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**Neurology Publish Ahead of Print**  
**DOI: 10.1212/WNL.000000000201385**

**Clinical Reasoning: A Teenage Girl With Progressive Hyperkinetic Movements, Seizures, and  
Encephalopathy**

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*Neurology*<sup>®</sup> Published Ahead of Print articles have been peer reviewed and accepted for publication. This manuscript will be published in its final form after copyediting, page composition, and review of proofs.

Errors that could affect the content may be corrected during these processes.

**Equal Author Contribution:**

**Contributions:**

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Apostolos Papandreou: Drafting/revision of the manuscript for content, including medical writing for content; Major role in the acquisition of data; Study concept or design; Analysis or interpretation of data

**Figure Count:**

2

**Table Count:**

0

**Search Terms:**

[ 46 ] All Education, [ 298 ] Spinocerebellar ataxia, [ 157 ] Mitochondrial disorders; see Genetics/Mitochondrial disorders (S), [ 318 ] Rett Syndrome, [ 227 ] All Pediatric

**Acknowledgment:****Study Funding:**

This study was supported by the National Institute for Health Research Biomedical Research Centre at Great Ormond Street Hospital for Children NHS Foundation Trust and University College London.

**Disclosures:**

Dr. Papandreou is funded by an NIHR Great Ormond Street Hospital Biomedical Research Centre Catalyst Fellowship. The other authors report no relevant disclosures.

**Preprint DOI:****Received Date:**

2022-03-01

**Accepted Date:**

2022-08-26

**Handling Editor Statement:**

Submitted and externally peer reviewed. The handling editor was Whitley Aamodt, MD, MPH.

**Abstract**

The 'epilepsy-dyskinesia' spectrum is increasingly recognized in neurogenetic and neurometabolic conditions. It can be challenging to diagnose due to clinical and genetic heterogeneity, atypical or nonspecific presentations, and the rarity of each diagnostic entity. This is further complicated by the lack of sensitive or specific biomarkers for most nonenzymatic neurometabolic conditions. Nevertheless, clinical awareness and timely diagnosis are paramount to facilitate appropriate prognostication, counselling, and management.

This report describes a case of a teenage girl who had presented at 14 months with a protracted illness manifesting as gastrointestinal upset and associated motor and cognitive regression. A choreoathetoid movement disorder, truncal ataxia, and microcephaly evolved after the acute phase. Neurometabolic and inflammatory investigations, EEG, brain MRI, muscle biopsy (including respiratory chain enzyme studies), and targeted genetic testing were unremarkable. A second distinct regression phase ensued at 14 years, consisting of encephalopathy, multifocal motor

seizures, absent deep tendon reflexes and worsening movements, as well as gut dysmotility and dysphagia. Video EEGs showed an evolving developmental and epileptic encephalopathy with multifocal seizures and nonepileptic movements. A brain MRI revealed evolving and fluctuating patchy bi-hemispheric cortical changes, cerebellar atrophy with signal change, mild generalized brain volume loss, and abnormal lactate on MR spectroscopy.

The article discusses the differential diagnostic approach and management options for patients presenting with neurological regression, encephalopathy, seizures, and hyperkinetic movements. It also emphasizes the utility of next generation sequencing in providing a rapid, efficient, cost-effective way of determining the underlying etiology of complex neurologic presentations.

**Key words:** mitochondrial DNA depletion syndrome (MDDS), *TWNK*, next generation sequencing, biomarkers, case report

## Section 1

A female with normal early neurodevelopment and nonconsanguineous White parents presented at 14 months of life, 1 month after her MMR vaccine, with pyrexia, vomiting, and protracted encephalopathy. After slow recovery over weeks, motor and language regression, ataxia, four-limb choreoathetosis, and hand-wringing stereotypies became evident. Extensive CSF, blood, and urine neurometabolic, inflammatory, and immunological investigations (including CSF cell counts, protein, lactate, oligoclonal bands, and autoantibodies), muscle biopsy (histopathology and respiratory chain enzyme analysis) and brain MRI were unremarkable. CGH array analysis and targeted genetic testing (e.g. *MECP2* sequencing) were normal. Whole exome sequencing (WES) failed due to poor DNA sample quality. The patient made slow subsequent developmental progress. Progressive microcephaly (from normal to 6<sup>th</sup> percentile) was detected on follow-up.

