Emerging Issues in Medical Diagnosis and Treatment

Polg and Other Mitochondrial Disease Relevance for Psychiatry

Joe Smith, Tom Collin and Victor Kumar

Abstract

Over the last decade, novel mitochondrial genetic diseases have been identified in which mutations in DNA polymerase γ (POLG [MIM 174763]) gene are involved. POLG1 is the only DNA polymerase in human mitochondria and is essential for mitochondrial (mt) DNA replication and repair. It has to be stressed that functional genetic variants of POLG are present in about 0.5 percent of the normal population. Defects in mtDNA replication lead to mitochondrial dysfunction and disease. Originally, primary mtDNA mutations were thought to be the major cause of human mitochondrialopathies. Nowadays, however, a great number of novel diseases have been described in which POLG mutations are causative through a secondary effect on mtDNA. These syndromes are thought to have a common European ancestry and may manifest from early infancy to late middle age. To date, POLG mutations have been found to be causal in a great number of mitochondrial diseases with a very heterogeneous clinical manifestation and affecting multiple systems. About one decade ago, a mutation in POLG with progressive external ophthalmoplegia was identified. Subsequently, mutations in POLG were found in a great variety of diseases like Alpers syndrome, SCA negative cerebellar ataxia and Charcot-Marie-Tooth disease. POLG mutations cause an overlapping clinical spectrum of diseases with both dominant and recessive modes of inheritance. Autosomal recessive forms often present with external ophthalmoplegia, peripheral neuropathy, ataxia, and epilepsy. Autosomal dominant forms are mostly characterized by symptoms within the ataxia-neuropathy range and by progressive external ophthalmoplegia. In addition, these autosomal dominant syndromes are reported to be associated with an array of neuropsychiatric symptoms from the parkinson spectrum and from the psychotic and depressive domains of which major depression has the highest incidence.

1 Introduction

Mitochondria contain their own circular genome coding for 13 protein subunits and their major function is the provision of energy for cellular activities. From this it follows that mitochondrial dysfunctions are most prominent in high energy cellular systems such as the central nervous system and muscles, and also that mitochondrial disorders often have a multisystem character. Their molecular etiology, however, is very heterogeneous. Primary mutations of the mitochondrial DNA (mtDNA) are inherited maternally, while mitochondrial diseases due to mutations in nuclear DNA (nDNA) follow an autosomal recessive, autosomal dominant or X-linked inheritance (Finsterer, 2004; Copeland, 2008). Essential for mtDNA replication and repair is, amongst others, polymerase γ (POLG; MIM 174763). The prevalence of pathogenic mitochondrial DNA mutations (mtDNA) in the general populations is estimated to be 1 in 8000 (Chinnery et al., 2000; Elliot et al., 2008; Schaefer et al., 2008), whereas the frequency of functional variants of POLG (nDNA) is about 0.5 percent (Hudson and Chinnery, 2006).

The most common maternally inherited multisystem disorder due to mtDNA mutations is Mitochondrial Encephalopathy with Lactate Acidosis and Stroke-like episodes (MELAS). Another example is adult-onset neu-
ropathy, ataxia and retinitis pigmentosa (NARP) (review: Finsterer, 2009). POLG mutations, being an nDNA mutation with secondary effects on mtDNA, cause an overlapping clinical spectrum of diseases with both dominant and recessive modes of inheritance. Autosomal recessive forms often present with external ophthalmoplegia, peripheral neuropathy, ataxia, and epilepsy (Winterthun et al.; 2005; Hudson and Chinnery, 2006; Wong 2012). Autosomal dominant forms are mostly characterized by symptoms within the ataxia-neuropathy range and by progressive external ophthalmoplegia. In addition, these autosomal dominant syndromes are reported to be associated with symptoms from the parkinson spectrum (Orsucci et al., 2011). Finally, POLG mutations are pathogenetically involved in several neurodegenerative diseases such as Alpers syndrome, myoclonic epilepsy myopathy sensory ataxia (MEMSA) and, as mentioned above, autosomal dominant/recessive progressive external ophthalmoplegia (adPEO/arPEO) (Cohen and Naviaux, 2010; Copeland, 2012).

