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Review article

Dystonia-Ataxia with early handwriting deterioration in *COQ8A* mutation carriers: A case series and literature review

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ABSTRACT

Cerebellar ataxia is a hallmark of coenzyme Q_{10} (CoQ_{10}) deficiency associated with *COQ8A* mutations. We present four patients, one with novel *COQ8A* pathogenic variants all with early, prominent handwriting impairment, dystonia and only mild ataxia. To better define the phenotypic spectrum and course of *COQ8A* disease, we review the clinical presentation and evolution in 47 reported cases. Individuals with *COQ8A* mutation display great clinical variability and unpredictable responses to CoQ_{10} supplementation. Onset is typically during infancy or childhood with ataxic features associated with developmental delay or regression. When disease onset is later in life, first symptoms can include: incoordination, epilepsy, tremor, and deterioration of writing. The natural history is characterized by a progression to a multisystem brain disease dominated by ataxia, with disease severity inversely correlated with age at onset. Six previously reported cases share with ours, a clinical phenotype characterized by slowly progressive or static writing difficulties, focal dystonia, and speech disorder, with only minimal ataxia. The combination of writing difficulty, dystonia and ataxia is a distinctive constellation that is reminiscent of a previously described clinical entity called Dystonia Ataxia Syndrome (DYTCA) and is an important clinical indicator of *COQ8A* mutations, even when ataxia is mild or absent.

1. Introduction

Primary coenzyme Q_{10} (CoQ_{10}) deficiency is a heterogeneous group of mitochondrial disorders with age of onset ranging from birth to the 7th decade. Mutations in ten genes (*COQ2, COQ4, COQ5, COQ6, COQ7, ADCK3, ADCK4, COQ9, PDSS1, PDSS2*) result in five major phenotypes: encephalomyopathy, severe infantile multi-systemic disease, cerebellar ataxia, isolated myopathy, and steroid-resistant nephrotic syndrome [1–6].

Different pathogenic mechanisms seem to account for the extreme clinical variability and unpredictable response to CoQ_{10} supplementation. Since CoQ_{10} has an essential role as an electron carrier and endogenous antioxidant, decreased ATP synthesis and increased reactive oxygen species production are likely two major pathogenic factors [7,8]. However, there is evidence that other mechanisms are involved, including disruption of the mitochondrial hydrogen sulfide oxidation pathway [9] resulting in reduction of sulfide quinone reductase (SQR) activity proportionally to CoQ_{10} levels [10]. SQR deficiency induces changes in the mitochondrial level of thiols, resulting in an alteration of the biosynthetic pathways for some neurotransmitters such as glutamate, serotonin, and dopamine, as seen in the cerebrum of $Coq9^{R239X}$ mice [9]. Despite significant advances in our

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understanding of the CoQ_{10} biosynthetic pathway, the precise composition of the CoQ_{10} biosynthetic complex and its regulatory factors remain unknown.

COQ8A encodes an atypical kinase [11], COQ8, which is thought to play a regulatory role in CoQ_{10} biosynthesis. Mutations in *COQ8A* represent the most common cause of primary CoQ_{10} deficiency and result in autosomal-recessive cerebellar ataxia type 2 (ARCA2; spinocerebellar autosomal recessive 9 [SCAR9]), a slowly progressive ataxic syndrome characterized by cerebellar atrophy and moderate CoQ_{10} deficiency in skeletal muscle. Variable associated clinical features include exercise intolerance, epilepsy, and intellectual disability. *COQ8A* knockout mice develop slowly progressive cerebellar ataxia and mild exercise intolerance, recapitulating ARCA2 [12]. The underlying molecular mechanisms are obscure, largely because COQ8A lacks a clear function. Interspecies biochemical analyses show that human COQ8A and its yeast homolog, Coq8p, are essential for CoQ_{10} biosynthesis via unorthodox protein kinase-like (PKL) functions [13] and possess ATPase activity that is activated by cardiolipin and phenolic compounds [14].

Cell lines derived from patients with *COQ8A* mutations display decreased CoQ_{10} content, high basal levels of oxidative stress, changes in mitochondrial metabolism and an increase in lysosomal content [15].

To date, 53 patients with 38 *COQ8A* mutations have been reported. Variable phenotypes, ranging from slowly progressive ataxia to infrequent severe forms with early onset ataxia, epilepsy and regressive course are described. Less obvious manifestations, including clumsiness, writing difficulties and speech disorder, characterize a subset of patients with a milder phenotype and a more slowly progressive course [16–29].

Here we report four new cases of *COQ8A* deficiency, three with childhood- and one with adult-onset. All share distinct yet mild phenotypes characterized by deterioration of writing, tremor, dystonia, and mild ataxic features. Furthermore we reviewed all published cases providing an overview of the different patterns of clinical presentation and evolution with respect to age at onset.

2. Methods

2.1. Clinical data

We reviewed clinical information, biochemical findings, genetic data, neuroimaging, and video recordings, of four unreported *COQ8A* patients. Written informed consent was obtained in accordance with institutional review board regulations and protocols to disclose clinical information, neuroimaging, and video recordings.