At 14 years, the patient could crawl, pull herself to supported standing, self-propel in a wheelchair, self-feed, and use nonverbal cues to communicate. She was short-sighted and hearing was normal. However, 4 weeks post her Human Papillomavirus vaccination, she developed acute-onset vomiting, progressive lethargy, and profound encephalopathy. Prominent hyperkinetic movements were noted, including four-limb choreoathetosis, multifocal myoclonus, four-limb and trunk dystonic posturing, orofacial/lingual dyskinesias, significant bulbar dysfunction and dysphagia. Limb tone was variable, with central hypotonia and areflexia. Serial video EEGs (**Figure 1**) showed multifocal, right-predominant epileptiform activity, partially responsive to antiepileptics. Repeat MRI (**Figure 2**) revealed patchy bi-hemispheric cortical T2 hyperintensities with diffusion-weighted restriction, progressive cerebellar atrophy, and mild generalized brain volume loss. MR spectroscopy showed an abnormal lactate peak.

Following a progressive two-month deterioration characterized by persistent encephalopathy, disabling hyperkinesias, and worsening dysphagia, she passed away due to upper airway secretion pooling and respiratory arrest.

Question for consideration

1. What is the differential diagnosis?

## Section 2

Our case's progressive, stepwise deterioration pointed to a neurodegenerative, mitochondrial, or neurometabolic disorder. Despite normal plasma/CSF lactate values and unremarkable muscle histopathology and respiratory chain analysis, mitochondrial cytopathies were considered. *POLG*-related disease and other mitochondrial DNA (mtDNA) depletion syndromes (MDDS)<sup>1</sup> may have similar clinical manifestations, including continuous focal motor seizures on a background of evolving encephalopathy. Other mitochondrial cytopathies including mitochondrial encephalomyopathy, lactic acidosis, and stroke-like episodes or MELAS -mostly due to the mitochondrial DNA (mtDNA) m.3243A>G *MT-TL1* pathogenic variant- were included in the differential, due to the MRI T2 hyperintensity, diffusion restriction, and abnormal MRS lactate peak.<sup>2</sup> However, there was no lactic acidemia on repeated measurements, and no ragged-red fibres on muscle biopsy.

Other neurogenetic and neurodegenerative conditions can have similar manifestations. Loss of skills, postnatal microcephaly, and emergence of hand-wringing stereotypies or other abnormal movements occur in *MECP2*-related and similar ('Rett-like')<sup>3</sup> disorders. Infantile neuroaxonal dystrophy caused by recessive *PLA2G6* mutations also presents with early-onset neurodegeneration, hyperkinetic movement disorders, axonal-type sensorimotor neuropathy, and later-onset epilepsy and bulbar dysfunction.<sup>4</sup> However, no other *PLA2G6*-related radiological findings (e.g., pallidal iron deposition, claval hypertrophy, or thin vertically-oriented corpus callosum) were present on serial neuroimaging.

Finally, the biphasic deterioration and fluctuating patchy cortical MRI changes could be consistent with inflammatory or post-infective processes. However, in both presentations CSF was acellular with normal glucose/protein and negative oligoclonal bands. Blood/CSF inflammatory markers, cultures, and autoantibodies were also negative.

Question for consideration

1. Can you think of other investigations to help establish the diagnosis?

### Section 3

The lack of ultra-sensitive or specific biomarkers for most nonenzymatic neurometabolic and mitochondrial conditions further complicates the differential diagnostic process in similar cases. Reliable biomarkers are crucial for facilitating rapid diagnosis and monitoring disease severity and response to therapeutic interventions. The latter is increasingly pertinent, as an ever growing number of disease-specific, effective, novel therapeutics become available.<sup>5</sup> Serum FGF-21, a cytokine which regulates lipid metabolism and the starvation response, can be useful when suspecting mitochondrial cytopathies; however, patient values can overlap with controls and similarly presenting nonmitochondrial conditions<sup>6</sup>. *POLG*-related disease is linked to distinct CSF neurotransmitter signatures (such as high homovanillic acid, 5-hydroxyindoleacetic acid and neopterin), but this is neither very sensitive nor specific.<sup>7</sup> In addition, such investigations are expensive, difficult to organize, or unavailable in many clinical settings.

