CASE REPORT

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Neuroradiological findings in a young patient bearing a new single mitochondrial gene mutation (case report)

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Abstract

Background: We present the clinical, MRI and CT findings in a case of a new mitochondrial genome mutation (tRNA arginine gene), characterized by brain calcifications which are indicative of Kearns–Sayre syndrome (KSS). Some radiological features resembled those of Fahr's disease (affecting the PDGFRB gene).

Case presentation: A 36-year-old male presented some typical clinical features of KSS, including onset before 20 years of age, pigmentary retinopathy, progressive external ophthalmoplegia and ptosis. However, the hallmark radiological finding of diffuse calcifications in the nuclear ganglia resembles some cases related to the PDGRFB mutation. Genetic investigation revealed a new mutation in the mitochondrial tRNA-arginine gene.

Conclusions: Brain calcifications are a common feature of mitochondrial diseases, but little is known about their pathophysiology. Here, we describe radiological similarities between a new mitochondrial DNA mutation and other genetic conditions, which are related to Fahr's disease. These similarities could provide new insights into putative genotype–phenotype correlations.

Keywords: Kearns–Sayre syndrome, Mitochondriopathy, Basal ganglia, Brain calcifications, Case report

Background

Mitochondrial dysfunction is emerging as a common contributor to neurodegeneration and spongiotic brain diseases and presents with a wide range of signs and severity (Ignatenko et al. 2020). The relationships between genotype and phenotype, as well as the exceptional variability of non-overlapping diseases, remain poorly understood (Chung et al. 2021).

Kearns–Sayre syndrome (KSS) is a rare, sporadic mitochondrial oculo-cranial-somatic neuromuscular disorder with an estimated prevalence of around 1/125,000 (Leal et al. 2016; Pasquini et al. 2020). KSS is usually associated with a single large-scale mitochondrial DNA (mtDNA) deletion, which can range from 1,000 to 10,000 base pairs in length (Khambatta et al. 2014). Over 150 deletions have been identified, the most common being a deletion of a 4.9 Kb fragment, which extends from base 8,469 to 13,147 and causes ~ 20% of cases (Alemi et al. 2007; Sequiera et al. 2021). In rare cases, KSS has also been associated with point mutations, frequently involving mitochondrial transfer RNA (tRNA) (Seneca et al. 2001; Emmanuele et al. 2011). These mutations are generally not inherited but instead arise spontaneously during early embryonic development (Ainslie et al. 2016). Normal mitochondrial function depends on the expression of the mitochondrial genome. Human mtDNA is a 16,569-kb circular molecule which contains 13 genes for the mitochondrial respiratory chain complexes subunits and

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24 genes for mitochondrial protein biosynthesis, including 22 tRNA genes (Scaglia 2008).

KSS classically presents before 20 years of age with a clinical triad of pigmentary retinopathy, progressive external ophthalmoplegia and cardiac conduction anomalies. Many additional manifestations have been described, including weakness, fatigue, elevated levels of lactate and pyruvate, mental retardation, short stature, ataxia, hearing loss, and certain endocrinopathies (e.g. diabetes, hypoparathyroidism, dysthyroidism and suprarenal alterations) (Khambatta et al. 2014; Zavatta and Clarke 2021; Sharma et al. 2016). High protein levels have also been identified in the cerebrospinal fluid (CSF) (Khambatta et al. 2014).

KSS is usually confirmed by the presence of "ragged red fibres (RRF)" on muscle biopsy and cytochrome c oxidase (COX) deficiency (Goldstein and Falk 2003; Challa et al. 2004). Ragged red fibres correspond to clumps of altered mitochondria in the subsarcolemmal region of the muscle fibre and can usually be identified when muscle is stained with Gömöri trichrome stain (Reichmann et al. 1996). Cytochrome c oxidase is an essential enzyme that is active in mitochondria and its deficiency can result from mutation in the mitochondrial genome since three of its 13 structural subunits are encoded by mtDNA (Shoubridge 2001). COX/succinate dehydrogenase is identified by double-labelling histochemistry staining (Ross 2011).

