Friedrich Nietzsche (1844–1900): a classical case of mitochondrial encephalomyopathy with lactic acidosis and stroke-like episodes (MELAS) syndrome?

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Friedrich Nietzsche (1844–1900): a classical case of mitochondrial encephalomyopathy with lactic acidosis and stroke-like episodes (MELAS) syndrome?

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Summary: Friedrich Nietzsche was one of the most influential and profound German philosophers. After prolonged illness, he died at the age of 55 in Weimar, Germany. The interest in his medical biography has always been strong while the cause of his illness and death has remained a mystery, intriguing philosophers as well as physicians. The diagnosis of syphilis proposed in the 19th century has been controversial until today and many other diagnoses have been discussed. This paper suggests that Nietzsche suffered from mitochondrial encephalomyopathy with lactic acidosis and stroke-like episodes syndrome.

Nietzsche's signs and symptoms

When Nietzsche was four years old, an ophthalmologist noted his anisocoria, anisometropia and myopia. By the age of 11 years he was already suffering from headaches and myalgia. Recurrent headaches and vomiting continued for decades after his school age years. These episodes usually lasted for several days at intervals of two to three weeks and often were triggered by psychological factors or weather conditions.[1]

From the age of 29 years Nietzsche was ill frequently. Dr Heinrich Schiess (1833–1914; Professor of Ophthalmology in Basel, Switzerland) found pigmentary changes in the retinae, anisocoria (dilated right pupil), diplopia with convergent strabismus, absence of stereoscopic vision, normal intraocular pressures, extreme myopia in the right eye, high myopia in the left eye, and a visual acuity of 20/100 in the right eye and 20/40 in the left eye. Nietzsche had always been myopic, wearing glasses of between 10 and 20 diopters for the previous 10 years. Three years later ophthalmologists found pigmentary changes involving the macula lutea in both eyes and the optical media were clear (Figure 1).

From the age of 31 years Nietzsche's abdominal and stomach problems became aggravated with pain and constipation. Recurrent headaches and eye pain accompanied by vomiting intensified. He complained about metamorphopsia, blurred vision, watering eyes and lid spasms. He had disturbances of speech and consciousness, vertigo and feelings of palsy lasting for hours.

When Nietzsche was 36 years old his condition improved somewhat and the episodes of headache, vomiting and eye problems lost some of their severity. However, psychiatric problems including mood changes, exaltation, depression and insomnia occurred from then onwards.

In 1888 at the age of 44 years Nietzsche experienced severe back pains and difficulty in walking. He broke down on the street in Torino in Italy. For the next few days he was in an agitated state, sang loudly, talked to himself, was aggressive and suffered from euphoria and delusions. Nietzsche was taken back to Basel and hospitalized for a week in the local psychiatric clinic where he was disoriented and in a state of agitation. His head was flushed, his pupils dilated (the right was the larger), he exhibited convergent strabismus, high myopia, amblyopia and reduced, slow pupillary reflexes without discrimination between accommodation and light reflexes. Tremor of the tongue and dysarthria were not observed, the patellar reflexes were brisk, the plantar reflexes were normal and a slight facial palsy was documented. He calmed down and gained clear consciousness again. Progressive paralysis (general paralysis of the insane, GPI) was recorded.

From 1889 to 1890 Nietzsche was hospitalized in the psychiatric clinic in Jena, Germany. On admission anisocoria was noted. The right eye displayed only an accommodation reflex; in the left eye, all pupillary reflexes were present and the pupil was slightly irregular. Ocular motility was regular with slight convergent strabismus and ptosis on the left side. Slight palsies of the right facial and glossopharyngeal nerves were found. The right shoulder was drooping and the left shoulder elevated; tremor of the tongue was not noted. The patellar reflex, the Achilles tendon reflex, the epigastric reflex, the plantar reflex and the anconeus reflex were brisk. His physician Professor Otto Binswanger (1852–1929), Professor of Psychiatry in Jena, Germany, suspected GPI in the course of syphilis and predicted a maximum life expectancy of two years; Nietzsche lived for another 10 years.

In the clinic in Jena, Nietzsche varied between bouts of clouded consciousness and excitation, exhibiting visual and auditory hallucinations and paranoia. His condition improved intermittently and often he was able to go for walks, play the piano and read.