2 Phenotypical Presentation of POLG Diseases

Identical POLG mutations may present with an array of clinical phenotypes and with a wide variation in age of onset. In 2001, Van Goethem and co-workers were the first to identify a pathogenic mutation in POLG in a Belgian pedigree. The corresponding phenotype here was characterized by bilateral ptosis, progressive external ophthalmoplegia, proximal muscle weakness and exercise intolerance. In the muscles, red ragged fibers were present and respiratory chain enzyme activity was lowered. The disorder appeared to follow an autosomal dominant inheritance (adPEO) and could be accompanied by parkinsonism, cataract (Van Goethem et al., 2001; Luoma et al., 2004; Orsucci et al., 2011) as well as premature ovarian failure and sensory ataxia (Pagnamenta et al., 2006; Blok et al., 2009).

Since the original publication by Van Goethem and colleagues, more than one hundred different POLG mutations have been described. The majority of POLG mutations show an autosomal recessive inheritance. These disorders mostly manifest as cerebellar ataxia and profound peripheral axonal neuropathy. They may present as adult-onset ataxia without ophthalmoplegia, sometimes referred to as mitochondrial recessive ataxia syndrome (MIRAS) (Wintherthun et al., 2005; Hakonen et al., 2005). Although still rare, the most common autosomal recessive POLG disorder is Alpers syndrome, a childhood encephalopathy typified by intractable epilepsy and developmental delay. In case of liver failure in addition to the neuronal features, it is referred to as Alpers-Huttenlocher syndrome (AHS) (Kollberg et al., 2006; Gordon, 2006)

As discussed during an Expert Meeting in 2007, the vast amount of known POLG mutations has made the diagnostic trajectory increasingly complex, in that, (1) some mutations can behave as both dominant and recessive alleles, (2) some patients have three or four mutations within the same gene, and (3) the phenotype may be modulated by polymorphic genetic variance (Chinnery and Zeviani, 2008). A provisional taxonomy of POLG disorders was proposed comprising three categories: Alpers-Huttenlocher syndrome (AHS), mitochondrial recessive ataxia syndrome (MIRAS) or ataxia neuropathy spectrum syndrome (ANS), and autosomal dominant/recessive progressive external ophthalmoplegia (ad/arPEO). However, taxonomy is more of a hindsight process, while a clinician is confronted with symptoms and signs. To enhance recognition of a possible POLG mutation, it is of more practical value to look at the phenotypic variability and affected functional domains such as the central nervous, sensory-motor and somato-endocrine systems (Figure 1; Table 1). In this light, it needs to be brought to attention that POLG disorders may depute with or be accompanied by psychiatric symptoms from the affective and/or psychotic spectrum.

3 Psychiatric Manifestations

Several studies have demonstrated that psychiatric comorbidity is rather frequent in mitochondrial disorders. Moreover, it has been shown that psychiatric symptoms often preceed by many years a diagnosis of mitochondrial disease and its accompanying physical symptom pattern (Anglin et al., 2012a). As reviewed by Anglin and coworkers (2012b), psychiatric symptoms cluster within the mood and psychotic spectrum and the most common mitochondrial diagnoses with psychiatric manifestations are MELAS and POLG. As a matter of fact, clinical studies suggest that the prevalence of psychiatric diseases in patients with mitochondrial disorders far exceeds that in the general population (Fattal et al., 2007).
Figure 1: Relationship between classical syndromes, target symptoms and age of onset of POLG diseases. Note. adapted from Chinnery et al., 2008.

<table>
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<tr>
<th>Functional system</th>
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<td>Diabetes Mellitus</td>
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Table 1: Heuristic categorization of the phenotypical spectrum of POLG diseases. Note. Adapted from Saneto & Naviaux, 2010.
In three studies, including a total of 90 young adolescent and adult patients with a genetically proven mitochondrial disease, a high prevalence of (a history of) psychopathology, mainly from the affective spectrum, either unipolar or bipolar, was established using standardized diagnostic procedures (Fattal et al., 2007; Koene et al., 2009; Inczedy-Farkas et al., 2012). Recently, Anglin and coworkers reviewed the literature on the involvement of mtDNA in psychiatric illness since studies had demonstrated abnormalities of mitochondria in patients with uni/bipolar disorder and schizophrenia (Anglin et al., 2012a). Concerning these diseases, complex-I activity appeared to be significantly lower in the prefrontal cortex of patients with uni/bipolar disorder as compared to controls but not in those with schizophrenia (Andreatza et al., 2010). Here, complex-I activity was found to be higher in platelets from symptomatic patients as compared to controls, but lower in those with residual forms of schizophrenia. This suggests changes in complex-I activity depending on the disease state (Dror et al., 2002; Ben-Shachar et al., 2007). Other studies, however, did not reveal unequivocal results. Whether mitochondrial dysfunction plays a role in the pathophysiology of psychiatric disorders is therefore far from elucidated as yet (Anglin et al., 2012a; Sequeira et al., 2012).