KSS-related neuroradiological findings are unspecific. Spongiosis, myelin loss and gliosis are the main pathological findings (Finsterer 2018; Alston et al. 2017), explained by increased T2-spin echo signal on MRI examination. In a recent study (Yu et al. 2016), MRI showed symmetric high T2 signals in cerebral and cerebellar white matter, as well as in the brainstem. Although both grey and white matter can be affected, patients most often show symmetric high T2-weighted MRI signal in subcortical U-fibres and in the periventricular white matter. Subcortical involvement is suggestive of KSS and is differentiated from the prevalent deep white matter lesions seen in other mitochondrial disorders and leukodystrophies. The subcortical abnormalities can extend into the deep cerebral white matter (internal capsule, splenium, cerebral and cerebellar peduncles), basal ganglia (46.7% of patients), thalamus (53.3%) and thalamocortical connections. The tegmentum of the brainstem, efferent cerebellar fibres to the thalamus and the dentate nuclei are also frequently involved (Yu et al. 2016; Demange et al.1989; Chu et al. 1999; Pasquini et al. 2020). It is quite common to have restricted diffusion (evidenced by diffusion-weighted imaging (DWI)) at the involved sites due to the status spongiosus of the tissue (Sacher et al. 2005). Occasionally, T2 prolongation areas also show siderocalcific

deposits, especially in basal ganglia and subcortical regions (Robertson et al. 1979). Finally, cerebral, cerebellar and brainstem atrophy may be reported (Chu et al. 1999).

This report presents a case of KSS in a 36-year-old male with white matter abnormalities and diffuse calcifications in the nuclear ganglia. These were explained by a newly identified single mutation in the mitochondrial tRNA arginine gene. The radiological and clinical features may be explained by KSS, but some aspects resemble Fahr's disease, a related genetic condition.

Case presentation

A 36-year-old male presented with some typical clinical findings of KSS, including onset before 20 years of age, pigmentary retinopathy, progressive external ophthalmoplegia (CPEO) and ptosis. The patient had a history of complex childhood-onset neurological disease with fatigue, muscle weakness, hearing loss, cognitive impairment, headaches, and ataxia. There was no evidence of alterations in cardiac conduction on electrocardiogram (ECG), as recently confirmed in our department. A muscle biopsy showed mitochondrial aggregates which altered the muscle fibre contour and created a "ragged" appearance (intracellular RRF; Gomori Trichrome staining; Vogel 2001). This was due to the accumulation of abnormal mitochondria underneath the plasma membrane. 35–40% of fibres were also COX-deficient using combined COX/SDH staining (Ross 2011), which confirmed mitochondrial disease.

Genetic investigation did not highlight any chromosomal alterations (karyotyping, chromosome microarray analysis) or mutations using whole exome sequencing (Ambry Genetics; Ploski 2016). MtDNA analysis (sequencing of mtDNA using Illumina MiSeq; McElhoe et al. 2014) did not find any known pathogenic point mutations associated with mitochondrial disease, but a new mutation (mtDNA; heteroplasmic variant, m10466C > T) was detected, which corresponded to the mitochondrial tRNA-arginine gene.

MRI and CT investigations showed mild involvement of the periventricular white matter (high T2 signal), without clear effects on subcortical tissue (Fig. 1). No local calcifications were evident at these sites. Ventricles and sulci were within normal size limits.