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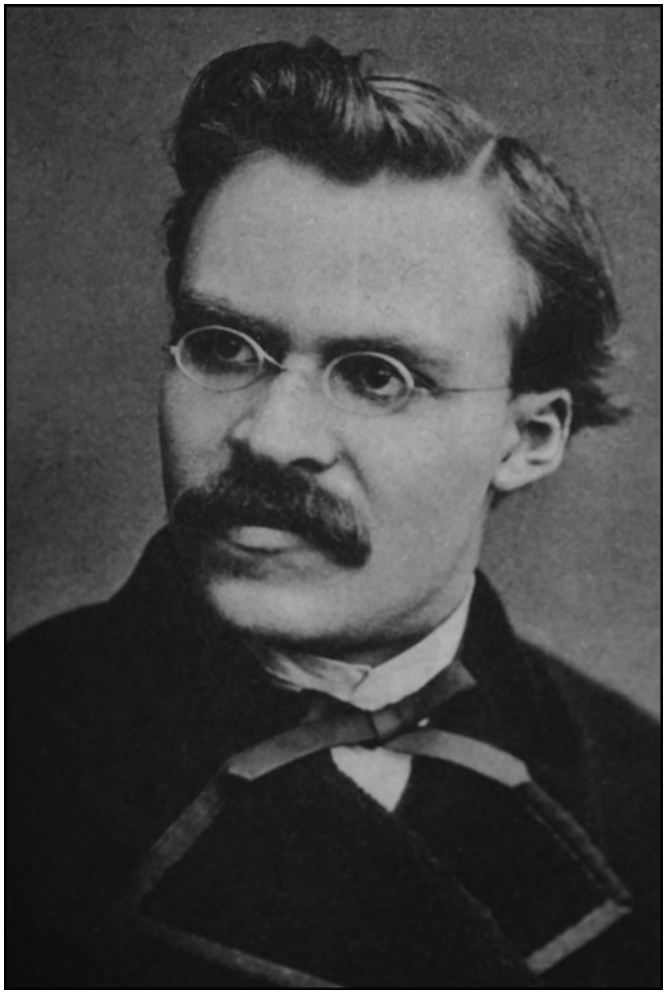

Figure 1 Friedrich Nietzsche at the age of 20 years (reproduced courtesy of the Goethe and Schiller Archive Weimar, Germany [GSA 101/11])

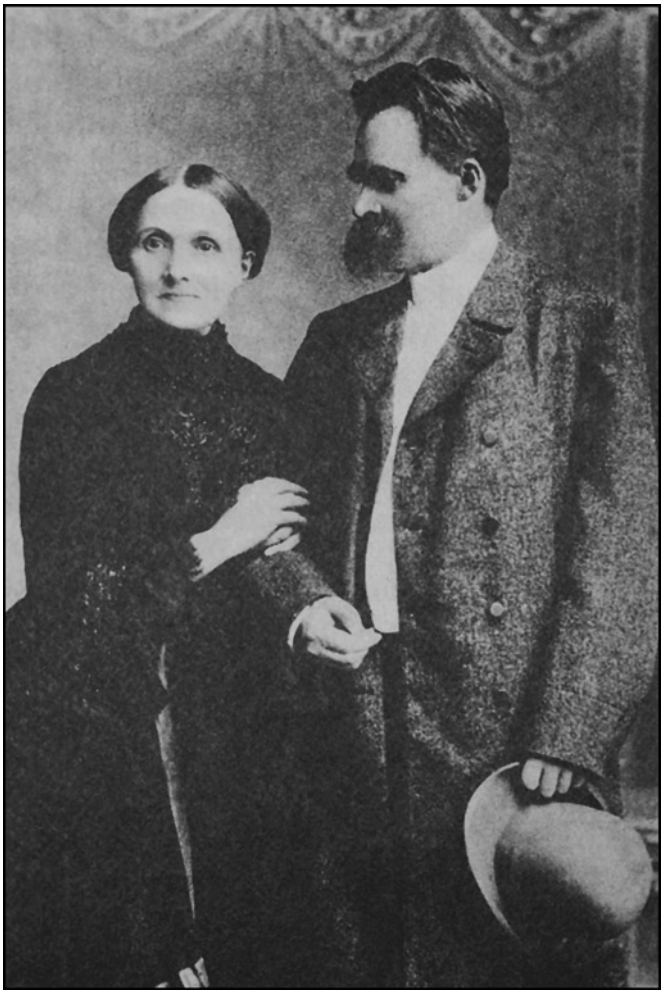

Figure 2 Nietzsche with his mother in the year 1891, (reproduced courtesy of the Goethe and Schiller Archive Weimar, Germany [GSA 101/43])

From 1890 to 1897 Nietzsche's mother and sister took care of him (Figure 2). In the beginning they went for short walks but his mental and physical abilities declined with signs of dementia, dysarthria, fading memory and motor stereotypes. From 1893 onwards, aged 49 years, he used a wheelchair and did not leave the house again. He lay on his bed stiff, tired and apathetic.

