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Case Report Open Access

A Tunisian Patient with CLCN2-Related Leukoencephalopathy

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Abstract

CLCN2 related leukoencephalopathy (CC2L OMIM#: 615651) is a recently identified rare disorder, caused by autosomal recessive mutations in *CLCN2* gene, leading to the dysfunction of its encoded CLC-2 chloride channel protein with characteristic brain MRI features of leukoencephalopathy.

We report the first Tunisian patient with clinical features of ClCN-2 related leukoencephalopathy. A 54-year-old female with a family history of leukemia, male infertility, motor disability and headaches who presented initially with a tension-type headache, and normal physical examination. At the follow up she developed mild gait ataxia and psycho-cognitive disturbances.

A previously reported homozygous NM_004366.6 (CLCN2): c.1709G>A (p.Trp570Ter) stop gained mutation was identified. This report expands the knowledge related to CC2L and highlights the clinical features in affected individuals of an African descent.

Keywords: CLCN2; MRI; CLCN2-related leukoencephalopathy

Introduction

CLCN2-related leukoencephalopathy (CC2L) also known as leukoencephalopathy with ataxia (LKPAT; OMIM#: 615651) is a recently identified rare autosomal recessive disorder, caused by mutations in *CLCN2* gene, resulting in ClC-2 chloride channel dysfunction and myelin micro vacuolization (Giorgio et al., 2017, Guo et al., 2019, , Hoshi et al., 2019) [1,2,3]. CC2L is characterized by nonspecific neurologic findings, mild visual impairment resulting from chorioretinopathy or optic atrophy (Bösl et al. 2001) [4], male infertility (Di Bella et al., 2014) [5], and characteristic findings on brain MRI (Depienne et al., 2013) [6]. The neurological deficits such as mild ataxia, cognitive impairment, and headaches are mild and lack specific manifestations. Patients are reported to remain ambulatory during follow-ups.

However, as specific clinical patterns of the disease, retinopathy and male infertility may be diagnostic clues that prompt, to a certain extent, a clinical suspicion of CC2L. Since the identification of CC2L in 2013 by Depienne et al, only 18 cases have been reported. Most patients show mild clinical phenotypes with prolonged survival. Herein, we report the first Tunisian patient with a previously reported *CLCN2* pathogenic mutation and a remarkable family history.

Case Report

A 56-year-old woman, born from a consanguineous marriage (Figure 1) presented initially to our clinical department at the age of 27 presenting with chronic headaches evolving for five years. Her family history was remarkable for male infertility (individual II.4 and II.5) and headaches (sister: individual II.3 and (children: individual III.2 and III.3). Her older son also showed psychiatric disturbances and aggressiveness. In addition, early infant deaths, leukemia, diabetes, and motor disability were observed in other family members.