2.2. Biochemical and molecular genetic studies

CoQ_{10} levels and quantitative reverse transcription polymerase chain reaction (qRT-PCR) for *COQ8A* were performed in muscle and fibroblasts for case 1. To assess COQ8A transcript levels, total RNA was extracted from patient and three control muscle samples using Trizol® and following manufacturer instructions. cDNA was synthetized using 100 μg of total RNA by SuperScript™ VILO™ cDNA Synthesis Kit (Invitrogen). Quantitative reverse transcription polymerase chain reaction (qRT-PCR) was performed using TaqMan assays for *COQ8A* (Hs00220382_m1) and normalized using *GAPDH* (Applied Biosystems Foster City, CA). Amplification of deleted cDNA region in patient 1 has been carried out by PCR using the following primers: 5′-GAAGGTGCA GGGTCAGGAT 3′-GCTGAGCGTCTGTTTGTGCTG.

2.3. Literature review

We reviewed 53 published cases obtained by Pubmed Search [16–29] using search terms *ADCK3*, *COQ8A*, and Coenzyme Q10 deficiency. We selected 47 cases from 13 articles [16–28] for which clinical history or informations about disease presentation and evolution were

Table 1
MRI findings, mitochondrial structural and biochemical studies and response to CoQ_{10} supplementation in 47 reported COQ8A deficient patients.

MRI findings (41/47)[a]		
Structural alteration (40/41)	**Pt (n./41)**	**Reference**
Cerebellar atrophy	24	[16-19, 21-23, 27,28]
Vermian atrophy	6	[18,20,23]
Cerebellar or vermian + brainstem atrophy	2	[18]
Cerebellar atrophy + stroke like abnormalities (3 with dentate hyperintensity)	7	[16,23,24,26]
Global atrophy	2	[19,25]
Mitochondrial structural and biochemical studies		
Muscle biopsy (23/47)[a]		
Structural study (11/23)		
Structural alterations (7/11)	**Pt (n./7)**	**Reference**
Increase of mitochondria	4	[16,19]
SDH hyperreactive + COX-deficient fibers	4	[19,24]
Lipid accumulation	3	[16,19]
Ragged Red Fibers (RRF)	1	[23]
Fiber size variation	1	[24]
RC[b] **assessment (17/23)**		
Abnormal 14/17	**Pt (n./14)**	**Reference**
Reduced CII + CIII activity	4	[16,18,23,27]
Reduced CI + CIII and CII + CIII activity	3	[16,20,24]
Combined respiratory chain deficiency	3	[19,22]
Impairment of malate + pyruvate and succinate oxidation	1	[16]
High activities of respiratory complexes	2	[16]
Abnormal complex activity ratios	4	[16,17]
CoQ_{10} levels (12/23)		
Abnormal 11/12		**Reference**
		[16,19,20,24,26-28]
Skin biopsy (9/47)[a]		
RC assessment (5/9 patients)		
Abnormal 3/5	**Pt (n./3)**	**Reference**
Slight increase in the CIV/CII + III ratio	2	[16]
Decreased activities of CI, CII and CIII	1	[21]
CoQ_{10} levels (7/9 patients)		
Abnormal 3/7		**Reference**
		[17,21]
Response to CoQ_{10} supplementation		
Patients treated 30/47[a]	**Pt (n./30)**	**Reference**
No clinical improvement	13	[16,19,23,26,28]
Clinical improvement or stabilization	13	[16,17,20-24,26-28]
Outcome is not reported	4	[16,23]

[a] Number of patients having a specific study or receiving CoQ_{10} supplementation/47 COQ8A deficient patients previously reported in the literature.
[b] RC; respiratory chain.