At the level of the basal ganglia, we found symmetric T1-shortening involving the head and body of the caudate nuclei, pallidus, putamen, and posterior-medial thalami (Fig. 2). The T2*GE sequence and a CT scan confirmed the presence of diffuse calcifications, particularly in the bilateral globus pallidus (Figs. 3, 4), where the T1-SE and T2-SE signal was hypointense. Some thin linear calcifications extended from the caudate into the
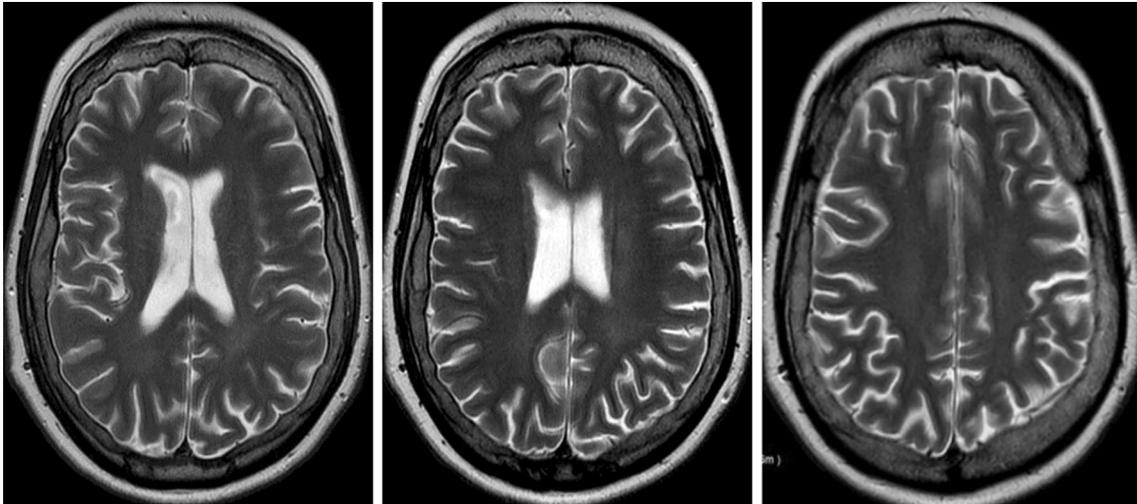
Fig. 1 Magnetic resonance axial sections T2 spin-echo sequence showing hyperintensities in the white matter
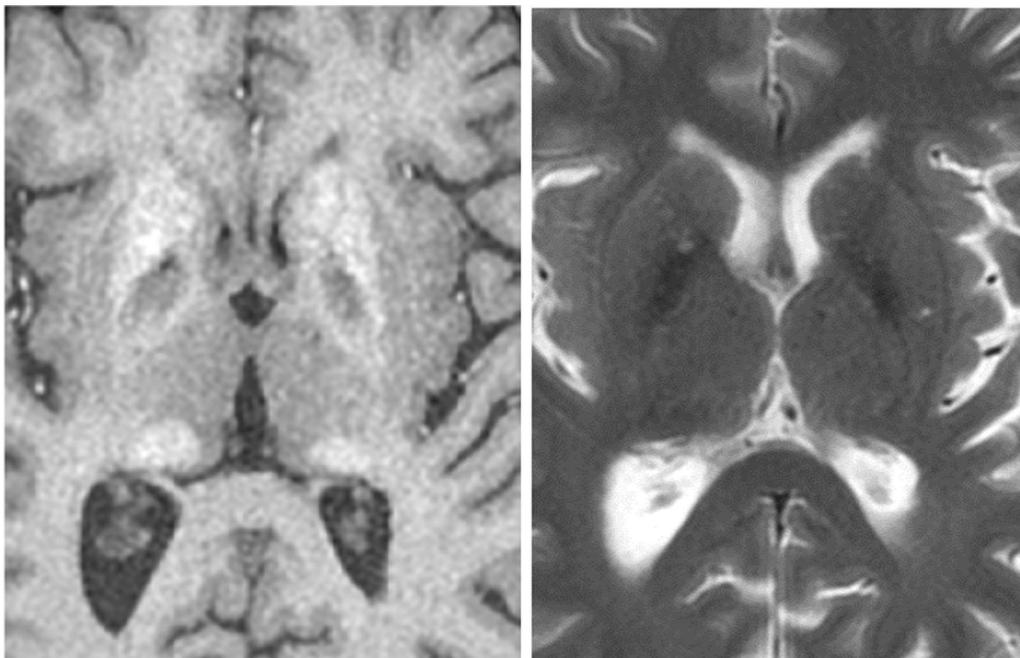

Fig. 2 a Magnetic resonance axial sections T1 spin-echo sequence showing areas of hyperintense signal in thalami and hypointense signal in pars medialis of the globus pallidus, **b** axial T2 spin echo hyposignal in pars medialis of the globus pallidus

semioval centre and towards the cortex, following vessels and cortical projections. The brainstem and the cerebellar white matter were not affected.

