Huntington disease-like phenotype in a patient with *ANO3* mutation

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A 71-year-old previously well white British female developed progressive involuntary tongue movements over one year, resulting in eating difficulty and 10kg weight loss. She had also noted involuntary perioral, facial and distal limb movements beginning 18 months earlier. These had progressively worsened. In the 3 years prior to presentation, she reported subjective memory decline, word finding difficulty and depressed mood, which improved with mirtazapine 30mg once daily. She had no history of neuroleptic exposure.   Her brother had died aged 40 years, following years of mental illness and substance abuse. She was estranged from her father, who was said to have had 'behavioural problems'. Her paternal grandmother and maternal aunt had Parkinson's disease.

The mini mental state examination (MMSE) was 28/30. There was mild dysarthria. The range of eye movements were normal. Saccadic initiation was slightly delayed but velocity and metricity were normal. Generalised chorea was evident, particularly affecting the distal limbs and perioral region (see video). She exhibited tongue chorea with normal motor function. There were mild dystonic fingers posturing. Finger tapping was irregular but without clear decrement in velocity and amplitude, and there were no other features of parkinsonism. She had marked difficulties in performing the Luria hand sequence and diffuse hyperreflexia but with flexor plantar responses (not shown in video). The remainder of the neurological examination was normal. Formal neuropsychometric testing revealed normal immediate and delayed recall, fluent conversational speech and intact object naming. There was mild executive dysfunction and reduced information processing speed. These features were felt to reflect a degree of fronto-parietal compromise with both cortical and subcortical features.

An extensive workup for chorea including complete blood count (CBC) with peripheral smear, sedimentation rate, ceruloplasmin, copper, liver function tests, thyroid-stimulating hormone (TSH), paraneoplastic profile, tests of connective tissue disorders, serum rapid plasma reagin (RPR), anti-thyroid peroxidase (TPO) antibodies and tissue transglutaminase antibodies were negative. Additionally, genetic testing for Huntington's disease, C9ORF72, FTL, SCA17, DRPLA, HDL2, MELAS, FTDP17, aprataxin and senataxin were unremarkable (see supplementary material). Her brain MRI showed old lacunar infarcts involving deep white matter structures and the body of the left caudate nucleus. Caudate volumes were preserved. A next-generation sequencing (NGS) gene panel revealed a heterozygous NM_031418.2:c.1969G>A (p.Ala657Thr) likely pathogenic (ClinVar, Varsome) missense variant in the *ANO3* gene.

The patient started tetrabenazine 25mg once daily for symptomatic management of tongue and perioral chorea. This resulted in marked symptomatic improvement and a resumption of normal feeding, without altering mood.

Discussion

This is, to our knowledge, the first case conclusively demonstrating that chorea can be an intrinsic *ANO3*-related movement disorder. Our patient's presentation with distal

limb and perioral chorea together with some cognitive and neuropsychiatric involvement bore superficial resemblance to Huntington's disease (HD), especially given the dominant family history of psychiatric disease. However, normal eye movements, reasonably preserved cognition and absence of motor impersistence argued against HD. Other features unsupportive of HD phenocopies included the absence of ataxia(SCA17), seizures(DRPLA), African ancestry (HDL-2) and motor neuronopathy or frontotemporal dementia(c9orf72)(Table2). We felt the unilateral old caudate infarct was unlikely causative given the progressive and generalized nature of the chorea.

Chorea has been described once previously as possibly associated with an *ANO3* gene mutation[1], however the genetic variant in this unusual case (consisting of mixed blepharospasm, dysarthria, dystonia, stereotypies and motor and vocal tics) was of uncertain significance, and the presentation further confounded by months of prior treatment with promethazine (which has known potential for inducing tardive movement disorders)[1].

The *ANO3* genetic product, anoctamin-3, is highly expressed in the brain, particularly in the striatum, as well as the frontal cortex, hippocampus and amygdala[2, 3]. Its exact role remains uncertain, though through indirect regulation of potassium channel function, it appears to modulate neuronal excitability[4, 5]. Altered striatal neuron excitability and output, as seen in HD for example[6] may therefore underlie the development of hyperkinetic choreodystonic movements in *ANO3* mutation carriers.

Our case also raises the question of whether psychiatric disorders may form part of the phenotypic spectrum of *ANO3* mutations. Some reports detail behavioural and/or neurodevelopmental issues,[2, 7] in *ANO3* mutation carriers (Table 1), and it is plausible abnormal ANO3 gene product could contribute to fronto-striato-limbic network dysfunction with resulting psychiatric and neurobehavioural manifestations.[2, 3, 7, 8] Whether psychiatric features in other published cases of *ANO3* could have been overlooked, or even whether a forme fruste of *ANO3* may manifest as a purely psychiatric disorder would be interesting to examine in future studies. Though the literature is too sparse to comment on genotype-phenotype correlations, it is interesting to note that previously published cases harboring the same variant as our patient also had neurobehavioural abnormalities[9].

This case illustrates the importance of considering ANO3 not only in isolated and combined dystonia syndromes, but also in choreiform disorders, especially if accompanied by an autosomal dominant family history. The relationship with psychiatric disease is intriguing, and worthy of further probing.