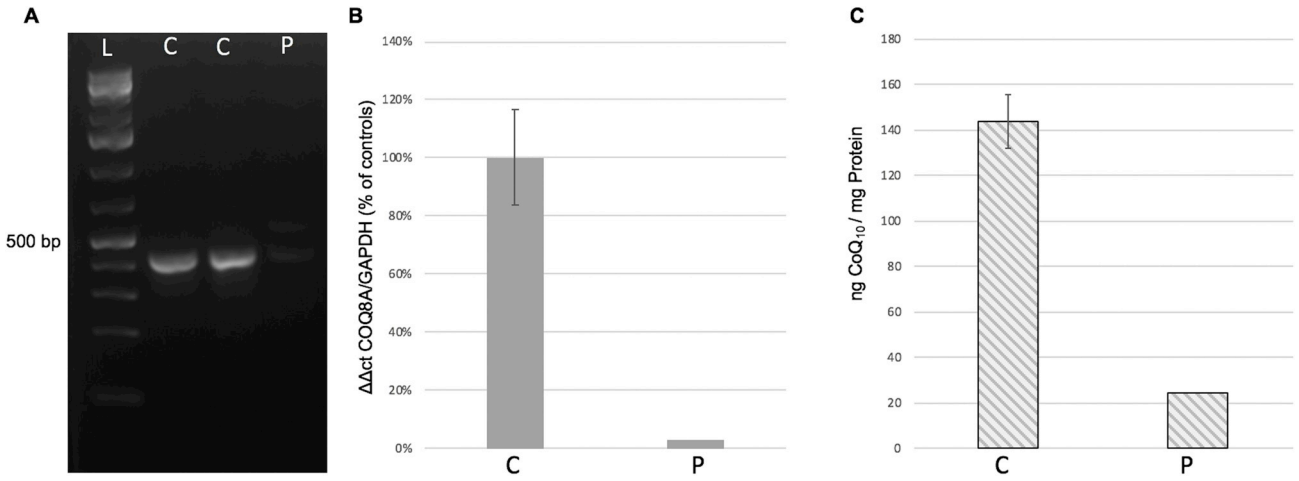

Fig. 1. Characterization of patient 1 skeletal muscle.
A. *COQ8A* cDNA amplification using primer overlapping the deletion site (exon 1–2 and 2–3). L: DNA molecular weight ladder. C: control cDNA. P: patient cDNA.
B. Quantitative PCR of *COQ8A* cDNA normalized over *GADPH*. C: average of 3 controls' muscle. P: patient cDNA. C Coenzyme Q_{10} levels, normalized over mg proteins. C: average of 3 controls muscle. P: patient muscle.

available. The patterns of clinical presentation and evolution were evaluated as a whole and stratified by age at onset (0–5:early childhood onset; 6–10:late childhood onset; 11–18:juvenile onset; > 18 years:adult onset). Clinical severity was classified as follows: 1) severe: presence of severe epilepsy and/or regression, association with poor cognitive and/or motor outcome such that subjects are reliant upon caretakers for all activities of daily living (ADLs including work and school); 2) moderate: presence of a multi-symptomatic and multisystem condition that can include: ataxic syndrome, epilepsy and cognitive impairment that cause difficulties with ADLs, which can still be performed independently; 3) mild: slow progression, less severe symptoms (ataxia is mild, epilepsy resolves with treatment) and absence of cognitive impairment. Ataxia was defined as displaying multiple abnormal cerebellar features including: ataxic gait, dysmetria, dysdiadochokinesia, action tremor, and/or ocular motility abnormalities. MRI findings, mitochondrial structural and biochemical studies (CoQ_{10} levels, respiratory chain (RC) assessment), and response to CoQ_{10} supplementation in reported patients are summarized in Table 1.

3. Results

3.1. Case 1

This 21 year-old woman was the full-term product of an uncomplicated pregnancy and delivery. Family history was notable for essential tremor in a paternal cousin, and Parkinson disease in the maternal grandmother. Neonatal and early development were normal. She was an intelligent girl with good academic performance through college. At age 13, she developed hand tremor and poor hand coordination with deterioration of handwriting. Initially, symptoms were mild and intermittent, then fixed, and increased with anxiety and albuterol administration. On examination at age 16 years, an asymmetric mild intention tremor was present at endpoint bilaterally, a postural component was present in wing beating position but absent with arms held extended forward (video 1). Additional symptoms noted over time included hand bradykinesia, subtle and variable speech dysfluency, slight laterocollis, and intermittent dystonic head tremor with demonstrable null point. Dystonic pen grip contributed to writing impairment. Ataxic features became obvious with mild arm dysmetria and dysdiadochokinesia, intermittent/episodic gait instability, and hypometric saccades.

Supplementary video related to this article can be found at https://doi.org/10.1016/j.parkreldis.2019.09.015.

Multiple pharmacological agents were ineffective in ameliorating the neurological manifestations (primidone, propranolol, topiramate, L-dopa, pramipexole). Tremor eventually improved on trihexyphenidyl/clonazepam combination therapy. Treatment with ubiquinol (800 mg/day) and high-dose vitamin B-complex was started at age 19 years. At age 21 years, after two years of CoQ_{10} supplementation, her tremor was stable and she was able to tandem walk normally. She had marked bradykinesia manifesting as slow finger tapping and persistent mild alteration of verbal fluency with hypophonia. Her global functioning was normal and she performed well academically.

Brain MRI, DAT scan, and EMG/NCS and comprehensive metabolic and genetic evaluation were normal (transferrin isoelectric focusing testing, plasma acyl-carnitine profile, urinary organic acids, plasma amino acids, ammonia, vitamin E, serum lactate and pyruvate, serum CoQ_{10}, prolactin, ceruloplasmin, biotinidase essay, vitamin B12, folate, AFP and genetic testing for: spinocerebellar ataxias types 1,2,3,6, and 7, Friedreich ataxia, DYT1 and DYT6/*THAP1*).

Whole exome sequencing detected a homozygous 27.6 kb deletion of 1q42.3 involving exons 1 and 2 of the *COQ8A* gene, confirmed by targeted oligonucleotide array [Chr1:227, 125, 473–227, 151, 023 (hg19)] (e-Supplemental Fig. 5). Skeletal muscle biochemistry in a clinical laboratory was confirmatory showing low levels of CoQ_{10} [12.2 μg/g tissue (reference: 23.63–48.11) 34% of mean 3.87 SD below the mean]. Repeat evaluation of muscle CoQ10 level done in by our group confirmed deficient levels (Fig. 1). Subject's fibroblast did not showed reduction of CoQ_{10} (Patient 38.34 ng/mg protein vs controls 40.09 ± 7.8 ng/mg protein), data that is in line with other previously reported cases [24]. To confirm that the patient's variant had functional effects on total *COQ8A* transcript levels a quantitative PCR was performed using a probe distal to the deletion site. Patient's muscle mRNA levels were indeed reduced compared with three different muscle control samples with patient *COQ8A* residual transcript levels of 5% (Fig. 1).

