eNeurologicalSci 6 (2017) 16–20

Contents lists available at ScienceDirect

eNeurologicalSci

journal homepage: http://ees.elsevier.com/ensci/

Case report

Adult-onset of mitochondrial myopathy, encephalopathy, lactic acidosis and stroke-like episodes (MELAS) syndrome with hypothyroidism and psychiatric disorders

Yu-Xing Ge, Bo Shang, Wen-Zhen Chen, You Lu, Jue Wang *

Department of Neurology, Tongji University Affiliated Tenth People's Hospital, 200072 Shanghai, PR China

ARTICLE INFO

Article history:
Received 1 November 2016
Accepted 2 November 2016
Available online 4 November 2016

Keywords:
MELAS
Mitochondrial disorders
Endocrine dysfunction
Psychiatric disorders

ABSTRACT

Mitochondrial myopathy, encephalopathy, lactic acidosis and stroke-like episodes (MELAS) is a clinical syndrome associated with mitochondrial disorders (MIDs). This report illustrates a case of MELAS syndrome with hypothyroidism and psychiatric disorders, which is different from the common clinical manifestations of MELAS syndrome, such as exercise intolerance, migraine-like headaches, hearing loss and seizures etc. There are considerable interests in the possibility that mitochondrial dysfunction may play a role in the pathogenesis of endocrine dysfunctions and psychiatric disorders in MELAS syndrome.

© 2016 The Authors. Published by Elsevier B.V. This is an open access article under the CC BY-NC-ND license (http://creativecommons.org/licenses/by-nc-nd/4.0/).

1. Introduction

Mitochondrial disorders (MIDs), presenting as multi-system affected, such as the central and peripheral nervous system, eyes, ears, endocrine glands, heart, kidney etc., single or multiple combination, are clinically, biochemically and genetically highly variable [1]. MIDs may onset at any age since birth until adulthood with acute or progressively chronic manifestation [2]. Mitochondrial encephalopathy, lactic acidosis and stroke-like episodes (MELAS) is a subtype of MIDs. Approximately 80% of patients with MELAS carry the A3243G mutation in the mitochondrial DNA [3,4]. An adult MELAS patient with a mutation at A3243G point, characterized by hypothyroidism and psychiatric disorders simultaneously is presented in this article.

2. Case report

The patient was a 37-year-old female, of 157 cm in height and 45 kg in weight. She was transferred to our department from a local hospital due to psychiatric features (both agitated behavior and auditory hallucinations), alexia and apraxia that had begun 10 days ago, followed by disorientation and generalized tonic-clonic seizures. She had a long history of episodic migraine-like headaches and progressive bilateral hearing loss for 3 years. However, she did not take any medication.

Her vital signs showed a normal body temperature of 36.8 °C, a hypotension of 90/56 mm Hg and pulse at 72 beats per minute. Because of the patient's psychiatric symptoms and application of sedative after seizure attacks, she could not cooperate with physical examination.

The laboratory data showed high anion gap metabolic acidosis with elevated levels of lactate and pyruvate. Serum levels of thyroid-stimulating hormone (TSH) and free thyroxine (FT4) were decreased. Her TSH level was low at 0.26 mU/L (normal range 0.35–5.5 mU/L), and FT4 concentration was 7.56 pmol/L (normal range 10.2–31 pmol/L). Both serum free and total triiodothyronine (FT3 and TT3) were significantly lower than normal range. FT3 concentration was 2.28 pmol/L (normal range 3.5–6.5 pmol/L), and TT3 concentration was 0.6 nmol/L (normal range 1.2–3.4 nmol/L). Moreover, elevated titers of serum anti-thyroglobulin and anti-thyroid microsomal antibodies were detected. Cerebral spinal fluid (CSF) studies were normal for cell counts and biochemistry, and negative for culture. CSF IgG index was 0.48 (normal range ≤ 0.7), and oligoclonal bands (OB) was negative.