The patient provided written informed consent to be videotaped, and to the publication of the video in both the printed and online modalities

Table 1. *ANO3*-associated phenotypes with mixed motor and non-motor involvement

Sequence mutation	AA changes	Phenotype	Age of onset	Ref
c.1969G>A	p.Ala657Thr	Generalised chorea with oromandibular involvement, cognitive and neuropsychiatric involvement	69	**Present case***
c.1969G>A	p.Ala657Thr	Cervical dystonia, blepharospasm, oromandibular dystonia,postural tremor, behavioral disorders associated with mental retardation	Childhood - 53	Miltgen et al,2016[9]
c.1796C>A	p.Ala599Asp	Early onset generalized dystonia, psychomotor regression and spasticity	3	Jim´enez de Domingo et al, 2020[10]
c.1952G>A	p.Ser651Asn	Early onset generalized dystonia starting in the lower extremities with multifocal myoclonic jerks, was behind in school with a mild attention deficit.	3	Yoo et al,2019[11]
c.1819A>T	p.Ile607Phe	Generalized dystonia, infantile Parkinsonism, bradykinesia, global developmental delay, myoclonus. Psychomotor regression	8	Nelin et al, 2018[7]

6 Table 2. Summary of important 'red flags' for the diagnosis of HD and
7 progressive HD-like syndromes[12,13,14]
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Condition	Average age of onset (years)	Inheritance	Chromosomal location	*Gene*	Red Flags
C9orf72 repeat expansions	54	AD	9p21	*C9orf72*	1. Typically associated with FTD–ALS 2. Psychiatric disorders 3. Parkinsonism
HDL1	20-40	AD	20p13	*PRNP*	1. Seizure 2. Prominent psychiatry features
HDL2	25-45	AD	16q24	*JPH3*	1. Sub-Saharan African ancestry. 2. Gait impairment 3. Predominant dystonia/parkinsonism
HDL4(SCA17)	25-40	AD	6q27	*TBP1*	1. Cerebellar ataxia 2. Predominant gait impairment 3. Seizure
DRPLA	Infancy to mid adulthood	AD	12p13	*ATN1*	1. Ethnicity-Japanese origin 2. Cerebellar ataxia 3. Eye movement abnormalities-e.g dysmetric saccades, square wave jerks,saccade pursuit, gaze evoked nystagmus, 4. Seizure 5. Progressive myoclonic epilepsy
Neuroferritinopathy	40	AD	19q13	*FTL1* [a]	1. Cumbrian or French origin 2. Facio-bucco-lingual 3. Predominant dystonia/ parkinsonism

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10　**Supplementary materials**
11　**Laboratory, instrumental and genetic investigations**
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Investigation	Result	Reference values
Full blood count	Normal	
Red cell count	4.37×10^{12}/L	$3.95 – 5.15 \times 10^{12}$/L
Hemoglobin	129 g/L	115 – 155 g/L
HCT	0.409 L/L	0.33 - 0.45
MCV	93.6 fL	80 – 99 fL
MCH	29.5 pg	27.0-33.5 pg
MCHC	315 g/L	320 – 360 g/L
RDW	13.2 %	11.5 – 15.0 %
Platelet count	208	150 – 400 x 109/L
Peripheral blood films	No acanthocytes detected	-
Total leucocyte count	6.70 x10^9/L	$3.0 – 10.0 \times 10^9$/L
Neutrophils	4.37×10^9/L	$2.0 – 7.5 \times 10^9$/L
Lymphocytes	1.98×10^9/L	$1.2 – 3.65 \times 10^9$/L
Monocytes	0.33×10^9/L	$0.2 – 1.0 \times 10^9$/L
Eosinophils	0.05×10^9/L	$0.0 – 0.4 \times 10^9$/L
Basophils	0.01×10^9/L	$0.0 – 0.1 \times 10^9$/L
Hba1c	5.8 %	4.0-6.0 %
Vitamin B12	483 pg/mL	197 – 771
Folate	7.0 ng/mL	3.9 - 20.0
ESR	42 mm/hr	1-20mm/hr
Renal and liver function test	Normal	
Thyroid profile/ anti-thyroid peroxidase (TPO) antibodies	Normal	
AFP	Normal	
Serum immunoglobulin	Normal	
VDRL/RPR/HIV antibodies	Negative	
Anti-nuclear antibody/Anti-dsDNA	Negative	
Lupus anticoagulant	Negative	
NMDAR Antibody/VGKC	Negative	
Serum copper and caeruloplasmin	Normal	
Paraneoplastic screening **Anti-Purkinje cell antibodies** **Anti-Tr antibodies** **Anti-Hu antibodies** **Anti-Yo antibodies** **Anti-Ri antibodies** **Anti-Ma-1 antibodies** **Anti-Ma-2 antibodies** **Anti-CV2 (CRMP-5) antibodies** **Anti-Amphiphysin antibodies** **Anti-Zic-4 antibodies** **Anti-Sox 1 antibodies**	Negative	

Anti-Tr antibodies		
Tissue transglutaminase antibodies	Negative	
NCS and EMG	Normal study	-
EEG	Normal study	-
Genetic testing for: *HTT* **(HD)** *C9orf72* *FTL* **(Neuroferritinopathy)** *TBP* **(SCA17)** *ATN1* **(DRPLA)** *JPH3* **(HDL2)** **Mitochondrial m.2343A>G** *MAPT* **(FTDP-17)** *APTX* **(AOA1)** *SETX* **(AOA2)**	Negative	

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Author roles:

1. Research project: A. Conception, B. Organization, C. Execution;
2. Data Analysis: A. Design, B. Execution, C. Review and Critique;
3. Manuscript Preparation: A. Writing of the first draft, B. Review and Critique.

SKK: 1A, 1B, 1C, 2A, 2B, 3A, 3B

EM: 1A, 1C, 2A, 2C, 3A, 3B

FM: 2C, 3B

GL: 2C, 3B

AL: 2C,3B

KB: 1A, 2C, 3B

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Video Legend

Video of the patient showing peri-oral and distal limb chorea, mild dystonic finger posturing and mirror movements on finger and foot tapping. There were no parkinsonian or cerebellar signs. Possible dystonic lip pursing is occasionally observed.