This case of genetic mitochondriopathy is characterized by symmetric basal ganglia calcifications (BGCs) and T2 hyperintensities in the white matter. Mitochondrial disorders (MDs) primarily affect muscles and the brain, where focal lesions, such as white and grey matter stroke-like lesions, atrophy, BGCs and subcortical calcifications, can be found (Finsterer and Kopsa 2005; Carafoli 2010; Finsterer and Torres de Carvalho 2017).

Basal ganglia calcifications. BGCs are not an unusual finding on CT scans (3–6 per 1,000) (Brannan et al. 1980) or on autopsy and are generally unrelated to

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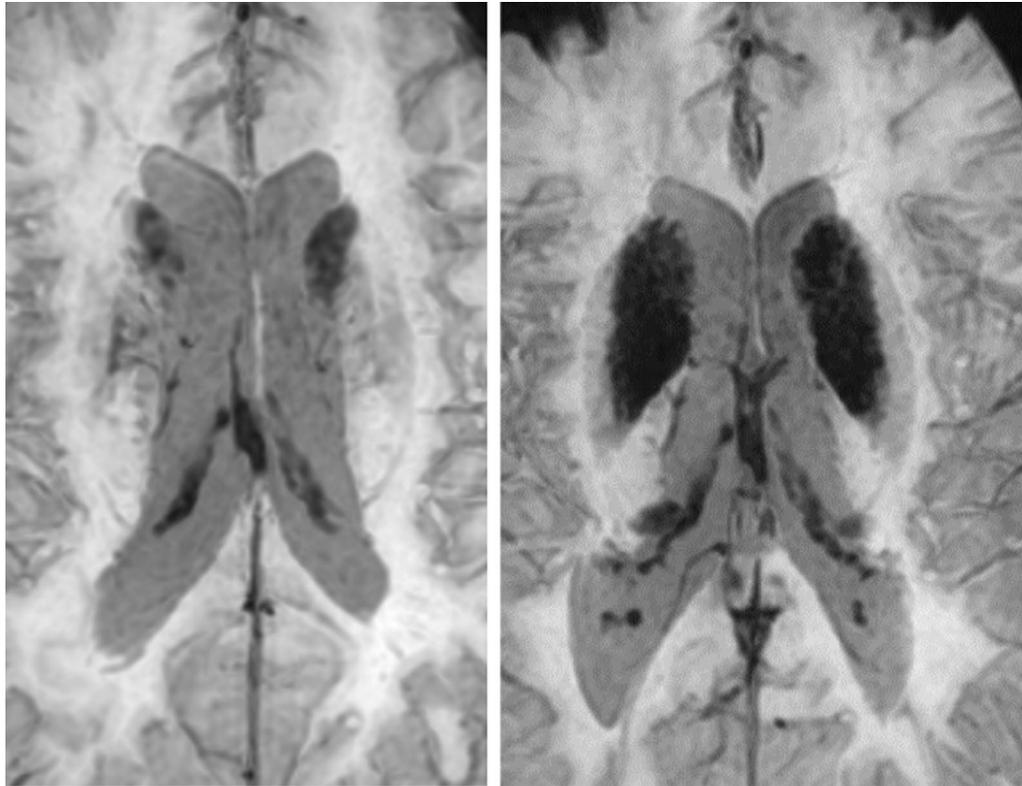
Fig. 3 T2* gradient recalled echo (GRE) sequence MRI axial sections showing extensive brain calcification
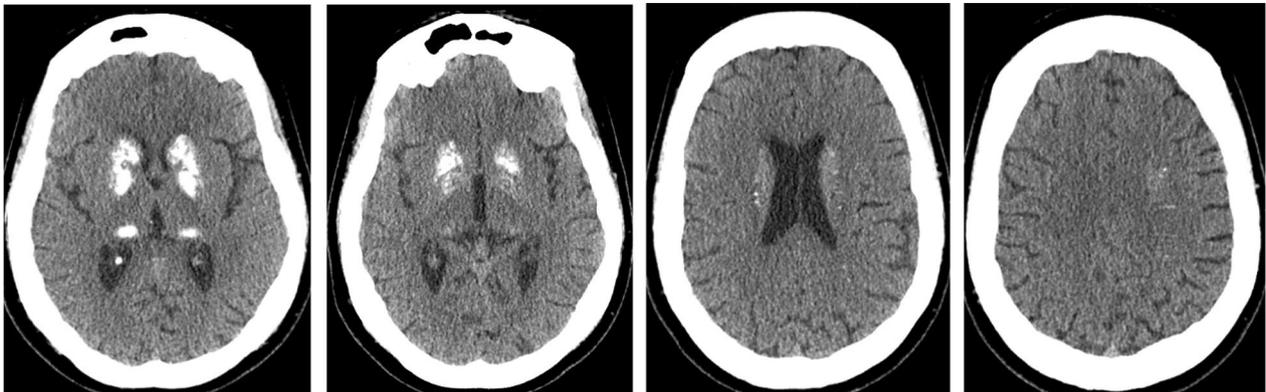
Fig. 4 Non-enhanced axial CT sections demonstrating bilateral, nearly symmetric calcifications in the basal ganglia and posterior thalamus. Less intense and punctuated calcifications present in the caudate nuclei