Computed tomography (CT) scan showed lesions of hypodense in the left temporal and parietal lobe, with brainstem and cerebellar atrophy (Fig. 1A). No evidence of subarachnoid or intracerebral hemorrhage. Vascular imaging of the cervical and cerebral arteries by CT angiography excluded the possibility of cerebrovascular disease (Fig. 1B). However, CT images were not conclusive to differentiate between the infectious or metabolic lesion. On day 5, brain magnetic resonance

Abbreviations: MELAS, mitochondrial myopathy, encephalopathy, lactic acidosis and stroke-like episodes; MIDs, Mitochondrial disorders; MRC, mitochondrial respiratory chain; ATP, adenosine triphosphate; CT, Computed tomography; MRI, magnetic resonance imaging; ROI, region of interest; CSF, Cerebral spinal fluid; OB, oligoclonal bands; NAA, *N*-acetyl aspartic acid; Cr, creatine; BAEP, Brainstem auditory evoked potential; DWI, diffusion-weighted image; ADC, apparent diffusion coefficient; FLAIR, fluid-attenuated inversion recovery; DNA, deoxyribonucleic acid; RFLP, restriction fragment length polymorphism.

* Corresponding author at: Department of Neurology, Tongji University Affiliated Tenth People's Hospital, 301 Middle YanChang Rd, Shanghai 200072, PR China.
E-mail address: Wangjue.shtj@outlook.com (J. Wang).

http://dx.doi.org/10.1016/j.ensci.2016.11.005
2405-6502/© 2016 The Authors. Published by Elsevier B.V. This is an open access article under the CC BY-NC-ND license (http://creativecommons.org/licenses/by-nc-nd/4.0/).

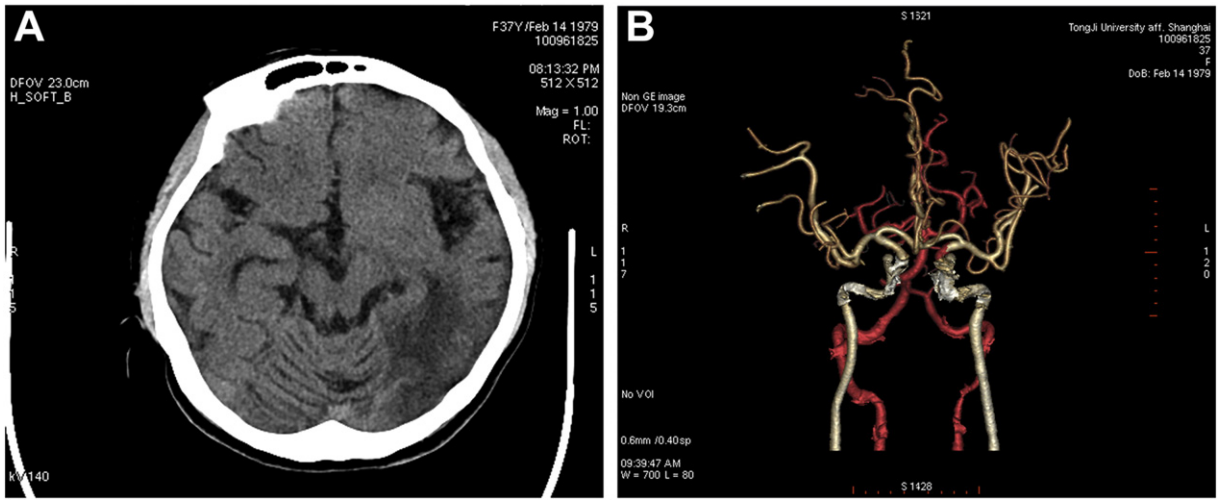

Fig. 1. CT scan showed lesions of hypodense in the left temporal and parietal lobe (Panel A). Three-dimensional reconstruction of CT vessel images (Panel B).