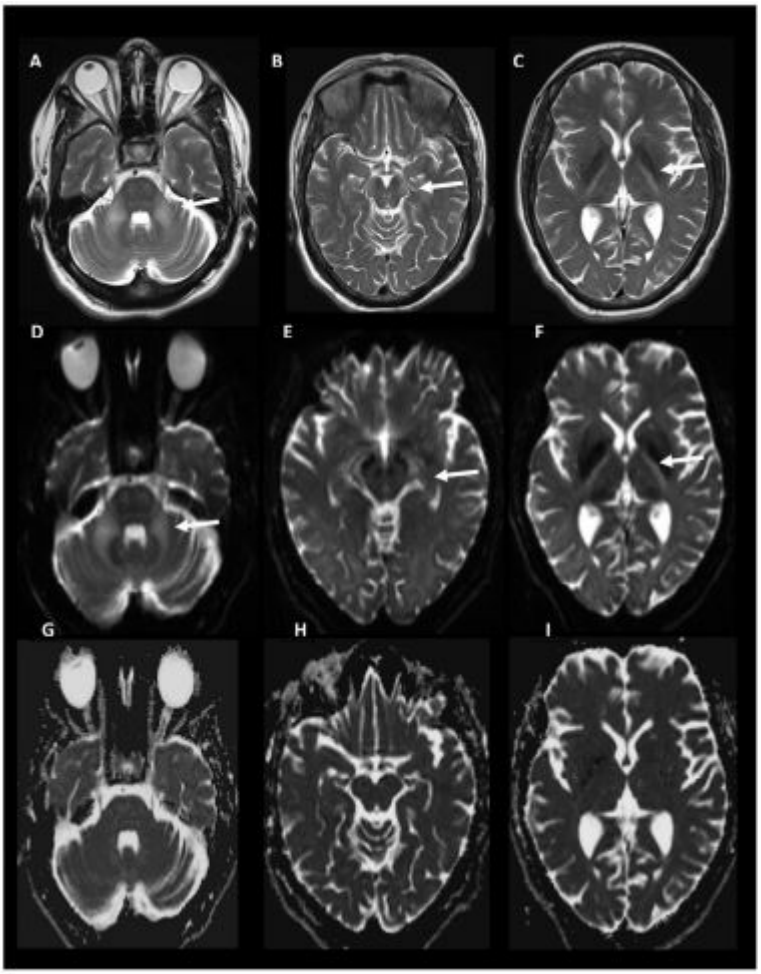

Figure 1: Cerebral MRI axial T2 weighted sequences **(A-C)** showing hyper T2 signal in the middle cerebellar peduncles **(A),** cerebral peduncles **(B)** and posterior limb of the internal capsule **(C)** Diffusion weighted sequences **(D-F)** showing hyperintensity in the middle cerebellar peduncles **(D),** cerebral peduncles **(E)** and posterior limb of the internal capsule **(F).** Apparent diffusion coefficient (ADC) map **(G-I)** does not show a restriction of the diffusion

The initial neurological examination, standard biological investigations and brain CT scan were normal. The diagnosis of chronic tension-type headache was retained according to the international classification of headaches disorders (second edition published in 2004).

After 7 years of follow up, during which the patient remained stable, she started complaining of gait disturbances and difficulties performing daily fine task activities. Moreover, she complained of memory disturbances. Neurological examination revealed cerebellar ataxia manifesting as dysarthria and broad-based gait associated with mild spastic paraplegia with brisk tendon reflexes in the lower limbs. Neuropsychological test revealed a mild memory deficit and a depressive mood.

Given the progression of symptoms, a conventional cerebral magnetic resonance imaging (MRI) was performed. Cerebral MRI showed bilateral T2-hyperintensities and diffusion restriction in the posterior limbs of the internal capsules, midbrain cerebral peduncles and middle cerebellar peduncles, without any signal abnormalities in the diffusion coefficient (ADC) maps. No 'meningeal stretch' in rostral axial brain image was found.

Biological work up including blood cell count, liver enzymes, renal function, glycemia, and lipid profile was normal, as well as specific blood tests (amino and organic acids chromatography - lactic /pyruvic acid and cupric concentrations). Thyroid check-up revealed hypothyroidism. Thyroid ultrasound did not show signs of thyroiditis. Immunological work up showed positive antiperoxidase antibodies and negative anti thyroglobulin antibodies.

Based on the suggestive characteristic brain MRI features of leukoencephalopathy, the diagnosis of CLCN2 leukoencephalopathy was suspected.

Exome sequencing was carried out using the TruSight® One Sequencing Panel and reagents provided by Illumina TruSight One Sequencing Panel. The panel covers 4,813 disease-associated genes. Fast read files were generated from the sequencing platform via the Illumina pipeline.

A previously reported homozygous variant, c.1709G>A, p.Trp570Ter (Depienne et al., 2013, Klassen et al., 2011) [6,7], was detected and then confirmed by Sanger sequencing (Figure 2). The nonsense mutation introduces a stop codon at position 570 leading to a protein truncated of 1882 amino acids.

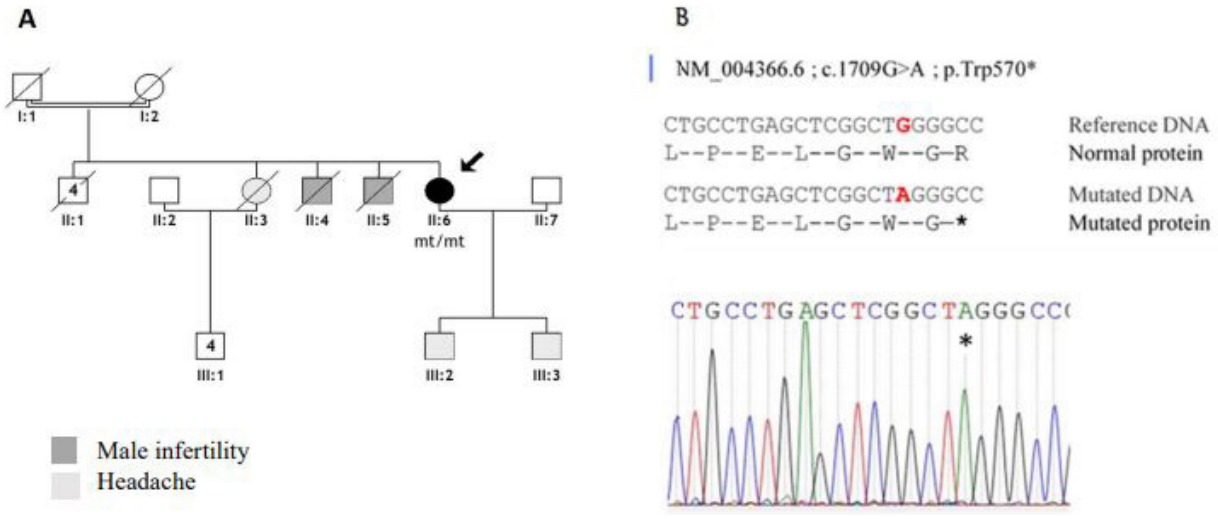

Figure 2: Pedigree and molecular findings **(A)** Pedigree of the index patient II.6. Her two brothers (II.4 and II.5) and sister (II.3) had suggestive symptoms of CLCN-2 related leukoencephalopathy, **(B)** Sequencing chromatograms. Mutation confirmation of the homozygous c.1709G>A nonsense mutation (mt/mt) by forward primer indicated by an asterisk