calcium abnormalities or neurological disease (Johnson et al. 2013; Verulashvili et al. 2006). CT and MRI scans are important for identifying calcification patterns and to establish possible differential diagnoses. The most appropriate tool is CT, since MRIs can underestimate calcium load (calcium deposits reduce the T1 relaxation time, on T2-images the lesions appear hypointense and on T2* gradient recalled echo (GRE), the signal is very low). BGCs, which consist of hydroxyapatite, zinc, iron and magnesium in a protein rich stroma, most commonly involve the globus pallidus, caudate and dentate nucleus. Other common intracranial calcifications include the

pineal gland, falx, arachnoid granulations, and choroid plexus. The specific pathogenesis of BGCs is unknown, but alterations in alkaline phosphatase activity, calcium metabolism and vascular supply have been proposed as possible mechanisms. Neuronal cell loss and gliosis are usually absent at the site of basal ganglia calcification, but when present, may determine neurological dysfunction. Patients with bilateral BGCs most commonly experience movement abnormalities, cognitive impairment and psychiatric symptoms. These symptoms may be due to neuronal degeneration and mineralization, affecting mainly dopaminergic transmission in the basal ganglia, which leads to fronto-subcortical loop dysfunction (including the motor, oculomotor, prefrontal, and anterior cingulate circuits). Congruently, PET and SPECT studies demonstrate decreased metabolism in the basal ganglia and frontal lobe of patients with BGCs (Oliveira and Oliveira 2013).

Symmetric BGCs can be idiopathic (Fahr's disease) (Tai and Batla 2015; Nicolas et al. 2013) or secondary to a long list of causes (Table 1). Fahr's disease is a genetic condition which can affect the *SLC20A2, PDGFB, PDGFRB* genes, where secondary (non-genetic) causes are not recognizable. Non-idiopathic Fahr's disease is commonly associated with parathyroid gland diseases.

In Fahr's disease, there is commonly a pattern of symmetric calcifications in the pallidus, thalamus and dentate nucleus. Other areas of calcification include the brainstem, cerebellum and cortical/subcortical white matter, but these are less consistently reported. Hypoparathyroidism is often associated with tissue calcification in the basal ganglia as consequence of altered calcium/phosphate homeostasis. The pattern of intracranial calcification in some *PDGFRB* patients (Nicolas et al. 2013), which primary involves the caudate nuclei, thalami and lenticular nuclei, is quite similar to that found in our patient.

BGCs have also been described in mitochondrial diseases, such as mitochondrial encephalomyopathy, lactic acidosis, and stroke-like episodes (MELAS), Leigh syndrome and KSS. However, these are uncommon (Finsterer and Kopsa 2005; Valanne et al. 1998) and calcium/phosphate metabolism is usually normal. Progressive and symmetric calcifications in the globus pallidus, putamen, caudate, thalamus and corona radiata are the most common radiological findings in MELAS, together with parietal stroke-like lesions and severe cortical atrophy (Valanne et al. 1998; Sue et al. 1998; Harrington et al. 1981).

Bilateral BGCs have been described in some cases of Leigh syndrome, mainly involving the putamen. The syndrome is characterized by symmetrical T2 hyperintensities in periventricular white matter, which is suggestive of hypomyelination (Valanne et al. 1998; Angural et al. 2018).