Mitochondrial respiratory chain enzyme complexes I + III and II + III were reduced to 44–55% of their respective normal reference means; citrate synthase was 52% of its normal mean and 1.7 SD below the mean. Muscle histology showed mild fiber size variation and electron microscopy was performed but interpretation limited by processing artifact.

3.2. Case 2

This 10 year-old girl was born at term after an uneventful pregnancy

but required emergency delivery due to maternal hypertensive crisis. Family history was negative for neurologic disorders. Mild hyperphenylalaninemia not requiring treatment (blood Phe 120–240 microM; r. v. < 120) [30] was detected by neonatal screening program. Genetic testing confirmed the presence of two heterozygous variants on *PAH* gene [c.611 A > G (p.Tyr240Cys); c.734T > C (p.Val245Ala)]. Motor and cognitive development were normal and she performed well academically.

At age 7 years, she developed writing difficulties, upper limb postural and action tremor, mild global incoordination, and fatigability. Impaired writing was the most disabling symptom. Examination at age 8 years showed postural and action tremor, arm and leg dysmetria, and slight postural and gait instability. She was able to perform tandem gait normally. The most obvious and disabling signs were difficulty writing and hand clumsiness with dysdiadochokinesia and bradykinesia. Dystonic pen gripping was observed during writing tasks (video 2). In the next few months handwriting and speech (scanning speech, dysfluency) worsened.

Supplementary video related to this article can be found at https://doi.org/10.1016/j.parkreldis.2019.09.015

A comprehensive metabolic work up (plasma amino acids, plasma acyl-carnitine profile, urinary organic acids, ammonia, serum lactate, prolactin, ceruloplasmin, serum and urinary copper, plasma oxysterols, chitotriosidase, arylsulfatase, and beta galactocerebrosidase enzymatic activity, cerebrospinal fluid study including glucose, lactate, protein level, amino acids, neurotransmitter metabolites, and pterins) were normal. CSF glucose (3.1 mmol/L; normal 3.3–4.4), albumin (82 mg/L; normal 100–300) and IgG (5.7 mg/L; normal.13–21) were slightly reduced. Brain MRI and sleep EEG were both normal. A custom Next Generation Sequencing (NGS) panel for hereditary ataxias revealed two previously described mutations in the *COQ8A* gene [c.1844G > A (p.Gly615Asp); c.589-3C > G (p.Leu197Valfs*20)] [23]. Carrier status was verified in each parent by Sanger sequencing confirming variants are in trans in the proband. CoQ10 supplementation (800 mg/day) was started at the age of 8.5 years and resulted in a clinical stabilization.

3.3. Case 3

This 54 year-old man had normal psychomotor development with normal intelligence. Family history was negative for neurologic disorders. Parents were second-cousins. Disease onset was at age 25 years with gait instability. First examination at 43 years of age revealed slight difficulty with tandem gait, slight dysmetria and dysarthria, brisk tendon reflexes with positive Trömner sign, flexor plantar response, and cervical dystonia with retrocollis. There was intermittent upper limb action and head tremor, and writing difficulties with abnormal dystonic pen grip (video 3). Mini mental state examination and complete neuropsychological evaluation were normal. Blood biochemistry (thyroid screening, alpha-fetoprotein, autoimmune screening, urinary organic acids, hexosaminidase enzymatic activity) was normal, except for mild hypercholesterolemia (221 mg/dL; normal < 190) and hyper-CKemia (160 IU/L; normal < 140). MRI showed mild vermian atrophy. DaT-scan and peripheral nerve conduction study were normal. Genetic tests for Friedreich ataxia and SCA6 were negative. A custom NGS panel for hereditary ataxias revealed a previously reported homozygous nonsense mutation in *COQ8A* [c.1042C > T (p.Arg 348*)] [18].

Supplementary video related to this article can be found at https://doi.org/10.1016/j.parkreldis.2019.09.015

3.4. Case 4

This 11 years old boy was born at term after an uneventful pregnancy and delivery. Early psychomotor development was normal. He presented at the age of three years with a subtle cerebellar syndrome characterized by action tremor, mild unbalance and gait clumsiness. Speech difficulties and mild cognitive impairment were present. Generalized seizures, onset at age 10 years, were well controlled on levetiracetam. Brain MRI showed cerebellar atrophy, mainly affecting the vermis. Motor and cognitive symptoms improved over time with rehabilitation therapy. Action tremor remained stable over time, particularly interfering with writing tasks. Clinical examination at the age of 10 revealed mild ataxic gait with impaired tandem, sway while standing on one leg, minimal dysmetria with tremor and dysdiadochokinesia. Dystonia and tremor were present on the right with arms outstretched, as well as during a writing task; handwriting was slow, macrographic and tremulous. The SARA (Scale for the Assessment and Rating of Ataxia) total score was 13.5. A custom NGS panel for hereditary ataxias revealed compound heterozygous variants in the *COQ8A* gene [c.901C > T (p.Arg301Trp); c.1331_1332insCACAG (p.Glu446AlafsTer33)], the first previously reported [28,29]. Carrier status was verified in each parent by Sanger sequencing confirming variants are in trans in the proband. Coenzyme Q_{10} (10 mg/kg/day) supplementation was started at the age of 10 years but has been taken only intermittently.

