
Muscle biopsy	3
Genetic confirmation	1

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Results – Clinical data

PATIENTS (n=5)	1	2a	2b	2c	3
Age of onset	40	45	45	32	28
Foot numbness onset	51	45	45	33	28
Ocular onset	40, P → D	54, D	55, D	43, D	30, D
Ataxia onset	51	55	55	32	30
Dysarthria onset	52	No	No	No	52
P-ptosis; D-diplopia; 2a, 2b, and 2c-siblings					

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Results – Diagnostic data

PATIENTS (n=5)	1	2a	2b	2c	3
Electrophysiology	Severe axonal, S>M, Irritative myopathy	N.D.	Moderate axonal, S>M, Irritative myopathy	N.D.	Mild axonal, S
Muscle biopsy	>10% COX- and SDH+	>30% COX- and SDH+	N.D.	N.D. .	Non specific myopathy, Mild denervation atrophy
POLG mutation	N.D.	N.D.	N.D. .	No mutation detected	2 VUS likely pathogenic (compound heterozygote)
M-motor, S-sensory, N.D-not done, 2a, 2b, and 2-siblings, VUS-variants of unknown significant					

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Literature review: SANDO

- Autosomal recessive systemic disorder with progressive clinical triad of sensory ataxic neuropathy, dysarthria and ophthalmoparesis (SANDO)
  - Initial sign is neuropathy
    - Large and small fiber sensory loss
    - Variable motor involvement
  - Later signs are ptosis, ophthalmoplegia
    - May also have dysarthria and facial weakness
- Mutation of the gene encoding mitochondrial DNA polymerase gamma enzyme (POLG1)
  - Mitochondrial DNA deletion

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Fadic, R., Russell, J. A., Vedanarayanan, V. V., Lehar, M., Kuncl, R. W., Johns, D. R. Sensory ataxic neuropathy as the presenting feature of a novel mitochondrial disease. Neurology 49: 239-245, 1997.

Literature review: Diagnostic findings

- Electrophysiology
  - Axonal neuropathy with reduced or absent SNAP
  - Distal denervation and occasional proximal myopathy
- Muscle pathology
  - Ragged red fibers
  - COX- and SDH+ fibers
- Genetic testing
  - Multiple POLG mutation ~ 78%
  - PEO1 (twinkle helicase)

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Discussions

- **"SANDO syndrome in a cohort of 107 patients with CPEO and mitochondrial DNA deletions"**
  - **Retrospective analysis**
  - **Identified a total of 11 patients with SANDO**
- **Conclusions**
  - **Most patients initially presented with ataxia**
  - **CPEO followed in the first decade of neuropathy**
  - **Vast majority caused by POLG mutations but other nuclear genes include PEO1**

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Hanisch F. et al. SANDO syndrome in a cohort of 107 patients with CPEO and mitochondrial DNA deletions. *J. Neurol. Neurosurg. Psychiatry*. 2014;*86*:*630–634*. *doi*: *10.1136/jnnp-2013-306748*

Discussions

- In our case series, the most common initial presenting symptom was foot numbness
- Most patients had sensory ataxia and ophthalmoparesis within a decade from symptom onset
- Dysarthria was delayed (12-24yrs.) present in the minority of cases

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Discussions

Presenting symptoms	Present study n = 5	CPEO cohort n = 11
Initial foot numbness	3 (60%)	Not reported
Initial Ataxia	1 (20%)	8 (73%)
Foot numbness/ataxia	5 (100%)	11 (100%)
Initial PEO	1 (20%)	3 (27%)
PEO	5 (100%)	10 (91%)
Initial dysarthria/dysphasia	0	1 (9%)
Dysarthria/dysphasia	2 (40%)	11 (100%)
PEO-progressive external ophthalmoplegia		

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Discussions

Diagnostic testing	Present study n = 5	CPEO cohort n = 11
Axonal sensory neuropathy	3/3 S>M	11 (100%) S>M
Muscle biopsy	2/3 >10% COX- and SDH+ >30% COX- and SDH+	9/11 COX- [1.3%-25%] Median 3.1%
Genetic testing (POLG)	1/2 *2 VUS likely pathogenic (compound heterozygote mutations seen in patients with SANDO)	6/10 *The 2 POLG- patients were PEO1+
S-sensory, M-motor, VUS-variants of unknown significance		

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Conclusions

- Foot numbness followed by ataxia and ophthalmoparesis is the presenting symptom in majority of SANDO cases
- Dysarthria was the least consistent finding of the triad and was delayed
  - SANO seem to be the most frequent phenotype
- Direct POLG mutation screening can avoid costly invasive muscle biopsy
- May benefit from additional PEO1 screening

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Thanks you

- **Questions?**

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4. Fadic, R., Russell, J. A., Vedanarayanan, V. V., Lehar, M., Kuncl, R. W., Johns, D. R. Sensory ataxic neuropathy as the presenting feature of a novel mitochondrial disease. Neurology 49: 239-245, 1997.

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