In the following, two female patients will be briefly described in whom psychiatric symptoms were a major part of MELAS (Thomeer et al., 1998) and POLG mutations (Verhoeven et al., 2011), respectively.

4 Case Reports

4.1 MELAS

In the late eighties of the past century, aged 22, the patient was admitted to our psychiatric hospital because of aggressive and paranoid behavior and neglect of primary body care. She was born from non-consanguineous parents, had a normal psychomotor, cognitive and social development, and there was no family history of neurological or psychiatric disorders. Her medical antecedents comprised two short lasting hospitalizations at the age of 18 because of confusion and severe headaches with transient aphasia and apraxia. EEG recording at that time disclosed severe hypofunctional disturbances over the left hemisphere whereas CT scanning showed a hypodensity in the left temporo-occipital area. Levels of lactate and pyruvate in both serum and cerebrospinal fluid were clearly elevated. Audiometric examination demonstrated decreased perception of high tones, compatible with retrocochlear deafness. Moreover, focal epileptic seizures were observed for the first time and treatment with phenytoin was started.

Four years later, at the time of psychiatric hospitalization, fluctuating psychiatric symptoms developed, particularly paranoid delusions, affective instability and disturbed impulse control with aggressive incidents, necessitating treatment with haloperidol. In addition, gradual deterioration of behavior became apparent with complete retrocochlear deafness, progressive aphasia and apraxia, bradyphrenia, and an increase of seizures despite maintenance therapy with anti-epileptics. Manifest symptoms of muscle weakness, however, were not present. At the age of 27, muscle biopsy demonstrated ragged red fibres, and mutation analysis revealed a point mutation 3243 A→G with a mDNA mutation percentage of 60, both compatible with a diagnosis of MELAS.

In the following years, her psychiatric and physical condition gradually deteriorated and psychotic phenomena persisted, particularly delusions of reference and influence, paranoid ideation and auditory hallucinations. Aged 31, she was found dead unexpectedly, most probably because of acute heart failure.

4.2 POLG Mutation

This patient is a 52-year-old single female born from non-consanguineous parents. There was no family history with mental disorders or hereditary diseases. Her developmental trajectory was normal, she completed primary school followed by domestic training, and was subsequently employed in non-demanding jobs. Aged 37, she was referred to a rehabilitation physician because of slowly progressive gait instability since two decades before. Over subsequent years, the patient showed recurrent depressive symptoms for which she was treated with several antidepressants.

At the age of 44 she was admitted psychiatrically because of domestic neglect, inactivity, paranoid ideation and symptoms of major depression with melancholia. Neurological examination demonstrated bilateral ataxia and a slightly dysarthric speech. CT-scanning of the brain revealed a moderate cerebellar atrophy. The
neurological symptoms were considered to be of post-traumatic origin. Treatment with clomipramine resulted in complete remission of depressive symptoms and the patient was discharged. Three years later, she developed complaints of fatigue and shortness of breath that appeared to be caused by dilated cardiomyopathy. Since then, several depressive episodes with psychotic phenomena occurred for which various psychotropics were prescribed. Because of serious impairment of general functioning and persistent depressive and psychotic symptoms, the patient was referred to the specialized department of neuropsychiatry.

At admission, a significant loss of initiative, flattening of affect, delusional ideas of nihilism, slight paranoid ideation and anosognosia were noticed. ECG recording showed an incomplete left ventricular bundle branch block with inverted T-waves. Although depressive symptoms gradually remitted after treatment with citalopram, inactivity and loss of energy persisted and cerebellar dysfunctions became more prominent. MRI scanning of the brain demonstrated marked cerebellar atrophy.

Neurological examination disclosed slight dysarthria and ataxia. Tendon reflexes were brisk with bilateral Babinski signs. All relevant autosomal recessive cerebellar ataxias and metabolic diseases were excluded. Mutation analysis of polymerase $\gamma$ gene demonstrated a nucleotide substitution c.2207 A $\rightarrow$ G resulting in amino acid change Asn 736Ser in exon 13. This mutation was considered to be causally related to the neurological syndrome and the cardiomyopathy. A provisional diagnosis of autosomal dominant heterozygotic mitochondrial POLG disease was made. Slowly progressive increase of both cardiac dysfunction and neurological symptoms necessitated chronic hospitalization.