3.5. Literature review of previously reported cases

3.5.1. Age at onset and presentation

Age at onset ranges from the first year to the third decade of life with the vast majority of cases presenting during childhood. Thirty-seven of the 47 patients (79%) had early childhood or late childhood-onset, while juvenile- and adult-onset were less frequent, respectively 6/47 (13%) between 11 and 18 years and 4/47 (8%) > 18 years (e-Supplemental Fig. 1).

Patients typically present with 1 or 2 clinical features including frank ataxia (16/47 patients; 34%) or a more subtle gait instability (10/47; 21%) in greater than half of the described patients. Other less frequent symptoms at onset were: developmental delay (8/47; 17%), seizures (7/47; 15%), writing difficulties (6/47; 13%), clumsiness (5/47, 11%), tremor (5/47; 11%), speech difficulties (3/47; 6%), regression (3/47; 6%), dystonia (2/47; 4%), myoclonus (2/47; 4%), chorea (1/47; 2%), exercise intolerance (1/47; 2%) (Fig. 2).

When stratified by age at onset (e-Supplemental Fig. 2), 12/25 (48%) of patients with early childhood-onset presented with ataxia, while ataxia at onset was less common when onset is after age 5 years (4/22; 18%). Other features of the early childhood-onset forms were: developmental delay (8/25; 32%), unsteady gait (5/25; 20%), regression (3/25; 12%) and writing difficulties (2/25; 8%). Other less frequently reported signs are summarized (Fig. 2).

Developmental/cognitive issues or neurological deterioration were rare when first neurological signs appear after 5 years of age (e-Supplemental Fig. 2). A regressive course was reported only in cases with early childhood onset. Of note, 25% of patients in this age group had a multi-symptom presentation, with more than 2 clinical features at onset.

With late childhood-onset, this condition can present with unsteady gait, epilepsy or a variable association of writing difficulties, clumsiness and tremor. Interestingly the most common presentation in this age group was epilepsy (4/12; 33%) followed by ataxia (3/12; 25%), clumsiness (2/12; 17%), and speech difficulties (2/12; 17%). Less frequent features at onset, were unsteady gait, writing difficulties, tremor, myoclonus, and dystonia (1/12; 8%). Juvenile onset was characterized by a variable combination of writing difficulties (2/6; 33%), clumsiness (2/6; 33%), and tremor (3/6; 50%) with ataxia, unsteady gait, myoclonus, or dystonia (1/6; 17%). Adult-onset was characterized by unsteady gait in 3 of 4 subjects (75%). Migraine (1/4; 25%), epilepsy (1/4; 25%), and tics (1/4; 25%) have also been reported as initial symptoms.

3.5.2. Disease course and severity

Mild to moderate impairment is typical in this condition, with an inverse correlation between age at onset and clinical severity. All cases with a severe disease course, and the vast majority with a moderate