In 1899 Nietzsche had left iritis with slight adhesions that were easily disrupted with atropine. The right pupil was dilated, the left pupil irregular and the pupillary light reflexes in both eyes were absent; he was probably blind. Nietzsche suffered strokes in 1898 and 1899 that paralysed the right side of his body. In 1900 he suffered one more stroke complicated by pneumonia. On 25 August 1900 Nietzsche died at the age of 55 years. Pathological examination was not undertaken.

Nietzsche's family medical background

Nietzsche's father, Carl Ludwig Nietzsche, died at the age of 36 years probably from a brain tumour. He had seven stepsiblings and two sisters. During his life he suffered from myopia and headaches. Nietzsche's mother, Franziska Nietzsche née Oehler, had six brothers and four sisters. Several members of Nietzsche's maternal family had migraine headaches and psychiatric or neurological illness.[2] His mother, Franziska Nietzsche, was reported to have anisocoria. Nietzsche had two siblings: his brother Ludwig Joseph died as a child of two years from 'cramps'; his sister Elisabeth suffered from migraine and myopia.

Mitochondrial encephalomyopathy, lactic acidosis, and stroke-like episodes

Mitochondrial encephalomyopathy, lactic acidosis, and stroke-like episodes (MELAS) is a progressive neurodegenerative disease and a multisystem disorder with a wide variety of clinical presentations.[3] Diagnostic criteria for the MELAS syndrome include stroke-like episodes before the age of 40, encephalopathy with seizures or dementia and lactic acidosis or ragged-red fibres on muscle biopsy. At least two of the following three features must also be present: normal early development, recurrent headaches and recurrent vomiting.[4] MELAS is a mitochondrial respiratory-chain disease

and is inherited maternally.[5] About 80% of patients are found to have a heteroplasmic A-to-G point mutation in the mitochondrial transfer RNA gene at base pair 3243. However, several more associated mitochondrial DNA mutations have been described.[6,7] Clinical expression is highly variable and depends on relative heteroplasmy and abundance of mutant mtDNA, tissue distribution of mutant mtDNA and the vulnerability of each tissue to impaired oxidative phosphorylation.[8] The prevalence of mitochondrial DNA mutations has been estimated at around 12/100,000 in the adult population.[9]

Hallmark features of MELAS are stroke-like episodes accompanied by migraine-like severe headaches and vomiting for several days. The symptoms usually manifest first between the ages of two and 10 years.[10] Maternal family members may also suffer from headaches.[6]

Other common symptoms of MELAS include pigmentary retinopathy, myoclonus, ataxia,[11] episodic coma, optic atrophy, cardiomyopathy,[12] ophthalomoplegia, hearing loss, diabetes mellitus, gastrointestinal dysmotility with pseudo-obstruction and pancreatitis[13,14] and nephropathy.[7] Pain in the extremities reflects peripheral neuropathy.[6] Polydipsia and polyuria may be signs of diabetes.[6] Complications include progressive intellectual decline leading to dementia, psychosis with depression, schizophrenia or bipolar disorder, progressive external ophthalmoplegia (PEO), ptosis, visual difficulties related to retinal pigmentary degeneration or cortical blindness as sequelae of progressive cortical atrophy and recurrent stroke-like episodes.[6,15] The cumulative effects may gradually impair motor ability, mental status and vision.

In addition to MELAS, the mitochondrial diseases include, among others, Leber's hereditary optic neuropathy, myoclonus, epilepsy, ragged-red-fibres (MERFF), Kearns-Sayre-syndrome, PEO and Leigh syndrome; clinical overlaps occur.[3] The diagnosis is established by screening for mutations in blood and muscle biopsy samples.

Discussion

The underlying illness of Nietzsche's long history of signs and symptoms has been discussed controversially. Most recent authors did not agree with the diagnosis of GPI that was made on his admission to Basel and Jena in 1889. Hayman[16] named this diagnosis a typical error of the time. However, a diagnostic alternative explaining all of Nietzsche's symptoms and considering his family background has not been suggested thus far. However, Nietzsche's multisystem disease meets all the cardinal criteria for the diagnosis of a mitochondriopathy, especially MELAS syndrome or MELAS overlap syndrome.