Overall, the most cost-effective, highest diagnostic yield investigation in similar situations is WES/whole genome sequencing (WGS), including immediate family members.<sup>8</sup> In our case, WES failed after first presentation and was not immediately repeated due to eventual clinical stabilization and slow regaining of developmental skills; thus, targeted gene testing to exclude pertinent entities

(e.g. *MECP2*, *PLA2G6*) was performed instead. However, during the second period of regression, rapid trio WES was requested. WGS can identify many small mtDNA deletions or mutations.<sup>9</sup> However, rapid trio WES (in parallel with mtDNA sequencing from stored muscle) was prioritized, due to the fast clinical deterioration and the test's two-week turnaround time. Eventually, compound heterozygous pathogenic *TWNK* variants were identified including novel maternally inherited c.1267A; p.(Thr423Ser) and previously reported, paternally inherited c.1523A; p.(Tyr508Cys).<sup>10</sup>

Importantly, mtDNA genome sequencing was not performed after the initial neuroregression but requested after the second. The test utilized stored muscle tissue, but analysis was eventually impossible due to an insufficient sample. Apart from mtDNA copy number reduction, defects in mtDNA replication also led to mtDNA mutations/deletions that could contribute to the clinical phenotype. When suspecting MDDS, mtDNA sequencing should be considered early on and/or in parallel with WES/ WGS.

Question for consideration

1. What do you think about the reported temporal relation to vaccinations?

#### Section 4

The temporal association between clinical deterioration and vaccinations are likely coincidental or the result of overreporting. Our patient was up to date with immunizations and had previously received several other vaccinations that did not provoke neuroregression. Adherence to childhood vaccinations should be advocated for all children, especially for mitochondrial disorders where infections are well-recognized triggers for neurodegeneration.<sup>11</sup> The pathophysiological mechanisms behind this are not well understood; however, the energy-deplete state could prime the brain for injury triggered and propagated by energy-demanding processes (e.g., infections).<sup>7</sup> Adverse effects of the host-defence mechanisms on the already-impaired mitochondrial function have also been hypothesized<sup>11</sup>.

#### Discussion

Cells contain thousands of mtDNA copies. MtDNA is maintained by several nuclear-encoded genes, mutations which lead to mtDNA depletion or defective maintenance. MtDNA quantity and quality reduction leads to a) defective mitochondrial respiratory chain complex subunit production and reduced energy within cells, and b) subsequent affected tissue and organ dysfunction that manifests in a heterogeneous spectrum referred to as MDDS.<sup>1</sup>

*TWNK* (also known as *C10orf2*) is a nuclear gene crucial for mtDNA replication and maintenance.<sup>1,10</sup> The encoded protein ('Twinkle'), the main mtDNA replicase in the mtDNA replisome, unwinds the mtDNA helix for replication by polymerase gamma (POLG). *TWNK* mutations cause a MDDS,<sup>1</sup> with variable clinicoradiologic manifestations.<sup>1,10,12</sup>

Our patient manifested with a clinicoradiologic constellation consistent with Infantile-Onset Spinocerebellar Ataxia (IOSCA).<sup>1,10,12</sup> *TWNK*-related MDDS presentations range from Progressive External Ophthalmoplegia in dominant inheritance to Alpers syndrome, *POLG*-like disorders, Perrault Syndrome (e.g., sensorineural hearing loss, ataxia, ovarian dysfunction) and IOSCA, in cases of

recessive/biallelic pathogenic variants.<sup>1, 10, 12</sup> The IOSCA spectrum encompasses progressive early encephalopathy with epilepsy, myopathy, sensory axonal neuropathy with areflexia, movement disorders (ataxia, orofacial dyskinesias, myoclonus), hearing loss, ophthalmoplegia, liver dysfunction, proximal renal tubulopathy and hypergonadotropic hypogonadism.<sup>12</sup> Several of these features were present in our case including progressive cerebellar atrophy and areflexia, suggestive of underlying neuropathy. Other IOSCA-related features were absent, as our patient exhibited pubertal signs (recent growth spurt, breast development), normal liver/kidney function, and no reported hearing difficulties, which emphasizes the clinical heterogeneity encountered in *TWINK*-related disorders and MDDS in general.<sup>1</sup> The mechanisms underpinning this heterogeneity are poorly understood; however, mutation types can influence clinical presentations, and the novel pathogenic variant identified in our patient might contribute towards the observed phenotype.