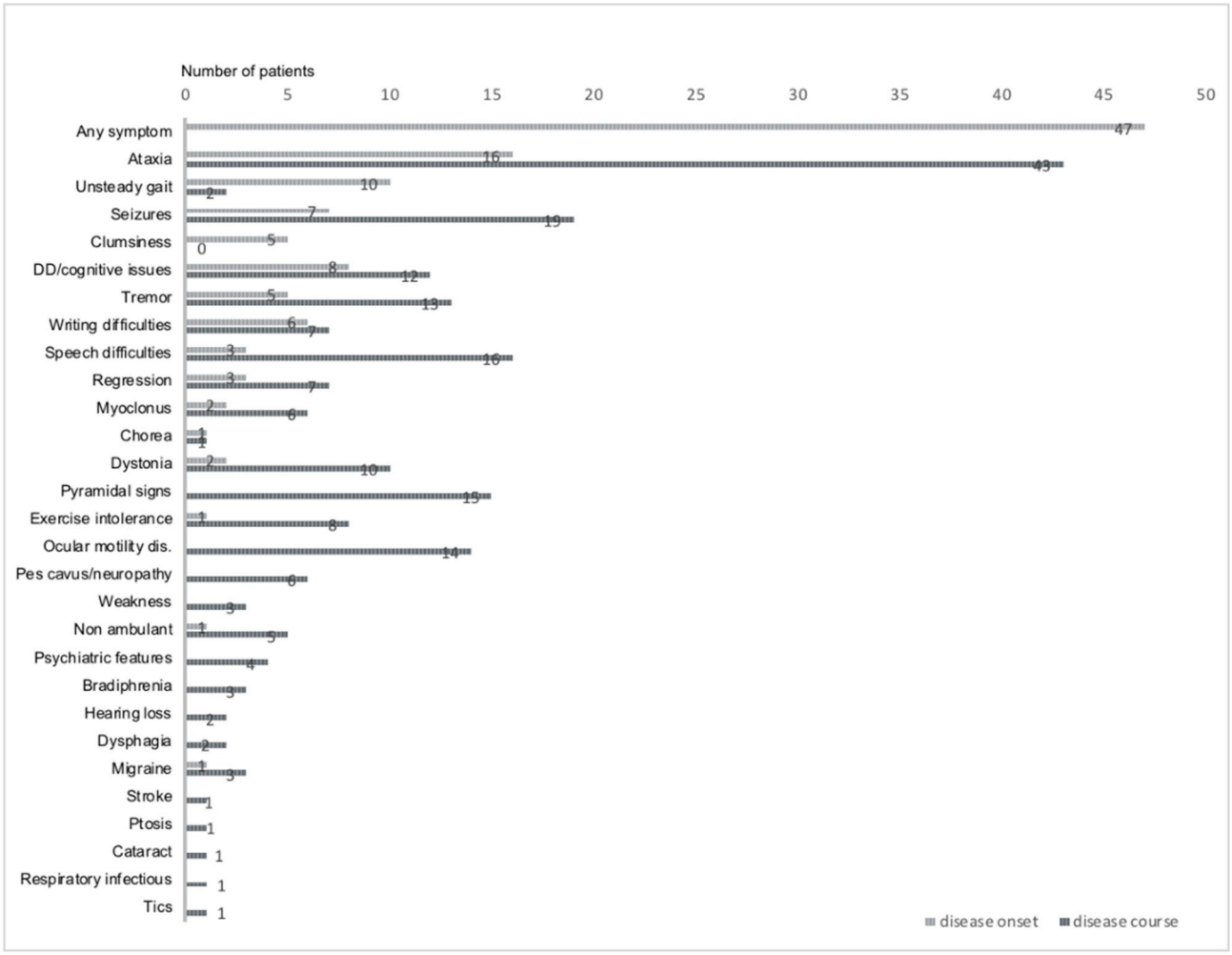

Fig. 2. Clinical Presentation and Disease Course: Frequency of symptoms described at onset and at last examination in the 47 patients with *COQ8A* mutations reported in the literature.

course onset before 5 years of age (e-e-Supplemental Fig. 3).

The natural history was characterized by progression to a multisystem brain disease, with severity inversely correlating with age at onset (e-Supplemental Fig. 3; e-Supplemental Table 1). With the exception of patients with juvenile onset, ataxia developed in 90–100% of reported patients. In addition, 19/47 (40%) of patients developed epilepsy, 16/47 (34%) speech difficulties/dysarthria, 15/47 (32%) pyramidal signs, 14/47 (30%) ocular motility abnormalities (8 patients with slow saccades and 6 with nystagmus), 13/47 (28%) tremor, 10/47 (21%) dystonia, 8/47 (17%) exercise intolerance, 6/47 (13%) myoclonus, and 6/47 (13%) pes cavus/neuropathy (Fig. 2).

Pyramidal signs, dystonia, ocular motility abnormalities (slow saccadic pursuit, nystagmus), exercise intolerance, and pes cavus/neuropathy were typical features of the late disease course. Speech difficulties such as dysfluency, hypophonic speech, bradylalia or dysarthria were common, and were associated with swallowing difficulties, as part of a more global bulbar involvement (e-Supplemental Table 1). Clinical evolution and the percentage of incidence of clinical features by age group in reported patients are shown in e-Supplemental Fig. 4.

Efficacy data regarding CoQ10 supplementation in 28 cases with *COQ8A* mutations including Case 1 and 2 and 26 previously reported cases are summarized in e-Supplemental Table 2. Cases where data regarding response to CoQ10 supplementation were available were selected and divided into *responders* and *non-responders*. In the *responders* group, ten cases had a moderate form, 5 cases a mild form and no patients had a severe phenotype; furthermore 5 patients had dystonia or writing difficulties. In the *non-responders* group 5 patients had a severe phenotype, 3 patients had a moderate and 5 patients a mild phenotype; only 2 patients had dystonia or writing difficulties. A few mutations recurred in the *responders* group [c.1750_1752delACC (p.Thr584del); c.1844dupG (p.Ser616Leufs); c.830T > C (p.Leu277Pro); c.1506+1G > A]; the c.895C > T (p.Arg299Trp) variant was found either in *responders* and *non-responders*.

4. Discussion

Here we report four new patients with six *COQ8A* pathogenic variants. Two of six variants have not previously been reported as pathogenic. The pathogenicity of the [Chr1:227, 125, 473–227, 151, 023 (hg19)] deletion in case 1 is supported by findings of diminished muscle CoQ10 levels and reduced *COQ8A* mRNA levels. The [c.1331_1332insCACAG (p.Glu446AlafsTer33)] variant in case 4 was considered pathogenic by the clinical testing laboratory as it leads to premature termination of the transcript. It is rare, absent from ClinVar [31] and present at a frequency of 1.7×10^{-5} in the ExAC database [32].

Despite different ages of onset, the patients described here, displayed an unusual phenotype with prominent writing deterioration and variable speech disorder with examination showing dystonic features with only mild ataxia. Our patients share with six reported cases, a combination of dystonia with only minimal ataxia that appears to affect a subset of *COQ8A* patients (Table 2). Unlike previously reported

Table 2
Previously reported COQ8A deficient patients with handwriting deterioration in setting of dystonia and ataxia.