imaging MRI (3.0 T) revealed a hypointensity lesion in the left temporal-parietal lobe on T1 weighted image (Fig. 2A), and increased signal intensity in the same region on FLAIR sequences (Fig. 2B) with a clearly restricted diffusion (Fig. 2C). The signal intensity on ADC sequence was mildly reduced (Fig. 2D). No obvious enhancement was found on Gd-DTPA enhanced images (Fig. 2E). MR spectroscopy was carried out as well. Compared to the ipsilateral normally appearing area (Fig. 2F), there was a significantly elevated lactate peak at 1.3 ppm in region of interest (ROI) with decreased NAA spectrum and reduced NAA/Cr ratio (Fig. 2G). The change of the spectrum reflected the severity of metabolic disorders, suggesting the local accumulation of lactic acid and disturbance of hypoxic processes.

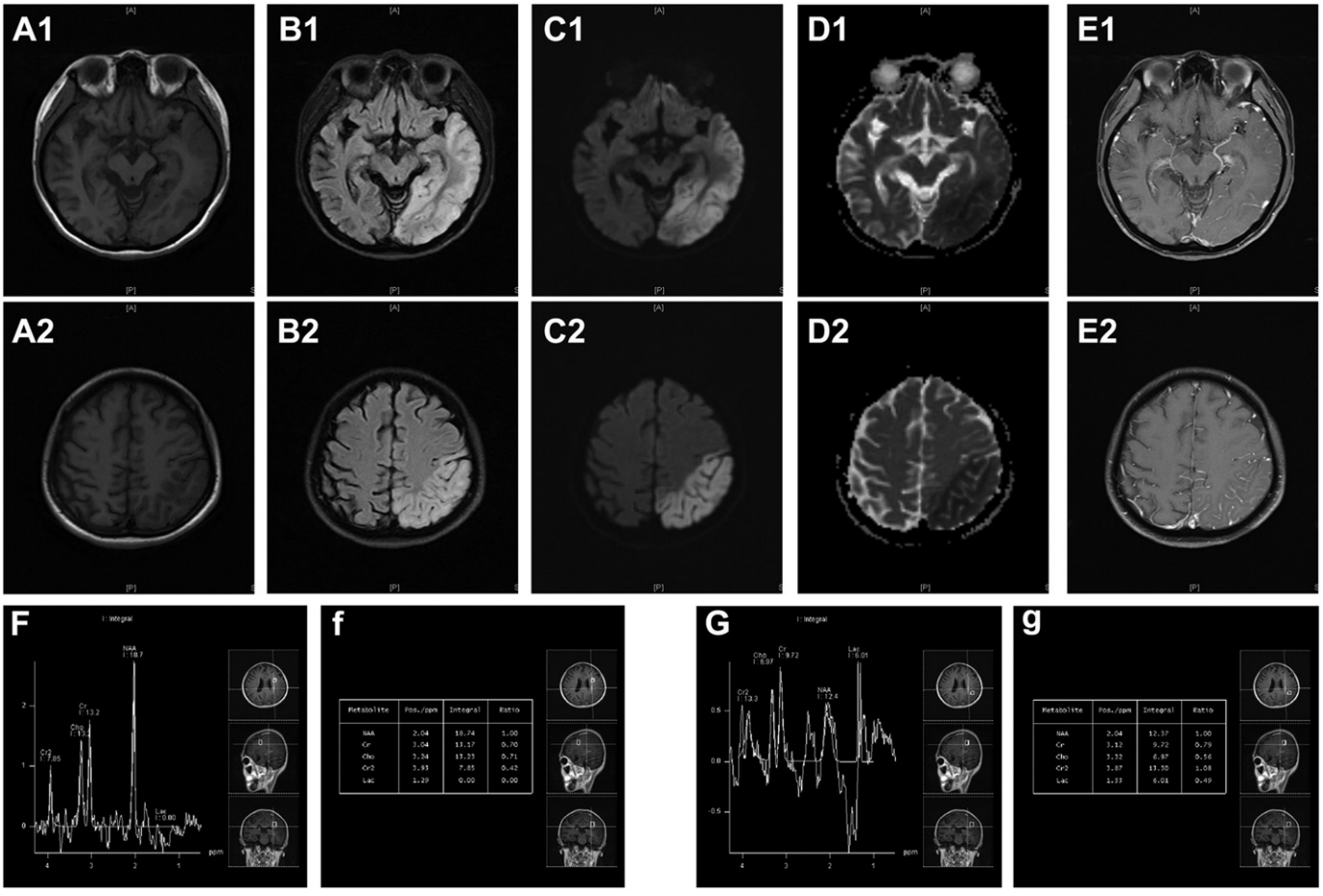

Fig. 2. Brain MRI (3.0 T) revealed a hypointense lesion in the left temporal and parietal lobe on T1 (Panel A), and increased signal intensity in the same region on Flair (Panel A) image with a clearly restricted diffusion (Panel C). The signal intensity on ADC sequence is mildly reduced (Panel D). No obvious enhancement was found on Gd-DTPA enhanced images (Panel E). Compared to the ipsilateral normally appearing area (Panel F), MR spectroscopy presented a significantly elevated lactate peak at 1.3 ppm in region of interest (ROI) (Panel G). Panels f and g are the molecular findings of metabolites respectively.

An electroencephalogram was performed on day 7 and displayed bilateral slow wave activities. Brainstem auditory evoked potential (BAEP) showed the bilateral sensorineural hearing loss. All the clinical and radiological findings were suggestive of mitochondrial disease. The final diagnosis of MELAS syndrome was confirmed by genetic analysis. The patient's peripheral blood leukocytes was detected by restriction fragment length polymorphism (RFLP) and revealed a mitochondrial DNA (mtDNA) mutation at A3242G point (Fig. 3).