Co-manifestation of epileptic seizures and nonepileptic abnormal movements is increasingly recognized in neurogenetic and neurometabolic conditions,<sup>13</sup> and important to consider for prompt recognition and treatment. As in our case, movement disorders can be prominent and disabling in mitochondrial cytopathies; they are primarily hyperkinetic in childhood, with more prevalent hypokinetic/Parkinsonian features in adulthood.<sup>7, 13, 14</sup> The 'epilepsy-dyskinesia' spectrum can be diagnostically challenging, due to clinical and genetic heterogeneity, frequently atypical or nonspecific presentations, lack of biomarkers, and rarity of each condition. Hence, a high index of suspicion and/or prompt referral to expert centers is warranted.

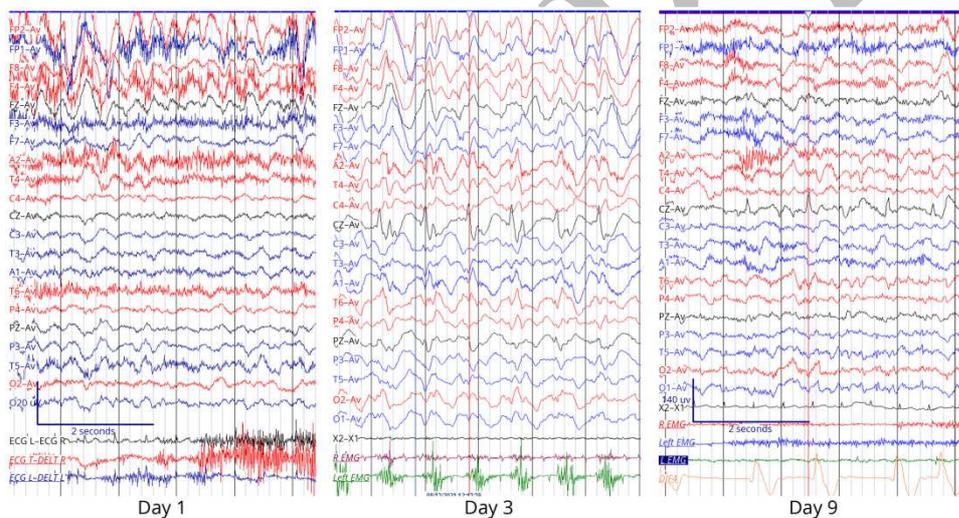
In our case, rapid trio WES facilitated early diagnosis, appropriate counselling, and further multi-disciplinary management towards palliation. Rapid sequencing modalities are becoming increasingly available in the clinical setting,<sup>8</sup> and associated with cost-effectiveness and high diagnostic yield. These tests should be considered early on when suspecting monogenic neurometabolic/neurodegenerative conditions.

Finally, management of mitochondrial cytopathies involves a multi-disciplinary team approach with the aim to alleviate disability, prevent secondary complications, and improve life quality. For our patient, especially after the latter regression, 'mitochondrial cocktails' were considered but not administered. Vitamin supplementation and antioxidant administration is often advocated and may have a role,<sup>15</sup> but efficacy-related data are scarce and more studies are warranted to further establish their utility.