In some patients, KSS has been associated with cerebellar and brainstem atrophy, as well as calcification in the basal ganglia (Chu et al. 1999; Valanne et al. 1998). In particular, some patients show punctate symmetric T2-hyperintensities in the globus pallidi or in the medial thalamic nuclei and tegmentum of the brainstem. In certain cases, CT scans show diffuse calcifications in the globus pallidi and caudate nuclei (Robertson et al. 1979; Valanne et al. 1998).

T2-hyperintensities in the white matter. Mitochondrial encephalopathies are associated with structurally and/or functionally abnormal mitochondria, which affects the brain because of its high dependence on oxidative metabolism. Cerebral and cerebellar white matter involvement is increasingly being recognized as a feature of mitochondrial disorders, consisting mainly of cyst-like lesions, neuroinflammation and demyelinating conditions. Clinically, patients with leukoencephalopathy most often present with recurrent episodes of neurological regression. Onset is often in infancy and progresses with a neurodegenerative course. In KSS, status spongiosus of white and grey matter is the most typical lesion and involves the cerebrum, cerebellum (white matter) and brainstem (grey matter). The disorder is also characterized by neuronal degeneration, astrocytosis and demyelination. In particular, the distinguishing feature of KSS is the involvement of subcortical white matter (areas of T2 prolongation, sometimes with subcortical calcifications), as opposed to the deep white matter pathology seen

Table 1 Secondary basal ganglia calcifications. Adapted from Tai and Batla (2015)

Endocrinopathies	Hypoparathyroidism, hyperparathyroidism
Inherited	Mitochondrial diseases, Cockayne syndrome, Pantothenate kinase-associated neurodegeneration (PKAN)
Birth hypoxia	
Infections	TORCH, tuberculosis, AIDS, toxoplasmosis
Toxic	Carbon monoxide or lead poisoning, radiotherapy, chemotherapy
Age-related	

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in other mitochondrial disorders. KSS-related lesions involve the frontal and temporal regions (subcortical U fibres), as well as the periventricular and deep white matter but spare the immediate periventricular layer. Leigh's syndrome is characterized by the presence of microcystic cavitation following necrosis of the temporal and frontal white matter. Transient infarct-like lesions are the hallmark of MELAS and mainly involve the temporo-parieto-occipital white and grey matter, with slight mass effect (Valanne et al. 1998; Sue et al. 1998; Bindu et al. 2018).

Conclusions

This case of a 36-year-old male presents a complex clinical and radiological condition with features resembling both KSS and Fahr's disease. A new mutation in the mitochondrial tRNA-arginine gene was identified. The correlation between tRNA mitochondrial genes and brain calcification has not been clarified and warrants further study. Studying this putative relationship could provide new insight into the pathophysiological pathways which lead to similar phenotypes and related genetic conditions. The interactions between mtDNA mutations and energy homeostasis could create new avenues for therapeutic intervention.

Abbreviations

KSS: Kearns–Sayre syndrome; mtDNA: Mitochondrial DNA; CSF: Cerebrospinal fluid; RRF: Ragged red fibres; COX: Cytochrome c oxidase; BGCs: Basal ganglia calcifications; MD: Mitochondrial disorders; TORCH: Toxoplasma gondii, others, rosolia, cytomegalovirus, herpes simplex virus; MRI: Magnetic resonance imaging; MELAS: Mitochondrial encephalopathy, lactic acidosis, and stroke-like episodes.

Author contributions

All authors contributed to the study conception and design. Material preparation was performed by Dr. PLM, Dr. AA, Dr. RC, Dr. CF, Dr. CR, Dr. AR, MS, and Dr. GV. The first draft of the manuscript was written by Dr. PLM, and all authors commented on subsequent versions of the manuscript. MS edited the final version of the manuscript. All authors read and approved the final manuscript.

Availability of data and materials

All the data are available for further investigations.

Declarations

Ethics approval and consent to participate

Consent to participate was obtained according to national and European regulations (Italian D.Lgs. 196/2003 and European Declaration 679/2016).

Consent for publication

This case report involves a human participant investigated in our Department for ordinary radiological follow-up. We confirm that the patient expressed his consent to share these images and this information with the scientific and medical communities. Their anonymity has not been compromised.

Competing interests

The authors declare that they have no competing interests.

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