Her medications included L-arginine, phenobarbital, co-enzyme Q and levothyroxine substitution therapy. The patient's condition continuously improved, and was discharged on day 23. Six months following discharge, this patient had no further seizure.

3. Discussion

Mitochondria are intracellular organelles responsible for the production of adenosine triphosphate (ATP) by the process called oxidative phosphorylation [5,6]. In this process, the energy is released by the breakdown of fuels such as glucose and fatty acids through the mitochondrial respiratory chain (MRC) [7].

Mitochondrial disorders usually involve multisystem. Tissues with a greater requirement for energy supply are more susceptible to MRC dysfunction, such as the central nervous system, muscles, myocardium, and endocrine glands. Therefore, the variety of clinical manifestation is extremely broad, including myopathy, myalgia following exercise, epilepsy, repeated stroke-like episodes, ataxia, hearing loss, retinopathy, migraine and cardiomyopathy. Endocrine problems such as diabetes mellitus, growth hormone deficiency and hypoparathyroidism are often described [8–10]. Thyroid involvement is distinctly rare, both hyperthyroidism and hypothyroidism have only been reported in single case [11,12].

In this report, hypothyroidism was observed as a unique feature. Considering the decreased TSH level, it is proposed that the pituitary or hypothalamic dysfunction and the deficiency in growth hormone (GH) may be the contributing factors. Whether mtDNA mutation was involved in the pathogenesis of thyroid gland itself is unknown. It is supposed that the mtDNA mutation was engaged in the development of hypothyroidism for the following reasons. Firstly, the mutant mtDNA may be widely but unequally distributed throughout the body of the MELAS patient and some proportion of mutant mtDNA had