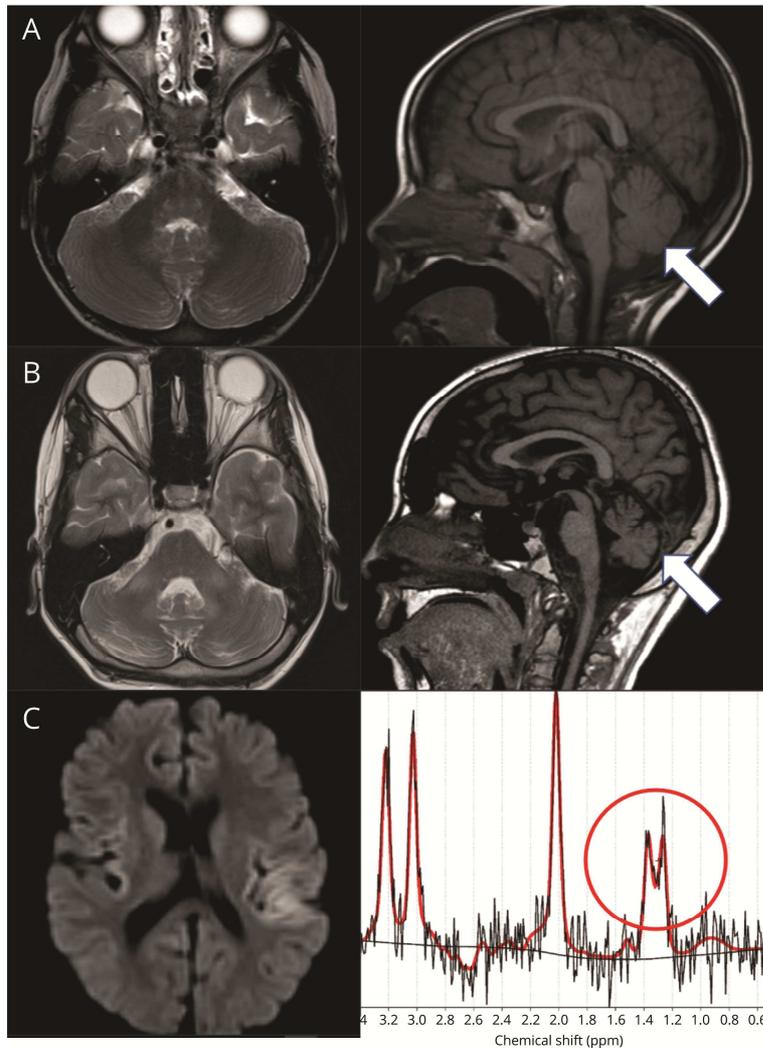
In conclusion, MDDS are clinically and genetically heterogeneous but should be considered in children with progressive or stepwise neurologic deterioration. Next generation sequencing represents a rapid, cost-effective, relatively high-yield investigation in these cases. To improve the diagnostic process, a high index of suspicion and early referral to expert centers is key, but more research is also needed for identification of disease-specific, sensitive biomarkers.

## FIGURE LEGENDS

**Figure 1. Video EEG. Day 1:** The first EEG done to exclude non-convulsive status was contaminated with excess movement and muscle EMG artefact. Underlying this, the EEG showed diffuse background attenuation with non-recruiting bifrontal 2-3Hz slow waves (and some spikes intermixed over the right frontocentral-temporal); this was partially responsive to antiepileptics. The last 2 channels are EMG polygraphy from the right and left deltoid. **Day 3:** Over the course of the next week, focal motor seizures were recorded, with some showing retained awareness; these were very difficult to delineate from the more pronounced and intrusive movement disorder. The seizures recorded consisted of clonic jerking of either lower limb, at times becoming bilateral. A midline focal ictal EEG correlate was seen [consistent sharp wave over Cz (vertex) preceding each clonus], and concordant with the semiology. Background shows diffuse rhythmic slowing with spikes and slow waves. The last channel in green is EMG polygraphy from the left quadriceps showing left leg clonus. **Day 9:** In the last recording over a 50-minute period, 14 self-terminating intermittent focal clonic seizures were recorded, involving the right lower limb. Many other movements did not have an ictal EEG correlate. The last channel in orange is EMG polygraphy showing clonus of the right foot. Preceding Cz sharp wave is seen. **Overall,** the EEG evolution was in keeping with a genetic developmental and epileptic encephalopathy with a movement disorder.



**Figure 2. MR Imaging. A:** Axial T2-weighted and sagittal T1-weighted images from a scan obtained at age 3 years. **B:** Corresponding images obtained at age 14 years showing progressive cerebellar atrophy (arrows), abnormal signal in the deep cerebellar white matter and in the middle cerebellar peduncles. **C:** Diffusion weighted imaging showing bilateral patchy areas of cortical diffusion restriction and a MR spectroscopy from the cerebellum showing an abnormal elevated lactate doublet peak (red circle).



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*Neurology* published online September 21, 2022

DOI 10.1212/WNL.0000000000201385

**This information is current as of September 21, 2022**

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