Ref/pt #	Onset/ last exam	Presentation symptoms	Clinical features	Severity	Variants (hg19)	Muscle biopsy	Skin Biopsy	MRI	Response to CoQ10
Gerards, 2010 [18] /IV	2y/20y	Ataxia	writing difficulties, fatigue, slight spasticity, dystonia, improvement of ataxia over time	mild	c.1042C > T (p.Arg348Ter) c.1136T > A (p.Leu379Ter)	N/A	N/A	cerebellar atrophy, brainstem atrophy	N/A
Hovarth, 2012 [19]/I	15y/46	Handwriting deterioration, clumsiness	Gait disturbance, dysarthria, dysphagia, migraine, tremor, slow ocular pursuit, bradyphrenia	mild	c.811C > T (p.Arg271Cys) c.911G > A (pAla304Thr)	Increased mitochondria, SDH hyperreactive fibers, COX-deficient fibers	N/A	cerebellar atrophy	no response (CoQ10 300 mg/day for 3 months)
Mignot, 2013 [23]/III	7y/27y	Writing difficulties, dystonia	Ataxia, dysmetria, saccadic pursuit, hand dystonia, head tremor, myoclonus, brisk reflexes	mild	c1523T > C (p.Phe508Ser) del exons 3 to 15 (base pair positions (227,150,977–227,195,656)	N/A	N/A	marked vermian atrophy	Outcome N/A (Ubiquinone 300 mg/day)
Mignot, 2013 [23]/V	4y/38y	Gait ataxia and writing difficulties	Ataxia, dysmetria, saccadic pursuit, cervical dystonia, brisk reflexes, epilepsy, SLE	moderate	c.895C > T (p.Arg299Trp) c.1228C > T (p.Arg410Ter)	N/A	N/A	cerebellar atrophy, stroke like lesions	Ubiquinone 300 mg/day for 1 month then withdrawn
Mignot, 2013 [23]/VI	4y/34y	Writing difficulties	Ataxia, dysmetria, saccadic pursuit, nystagmus, hand dystonia, postural tremor, brisk reflexes, epilepsy	moderate	c.895C > T (p.Arg299Trp) c.1228C > T (p.Arg410Ter)	N/A	N/A	vermian atrophy	Ubiquinone 300 mg/day for 1 month then withdrawn
Chang, 2018 [28]/I	11y/25y	Focal dystonia, writing difficulties	Ataxia, dysarthria, tremor, dystonia	mild	c.901C > T (p.Arg301Trp) c.1399–3_1408del	Low CoQ10	N/A	normal	marked clinical improvement (CoQ10 800 mg/day)

N/A: not assessed; UL: upper limbs; RC: respiratory chain; SDH: succinate dehydrogenase; COX: cytochrome oxidase; SLE: stroke like episode; y; years.

subjects who all displayed cerebellar atrophy, brain MRI was normal in our patients 1 and 2. Although the origin of hand clumsiness may in part be cerebellar, particularly when associated with gait ataxia, the dystonic nature of hand clumsiness and neck tremor has been demonstrated in *COQ8A* patients through electromyographic recordings [23,28].

We systematically reviewed all cases published in English using search terms *ADCK3*, *COQ8A*, and Coenzyme Q10 deficiency and evaluated the different patterns of presentation and evolution with respect to age at onset. Evaluation of the frequency of specific manifestations in this condition is likely an underestimate due to under-reporting of particular features in published reports. Our analysis revealed that the clinical course of *COQ8A* related disorders can be extremely variable. A slowly progressive or self-limited cerebellar ataxia with cerebellar atrophy is typical, often associated with seizures and, later in the disease course, exercise intolerance, pyramidal involvement, and dystonia. CoQ_{10} levels are reduced in skeletal muscle and less frequently in fibroblasts, but their correlation with disease severity is still debated [33], as is the efficacy of CoQ_{10} supplementation. Severe forms seem to be less responsive to CoQ10 supplementation while patients with a combination of dystonia and ataxia tend to have a better response. However, larger samples and controlled studies are needed to establish if patients with DYTCA phenotype are more responsive to supplementation therapy (e-Supplemental Table 2).

In early or late childhood-onset cases, severity inversely correlated with age at onset. Presenting symptoms differed depending on age at onset. Children between 0 and 5 years tend to present with ataxia or gait instability associated with developmental delay or regression, while with onset between 6 and 18 years, first symptoms often included variable incoordination, epilepsy, tremor, and writing deterioration. Significant cognitive issues and regression were typical of early onset presentations as is a high incidence of epilepsy, pyramidal signs, exercise intolerance, dystonia, ocular motility disturbances, and tremor. Patients with juvenile onset showed a less severe course and, as in our cohort, cerebellar symptoms were mild compared to other associated motor issues, such as writing difficulties, hand dystonia, tremor, speech abnormalities, and neuropathy (e-Supplemental Fig. 4). [18,19,21–23]. Migraine is rare, but worthy of note as stroke and stroke like episodes have been described [19,26]. The natural history is characterized by progression to a multisystem brain disease, with ataxia eventually occurring in all groups.