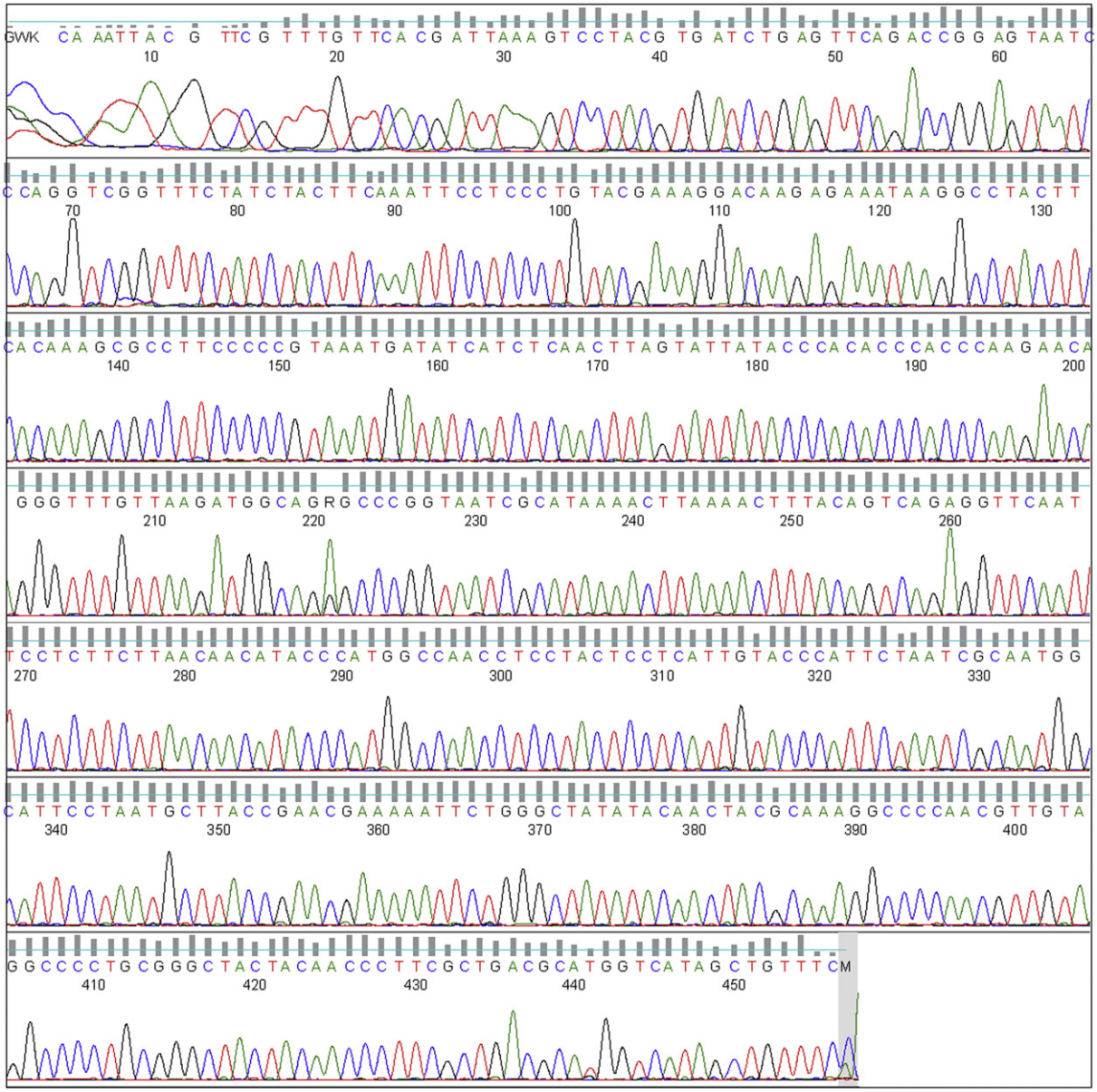

Fig. 3. Mitochondrial DNA (mtDNA) mutation at A3242G point.

been reported in the thyroid tissue [13]. Therefore, thyroid dysfunction may occur while the amount of the mutant mtDNA attains the certain threshold. Secondly, we found the obviously elevated titers of serum anti-thyroglobulin and anti-microsomal antibodies without morphological abnormality on ultrasonic examination. This observation suggested that mutant mtDNA may produce some antigens which in turn induced autoimmune response that result in the dysfunction of target gland. Thus, clinicians should be aware of the possibility of endocrine insufficiency accompanied by MIDs.