Nietzsche's main symptoms include congenital anisocoria, strabismus, high progressive myopia, early onset of recurrent headaches accompanied by vomiting, myalgia, retinal pigmentary granulations, transient nerve palsies, ptosis, intestinal atony, disturbances of speech and consciousness, mood disorders, psychiatric problems and dementia.

The early onset of recurrent headaches, accompanied by vomiting and myalgia, is frequently experienced by patients with MELAS.[6,10] These symptoms were documented in Nietzsche's school records.

Nietzsche's anisocoria was congenital and inherited maternally. A common cause for anisocoria in childhood is Adie's tonic pupil, characterized by poor pupillary light reaction, sector palsies of the iris and an enhanced pupillary response to near effort,[17,18] resulting from loss of parasympathetic neurons in the ciliary ganglion.[19] Pupillary constriction on accommodation is less affected since, compared with the iris sphincter, the ciliary muscle is innervated approximately thirty times more strongly. On admission in Basel in 1889, Nietzsche's right pupil was dilated, reacted sluggishly to light with only the accommodation response present, while the left pupil was smaller and reacted to all stimuli. In the late 19th century this was readily associated with a typical Argyll Robertson pupil, a hallmark of central nervous system syphilis. However, in neurosyphilis the pupils are usually miotic, difficult to dilate and affected bilaterally; light-near dissociation is common.[20] The onset of symptoms in Nietzsche's childhood makes Adie's tonic pupil a conclusive diagnosis.

Nietzsche had high myopia and metamorphopsia. He complained repeatedly of various visual disturbances including sensitivity to light, pain and blurred vision. These complaints are common in degenerative myopia where vitreous liquefaction and posterior vitreous detachment may occur, complicated by macular choroidal neovascularization (CNV). Clinically CNV is characterized by metamorphopsia followed by loss of central vision.[21]

Nietzsche's retinae showed pigmentary granulations; chorioretinopathy with pigmentary disturbances and macular involvement is a frequent finding in MELAS.[22–26] In addition, ptosis and strabismus often occur in mitochondrial myopathy.[6] Together with degenerative myopia, mitochondrial disease would account for all of Nietzsche's eye symptoms; he probably died with cortical blindness as a result of cortical atrophy due to stroke-like episodes.

Nietzsche's limb pains may have been manifestations of mitochondrial peripheral neuropathy.[6] Hyperreflexia in the course of MELAS has also been described.[7]

From the age of 20, transient abdominal pain and constipation occurred. In MELAS acute onset of gastrointestinal manifestations including abdominal pain, ischaemic colitis, pancreatitis and intestinal pseudo-obstruction are common findings.[6,13,14]

Nietzsche suffered from vertigo, palsies, transient disturbances of speech and consciousness, and he had psychiatric problems including severe changes in mood, agitation, depression, and visual and auditory hallucinations. Complications of MELAS include depression, bipolar disorder,[6] paranoid behaviour, hallucinations, illusions, confusion and aphasia.[27] Nietzsche's mental, intellectual and physical abilities declined between 1889 and 1900 when he died from a final stroke accompanied by pneumonia in a state of dementia and palsy. In MELAS intercurrent neurological episodes and serial development of multifocal brain lesions lead to progressive cortical atrophy, palsy and progressive dementia.[6]

Conclusive evidence for syphilis did not exist and therefore infection remains speculative. The definite test for syphilis, the Wassermann test, was developed in 1906 but was not available at the time. In the 19th century several of Nietzsche's symptoms were readily interpreted as syphilis. However, his clinical course is very improbable for syphilis. Around 1900, patients with neurosyphilis had a mean average survival time of two or three years,[28] whereas Nietzsche lived ten more years after the diagnosis of GPI in 1889.

For the last hundred years and even recently authors have suggested various diagnoses including frontotemporal dementia,[28] meningioma[29] and other tumours.[30] However, it is important to take into account Nietzsche's full clinical history and that of his family. In summary, the onset of disease in childhood, maternal inheritance, typical symptoms and complications and the course of the disease make it likely that Friedrich Nietzsche suffered and died from MELAS syndrome or MELAS overlap syndrome. High myopia and a congenital tonic pupil complicated his eye condition.

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