Based on our review, no clear conclusion can be made about genotype phenotype correlation in this condition. Many *COQ8A* mutations are rare or private. In addition, amongst the more common no clear patterns have emerged. Subjects harboring the c.895C > T (p.Arg299Trp) variant described in 7 subjects, have varied age of onset and disease severity.[19,26] Subjects with the c.1042C > T (p.Arg348Ter) also described in 7 subjects, have almost similar age at onset (3–9 years) and severity (all of moderate severity) when mutation are homozygous and different age at onset in compound heterozygous subjects.[18,29]

There was no difference in age of onset and severity between subjects with missense and nonsense mutations or for mutations distributed throughout specific regions of the protein.

Similarly, with regard to response to therapy (e-Supplemental Table 2), a few mutations recurred in the *responders* group [c.1750_1752delACC (p.Thr584del); c.1844dupG (p.Ser616Leufs); c.830T > C (p.Leu277Pro); c.1506 + 1G > A], but others were equally represented in *responders* and *non-responders* and thus no conclusions can be drawn regarding the relationship of response to therapy and genotype.

In *COQ8A* mutant patients, it is unclear whether dystonia results from basal ganglia pathology or alternatively is a consequence of primary cerebellar disease. Dystonia typically results from dysfunction of basal ganglia circuitry [34]. However, for dystonia, a growing body of evidence is challenging the traditional view of basal ganglia based pathophysiology, describing instead a network model in which dystonia

may be caused by defects in one or more nodes of the highly interconnected motor system that includes both the cerebellum and basal ganglia [35–38]. Under pathological conditions, these interconnections can enable abnormal activity in the cerebellum to alter basal ganglia function, resulting in dystonic movements [39]. Furthermore, functional connectivity studies in focal hand dystonia and writer's cramp have demonstrated abnormal reciprocal excitatory connectivity in the cortico-cerebellar circuitry, possibly due to an impaired GABAergic neurotransmission in the cerebellum and sensorimotor cortex with loss of inhibitory control [40,41].

Patients displaying a slowly progressive cerebellar ataxia with dystonia are relatively rare and can cause considerable diagnostic uncertainty and challenges. A combination of dystonia and mild cerebellar ataxia has been referred to as dystonia cerebellar ataxia (DYTCA) syndrome.[46] Multiple reported DYTCA cases lacked a genetic etiology [42–44]. The most common genetic etiologies presenting with a combination of dystonia and ataxia include the spinocerebellar ataxias (SCAs), in which dystonia can be the presenting feature and can even predate ataxia by many years [45]. Task specific dystonia in the form of writer's cramp has been reported in SCA3 [46], SCA6 [47,48], SCA7 [49], and SCA14 [50,51]. Other etiologies include mitochondrial cytopathies. Doss and colleagues described a mutation of *COX20* in two siblings with mitochondrial complex IV (cytochrome *c* oxidase [COX]) and CoQ_{10} deficiencies [52]. Furthermore Schreglmann and colleagues recently reported three patients with a familial m.8244 A > G mutation, typically associated with myoclonus epilepsy and ragged red fibers (MERRF) who instead presented with isolated writer's cramp preceding later development of pan-cerebellar syndrome [53]. The complex movement disorder manifested by our cases and reported patients (Table 2), indicate that *COQ8A* deficiency should be added to the differential diagnosis for DYTCA syndrome and focal dystonia, including writer's cramp. Since this is a potentially treatable condition proper metabolic studies (CoQ10 dosage and RC assessment in muscle or fibroblasts) and early genetic testing should be performed in the diagnostic work-up of patients, especially children, with writer's cramp or focal dystonia with or without signs of ataxia.

The atypical presentation with prominent writing deterioration, possibly representing the initial manifestation of cerebellar disease, is an example of the extreme phenotypic variability of CoQ_{10} deficiency, and further broadens the spectrum of neurological manifestations associated with mitochondrial dysfunction.

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Final disclosures

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Ethical approval and informed consent

All authors declare that the manuscript is in accordance with the statement of ethical standards for manuscripts submitted to *Parkinsonism and related disorders*. Authors declare that patients 1 and 3 and parents of patients 2 and 4 have consented for video publication and provided a signed release form authorizing the offline and/or online distribution of this video material.

Data availability

Any anonymized data not published within the article will be shared by request from any qualified investigator.

Author roles

GS: conception and design of the study, analysis and interpretation of data, drafting the article
BE: analysis and interpretation of data
CR: analysis and interpretation of data, revising the article for important intellectual content
ST: acquisition of data
QCM: acquisition of data, analysis and interpretation of data
LM: acquisition of data
VG: acquisition of data
ZG: analysis and interpretation of data
DNM: analysis and interpretation of data
GD: analysis and interpretation of data
FA: revising the manuscript critically for important intellectual content
BE: revising the manuscript critically for important intellectual content
SFM: analysis and interpretation of data, revising the manuscript critically for important intellectual content
LV: revising the manuscript critically for important intellectual content
HR: revising the manuscript critically for important intellectual content
HM: analysis and interpretation of data, revising the manuscript critically for important intellectual content
FJR: analysis and interpretation of data, drafting the article, revising the manuscript critically for important intellectual content

Declaration of competing interest

None.

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Appendix A. Supplementary data

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