Psychiatric disorder was another feature of this patient. It has been increasingly recognized that mitochondrial dysfunction may be associated with neuropsychiatric abnormalities [14–16]. Patients with MELAS syndrome have a prevalence of depression, bipolar disorder, delusions of persecution or erratic behaviors. Some patients carrying the A3243G mutation in the MTTL1 gene have developed schizophrenia [17]. Others with the G3274A or C3256T mutation also have been reported to associate with psychosis [18,19]. The underlying mechanism remains unknown. As is known, adenosine triphosphate (ATP) is a high-energy compound utilized for the metabolic processes of neurons, which mostly occurs in mitochondria as products of oxidative phosphorylation. Therefore, mitochondria dysfunction results in a severely lessened ATP production. Previously studies have suggested that ATP depletion and the consequent deficiency of the Na^+/K^+-ATPase and Ca^{2+}-ATPase leads to increased Na^+ and Ca^{2+} concentration, which impairs plasma membrane potential [20–22]. The augmentation of intracellular Ca^{2+} may also induce the demyelination [23,24], dysregulate the apoptosis [25,26], and affect the storage, release or uptake mechanisms of neurotransmitters including dopamine, glutamate and GABA, etc. [27–30]. All these would result in structural and functional remodeling in synapses, and alter the intracellular signaling transductions and axonal projection. It is thus proposed that chronic MRC dysfunction and ATP deficiency are probably related to the etiology and pathogenesis of psychiatric disorders in MIDs. In addition, the site and scope of lesions may contribute to the psychiatric problems. As is known, each domain of cerebral cortex receives inputs respectively, further connects each other, and performs their functions precisely [31–33]. For example, the left temporal lobe holds the primary auditory cortex, which is important for processing of semantics in both speech and vision in humans. The patient with temporal and occipital lobes lesion undergoes severe hyperanxiety, visual and auditory hallucinations [34]. As detected by brain MRI (fig.2), our patient's lesions were located in the left temporal and parietal lobes, which may account for her obvious auditory hallucinations in the early stage. It has been proven that cortical and subcortical white matter lesions gave rise to psychiatric symptoms by impeding the white matter pathways and interfering with equilibrium of neurotransmitter adjustment [35–38]. Moreover, whether hypothyroidism gave rise to the psychiatric symptoms is uncertain [39,40]. Further researches are needed to elucidate the mechanism of psychiatric disorders in MIDs.

4. Conclusion

The case of our patient shows that MELAS can present with hypothyroidism and psychiatric disorders. It broadened the clinical manifestation spectrum of the MELAS syndrome. Elevation of serum lactate and typical features with MR spectroscopy provide clues to diagnose the underlying mitochondrial disorder. Definite diagnosis can be made by genes detection.

Acknowledgement

This work was supported by grants from the National Natural Science Foundation of China (No. 81301104).