Functional studies show that Trp570Ter results in decreased protein expression and abnormal protein localization (Depienne et al., 2013) [6]. This variant is predicted to cause the loss of normal protein function either through protein truncation or nonsense-mediated mRNA decay.

Discussion

In this study, we report a case of an adult woman born of a consanguineous union with a confirmed CLCN2 mutation. This is the fifth reported patient with a CLNC2-related leukoencephalopathy from North Africa.

The c.1709G>A mutation, identified in our patient, has been previously reported as an apparently homozygous pathogenic variant in two unrelated North African patients with an adult-onset leukodystrophy (Depienne et al., 2013) [6]. It has also been reported in an individual with idiopathic generalized epilepsy; however, no further information was provided (Klassen et al., 2011) [7]. Mutations in CLCN2 gene induces a dysfunctional role for ClC-2 chloride channel causing an increase in turnover, an abnormal opening of the protein channel, leading to intramyelin oedema (Depienne et al., 2013) [6]. The other two patients have been reported carrying homozygous mutation c.430-435del (Depienne et al., 2013) [6] and c.1769A>C (Giorgio et al., 2017) [1] respectively. The latter was reported as a subclinical form of CC2L discovered following the incidental detection of asymptomatic bilateral optic atrophy in an adult Moroccan woman.

The clinical features manifested by our patient and the reported patients carrying the same c.1709G>A mutation in the CLCN-2 gene.

Our patient showed a similar clinical phenotype of slow progression of symptoms and mild cerebellar ataxia. However, headaches that were the most prominent clinical feature lasting for several years as the unique clinical manifestation, psycho-cognitive disturbances, as well as spastic paraplegia have not been previously associated with this mutation. Moreover, our patient had hypothyroidism with positive anti thyroid antibodies. Zhuoxin Guo et Al reported a combined endocrinological disturbance (hyperthyroidism and hyperparathyroidism) in his patient. Endocrine involvement may be explained by the high expression of CLC2 in the glands but further studies are needed (Wang et al., 2017) [8].

Other family members presented with a clinical phenotype that might be related to the CLC2 (headaches, psychiatric disturbances, azoospermia). Unfortunately, these symptomatic patients died, and genetic confirmation could not be performed.

Our patient's two brothers presented with azoospermia. Association between CCl2 and azoospermia has been reported once. One male with azoospermia (but without neurological dysfunction) was found to have CC2L during a work-up for infertility (Di Bella et al., 2014) [5]. Another male with a history of infertility was diagnosed with CC2L when he was investigated for severe headaches.

MRI findings in patients with CC2L are of importance for the clinician to guide the genetic diagnosis. The major criteria are the involvement of the posterior limbs of the internal capsules, cerebral peduncles, and middle cerebellar peduncles (Guo et al., 2019) [2]. Our findings were in accordance with the major brain MRI features. In our patient we report DWI hyperintensity with no restriction in the ADC maps.

As reported by Guo et al, the presence or absence of abnormal signal in ADC maps may be in part accounted for the differences in free water content which could be affected by the size of both myelin vacuoles and extracellular space in the lesions.

Since its discovery in 2013, *CLCN2*-related leukoencephalopathy has been reported in fifteen probands (VanderKnaap et al., 2015) [9] with eighteen pathogenic variants. Consequently, the phenotypic spectrum may only be partially known and statements about relative frequency of features are of limited value.

CLCN2-related leukoencephalopathy should be suspected in individuals with suggestive neurological, visual and brain MRI findings. Another supportive finding may be male infertility caused by oligospermia/azoospermia [10].

The prevalence of CC2L is unknown. The small number of known affected individuals suggests that the disease is exceedingly rare. Numerous individuals with CC2L, however, may also remain undiagnosed because they stay asymptomatic at an advanced age, lack a specific clinical phenotype, or have findings (e.g., headaches or infertility due to azoospermia or oligozoospermia) that do not prompt evaluation by brain MRI.

Conclusion

In conclusion, we report the first Tunisian and the fifth North African patient with CC2L. Giving the small number of known affected individuals to date, our report is valuable to the literature as it expands the knowledge about the disorder. Moreover, our patient had the same p.Trp570Ter mutation as two other patients from the same origin, indicating a possible high prevalence of this variant.

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