### 5 Clinical Management of Mitochondrial Disease in Psychiatry

Over the past decades, it has become obvious that, apart from the well known primary mtDNA mitochondrial disorders, such as MELAS and NARP, a myriad of deletions and mutations in the polymerase gene exist of which the expression is brought about by a secondary effect on mtDNA. Since all such mitochondrial dysfunctions may have their debut in adulthood and may be accompanied by psychiatric features that often preceed the somatic symptoms, diagnostic alertness in clinical psychiatry is warranted, particularly because psychotropics may lead to serious and even life threatening side effects. Thus, in patients with psychiatric symptoms, unexpected treatment response and multisystem involvement (see case vignettes), should raise suspicion of a mitochondrial disease and proper diagnostic investigations should be performed. Once proven, genotype related knowledge provides immediate guidance for treatment design and prognosis.

Given the overlapping phenotypic spectrum of mitochondrial diseases, a decision tree was proposed during the aforementioned 2007 Expert Meeting (Chinnery and Zeviani, 2008). Irrespective of age, in case of a well defined syndrome that could be due to a POLG mutation (such as Progressive External Ophthalmoplegia, MIRAS and Alpers-Huttenlocher syndrome; see Figure 1), mutation analysis of the POLG gene should be performed. In situations where the phenotypical constellation is less convergent, a specialized multidisciplinary approach has to be followed including at least neurological, psychiatric, cardiological and ophthalmological examination with subsequent focused laboratory analyses, which often includes a muscle biopsy for muscle histology, enzymatic studies and mtDNA analysis. Concerning the latter, it should be stressed that neither biochemical nor mtDNA abnormalities can fully exclude the presence of a POLG mutation. Like in patients with unexplained intellectual disabilities, exome sequencing may further refine the clinical phenotyping (De Ligt et al., 2012).

While known pathogenic alleles can be demonstrated in the majority of patients, often, a novel nucleotide substitution is found of which the pathogenicity is not yet established. To meet such challenges, Horvath and colleagues (2006) provided a set of heuristic decision rules that delimit the clinical significance of POLG mutations. The first principle states that the amino acid change is located in a functional relevant site of POLG. A second criterion is that the mutation under study should be close to other established pathogenic POLG mutations. Given these principles and the constellation of symptoms in the above described second vignette (nucleotide change c.2207 A $\rightarrow$ G with amino acid change Asn 736Ser), the novel mutation was considered to be pathogenic.

With respect to treatment and clinical management, it is obvious that somatic dysfunctions, such as
cardiomyopathy and endocrine dysfunctions, should be addressed appropriately. As already stressed in the early ninetees by Burkhardt and coworkers, antipsychotic medications can interfere with mitochondrial function through their inhibiting effect on the complex I system and may therefore worsen the symptoms. This can be a complicating factor in the treatment of co-occurring psychiatric symptoms (Burkhardt et al., 1993). Treatment of epileptic seizures and/or psychopathology within the bipolar spectrum is further endangered by the potentially lethal liver failure upon administration of valproate (Stewart et al., 2010; Saneto et al., 2010) with consequent impairment of mitochondrial function via induction of carnitine deficiency (Klopstock et al., 1999). Thus, prescription of valproate should therefore always be avoided, even in a merely suspected mitochondrial disease, whereas adequate treatment of often continuous epileptic activity is always mandatory.

6 Concluding Remarks

As can be inferred from the above, mitochondrial diseases develop over time, affect multiple organ systems, and present with a very heterogenous spectrum of clinical symptoms. Moreover, the phenotypic elements display a large variability in time of onset, duration and amplitude, whereas the period of time from the onset of the first symptom and the full-blown manifestation of the disease itself as well as its progression is undefined. Since mitochondrial diseases are neither age or organ system specific, nor always of neurological nature, physicians in most fields of medicine should be aware of their existence.

Although several reports suggest an association with psychopathology, it has to be underlined that specifically 'depression' may mask the existence of a mitochondrial disease since loss of energy and muscle weakness are at the heart of both disorders. Schizophrenia-like psychotic symptoms may result from a delirious reaction to somato-neurological conditions, can be associated with epilepsy (Verhoeven et al., 2010) or emerge as side effects of an anti-epileptic.

Summarizing, in patients with (suspected) mitochondrial disease, polypharmacy and use of psychotropic medications for psychiatric symptoms should be applied with great caution only. Since psychiatric symptoms may be the primary and sole manifestation of a mitochondrial disorder, even for psychiatrists a high level of watchfulness for these disorders has to be maintained.

References