References

[1] S. DiMauro, E.A. Schon, Mitochondrial respiratory-chain diseases, N. Engl. J. Med. 348 (2003) 2656–2668.
[2] M. Bohm, E. Pronicka, E. Karczmarewicz, et al., Retrospective, multicentric study of 180 children with cytochrome C oxidase deficiency, Pediatr. Res. 59 (2006) 21–26.
[3] Y. Goto, S. Horai, T. Matsuoka, et al., Mitochondrial myopathy, encephalopathy, lactic acidosis, and stroke-like episodes (MELAS): a correlative study of the clinical features and mitochondrial DNA mutation, Neurology 42 (1992) 545–550.
[4] N. Manwaring, M.M. Jones, J.J. Wang, et al., Population prevalence of the MELAS A3243G mutation, Mitochondrion 7 (2007) 230–233.
[5] H.M. Kalckar, Metabolic enzymes of mitochondria, Acta Medica Scand. Suppl. 266 (1952) 615–621.
[6] G.E. Palade, The fine structure of mitochondria, Anat. Rec. 114 (1952) 427–451.
[7] E.P. Kennedy, A.L. Lehninger, Oxidation of fatty acids and tricarboxylic acid cycle intermediates by isolated rat liver mitochondria, J. Biol. Chem. 179 (1949) 957–972.
[8] H. Isotani, Y. Fukumoto, H. Kawamura, et al., Hypoparathyroidism and insulin-dependent diabetes mellitus in a patient with Kearns-Sayre syndrome harbouring a mitochondrial DNA deletion, Clin. Endocrinol. 45 (1996) 637–641.
[9] S. Romano, D. Samara, H. Crosnier, et al., Variable outcome of growth hormone administration in respiratory chain deficiency, Mol. Genet. Metab. 93 (2008) 195–199.
[10] D. Chretien, P. Rustin, T. Bourgeron, et al., Reference charts for respiratory chain activities in human tissues, Clin. Chim. Acta 228 (1994) 53–70.
[11] P. Balestri, S. Grosso, Endocrine disorders in two sisters affected by MELAS syndrome, J. Child Neurol. 15 (2000) 755–758.
[12] C.Y. Yang, H.C. Lam, H.C. Lee, et al., MELAS syndrome associated with diabetes mellitus and hyperthyroidism: a case report from Taiwan, Clin. Endocrinol. 43 (1995) 235–239.
[13] N. Shiraiwa, A. Ishii, H. Iwamoto, et al., Content of mutant mitochondrial DNA and organ dysfunction in a patient with a MELAS subgroup of mitochondrial encephalomyopathies, J. Neurol. Sci. 120 (1993) 174–179.
[14] O. Fattal, J. Link, K. Quinn, et al., Psychiatric comorbidity in 36 adults with mitochondrial cytopathies, CNS Spectr 12 (2007) 429–438.
[15] P. Kaufmann, K. Engelstad, Y. Wei, et al., Protean phenotypic features of the A3243G mitochondrial DNA mutation, Arch. Neurol. 66 (2009) 85–91.
[16] A. Kiejna, S. DiMauro, T. Adamowski, et al., Psychiatric symptoms in a patient with the clinical features of MELAS, Med. Sci. Monit. 8 (2002) CS66–CS72.
[17] Y. Ueda, A. Ando, T. Nagata, et al., A boy with mitochondrial disease: asymptomatic proteinuria without neuromyopathy, Pediatr. Nephrol. 19 (2004) 107–110.
[18] M. Jaksch, H. Lochmuller, F. Schmitt, et al., A mutation in mt tRNALeu(UUR) causing a neuropsychiatric syndrome with depression and cataract, Neurology 57 (2001) 1930–1931.
[19] S. Amemiya, M. Hamamoto, Y. Goto, et al., Psychosis and progressing dementia: presenting features of a mitochondriopathy, Neurology 55 (2000) 600–601.
[20] C. Moisin, N. Balta, V. Filcescu, et al., Activity of Na+/K+-ATPase and of Ca++-ATPase under the action of adenosine triphosphate in experimental myocardial hypertrophy, Rom. J. Physiol. 35 (1998) 303–311.
[21] R. Carini, G. Bellomo, A. Benedetti, et al., Alteration of Na+ homeostasis as a critical step in the development of irreversible hepatocyte injury after adenosine triphosphate depletion, Hepatology 21 (1995) 1089–1098.
[22] M. Erecinska, F. Dagani, Relationships between the neuronal sodium/potassium pump and energy metabolism. Effects of K+, Na+, and adenosine triphosphate in isolated brain synaptosomes, J. Gen. Physiol 95 (1990) 591–616.
[23] B. Soliven, Calcium signalling in cells of oligodendroglial lineage, Microsc. Res. Tech. 52 (2001) 672–679.
[24] J.A. Benjamins, L. Nedelkoska, Release of intracellular calcium stores leads to retraction of membrane sheets and cell death in mature mouse oligodendrocytes, Neurochem. Res. 21 (1996) 471–479.
[25] P.M. Abdul-Muneer, M. Long, A.A. Conte, et al., High Ca2+ influx during traumatic brain injury leads to caspase-1-dependent neuroinflammation and cell death, Mol. Neurobiol. (2016).
[26] R.M. La Rovere, G. Roest, G. Bultynck, et al., Intracellular Ca2+ signaling and Ca2+ microdomains in the control of cell survival, apoptosis and autophagy, Cell Calcium. (2016).
[27] R. Ruiz, J.J. Casanas, L. Torres-Benito, et al., Altered intracellular Ca2+ homeostasis in nerve terminals of severe spinal muscular atrophy mice, J. Neurosci. 30 (2010) 849–857.
[28] G. Cui, B.E. Bernier, M.T. Harnett, et al., Differential regulation of action potential- and metabotropic glutamate receptor-induced Ca2+ signals by inositol 1,4,5-trisphosphate in dopaminergic neurons, J. Neurosci. 27 (2007) 4776–4785.
[29] C. Hille, B. Walz, Dopamine-induced graded intracellular Ca2+ elevation via the Na+Ca2+ exchanger operating in the Ca2+-entry mode in cockroach salivary ducts, Cell Calcium 39 (2006) 305–311.
[30] A.G. Millar, R.S. Zucker, G.C. Ellis-Davies, et al., Calcium sensitivity of neurotransmitter release differs at phasic and tonic synapses, J. Neurosci. 25 (2005) 3113–3125.
[31] B.T. Yeo, S.B. Eickhoff, Systems neuroscience: a modern map of the human cerebral cortex, Nature 536 (2016) 152–154.
[32] M.F. Glasser, T.S. Coalson, E.C. Robinson, et al., A multi-modal parcellation of human cerebral cortex, Nature 536 (2016) 171–178.
[33] S.T. Govindarajan, J. Cohen-Adad, M.P. Sormani, et al., Reproducibility of T2 * mapping in the human cerebral cortex in vivo at 7 tesla MRI, J. Magn. Reson. Imaging 42 (2015) 290–296.
[34] R.E. Anglin, S.L. Garside, M.A. Tarnopolsky, et al., The psychiatric manifestations of mitochondrial disorders: a case and review of the literature, J Clin Psychiatry 73 (2012) 506–512.

[35] M. Bellani, F. Boschello, G. Delvecchio, et al., DTI and myelin plasticity in bipolar disorder: integrating neuroimaging and neuropathological findings, Front Psychiatry 7 (2016) 21.
[36] A. Saricicek, N. Zorlu, N. Yalin, et al., Abnormal white matter integrity as a structural endophenotype for bipolar disorder, Psychol. Med. 46 (2016) 1547–1558.
[37] M.A. Landek-Salgado, T.E. Faust, A. Sawa, Molecular substrates of schizophrenia: homeostatic signaling to connectivity, Mol. Psychiatry 21 (2016) 10–28.
[38] M.J. Stuart, B.T. Baune, Chemokines and chemokine receptors in mood disorders, schizophrenia, and cognitive impairment: a systematic review of biomarker studies, Neurosci. Biobehav. Rev. 42 (2014) 93–115.
[39] R. Bunevicius, A.J. Prange Jr., Thyroid disease and mental disorders: cause and effect or only comorbidity? Curr Opin Psychiatry 23 (2010) 363–368.
[40] C. Almeida, M.A. Brasil, A.J. Costa, et al., Subclinical hypothyroidism: psychiatric disorders and symptoms, Rev. Bras. Psiquiatr. 29 (2007) 157–159.