Case Report

Expanding gray zones in ERCC2 mutations; a patient with XP phenotype and acute post-infectious leukodystrophy

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ABSTRACT

Mutations in ERCC2, a Nucleotide Excision Repair (NER) gene leads to Xeroderma pigmentosum (XP), Trichothiodystrophy (TTD) and Cockayne Syndrome (CS) phenotypes with various severities. While patients undergo XP disease are primarily suffering from skin hypersensitivity but rarely having central nervous system problems, TTD and CS patients are mostly having neurological disorders. In addition to that severe changes in hair and nail texture are especially unique to TTD. Hereby we report a previously healthy patient developed a rapid neurological decline and severe leukodystrophy due to an acute infection in which kept up with mild UV sensitivity and mild developmental delay. Pathophysiology of infection related neurodegeneration and DNA repair genes are also discussed.

Key words: XP/TTD, ERCC2 mutation, DNA repair, leukodystrophy, UV sensitivity

The nucleotide excision repair (NER) pathway, includes a minimum number of 28 genes, and mainly serves to repair DNA parts that are damaged by ultraviolet (UV) radiation in sunlight and also has a role in the nervous system [1, 2]. ERCC2 is one of the major genes in this pathway that codes instructions for production of XPD which is an essential subunit of proteins known as the general transcription factor IIH (TFIIH) complex. Two major features of TFIIH complex are involved in gene transcription in the meanwhile they assist in the repairing of damaged DNA [3]. Defected NER genes identify several rare clinical diseases such as Xeroderma Pigmentosum (XP), Trichothiodystophy (TTD) and Cockayne Syndrome (CS) [4, 5].

XP patients have clinical features such as severe UV sensitivity leading to skin cancer. Approximately 30% of these patients also have neurological abnormalities such as diminished or absent deep tendon reflexes and sensorineural hearing loss. Moreover, intellectual capacity improves during the postnatal period; however, it could be followed by deterioration over years. In addition, MRI findings show cerebellar and cerebral atrophy with involvement of the white matter. Ventricular enlargement may also be seen [6].

Skin cancer tendency is usually not observed in TTD patients, however majority of the patients have UV sensitivity. TTD patients also have mental retardation, short stature, frequent infections, ichthyosis, onychodystrophy and genital abnormalities. Furthermore, the MRI findings of those patients primarily demonstrate hypomyelination on the cerebral white matter on the other hand atrophy of the brain is rarely detected [7-9]. Mutation in ERCC2 gene also causes CS which is characterized by dysmorphic face with deep-set eyes, protruding ears and aged facial appearance. CS patients have postnatal failure of brain growth and additionally may have short stature, sexual abnormalities and ataxia. In addition to decreased or

absent myelination, cerebral atrophy and calcification of the basal ganglia are also observed in MRI [10, 11].

Hereby we report a patient with mild developmental delay and UV sensitivity and leukodystrophic pattern in MRI, which was triggered after an acute infection.

CASE REPORT

A 3-year-old patient referred to emergency service and was hospitalized due to bloody diarrhea. He was born at term without any complications from healthy consanguineous parents. He walked at 2 years and was able to talk with 10-15 words at that age. Fecal investigations suggested amebiasis as the cause for bloody diarrhea. After recovery, hand tremors followed by restlessness occurred. Eventually he lost head control and severe ataxia was generated. On the first examination, he had no head control, could not sit unsupported and was lacked of eye tracking. Deep tendon reflexes were brisk. He also developed dysarthria and reduced speech. Routine biochemical tests were within normal ranges except moderately high cholesterol levels and liver function tests. Liver function tests normalized by time; however, cholesterol levels remained high. Lysosomal enzymes levels and electromyographic studies were all within normal ranges.

Magnetic resonance imaging (MRI) and spectroscopy (MRS) of the brain were performed on a 1.5-T system. Multivoxel MRS was performed by using the point-resolved two-dimensional chemical shift imaging (CSI) (TR: 1500; TE: 135/35 ms). Voxels were placed in deep white matter of frontal and occipital lobes and basal ganglions. N-acetylaspartate, choline, creatine, myo-inositol, lactate and glutamine/glutamate peaks were analyzed. Cranial MRI at that time showed diffuse white matter demyelination sparing grey zones and brain stem. Moreover diffuse dysmyelination with increased T2 signals was noted throughout the supratentorial white matter. At short and long echo MRS, increased myoinositol peak correlates with gliosis, increased glutamine/glutamate peak correlates with acute excitotoxic injury were seen. Elevated lactate levels demonstrated an acute response. Choline peaks also made a minimal increase (Figure 1).

According to clinical and MRI findings; DNA was extracted from peripheral blood. Amplified PCR samples are used for gene libraries by using NEXTERA XT (ILLUMINA, USA) kit protocol. All exons and exon intron boundaries of five Vanishing White Matter disease genes (EIF2B1-EIF2B5) were sequenced on the MiSeq platform. No mutation was detected on these five genes. On the second step we performed exome sequencing on the NextSeq500 platform. Variants were analyzed using Variant Studio and pathogenicity was evaluated using Alamut and HGMD Pro databases. In order to identify the causative gene mutation, exome sequencing revealed a homozygous missense change in the ERCC2 gene [NM_000400:c.C334T:p.R112C]. This variant was previously reported to cause Trichothiodystrophy [12].

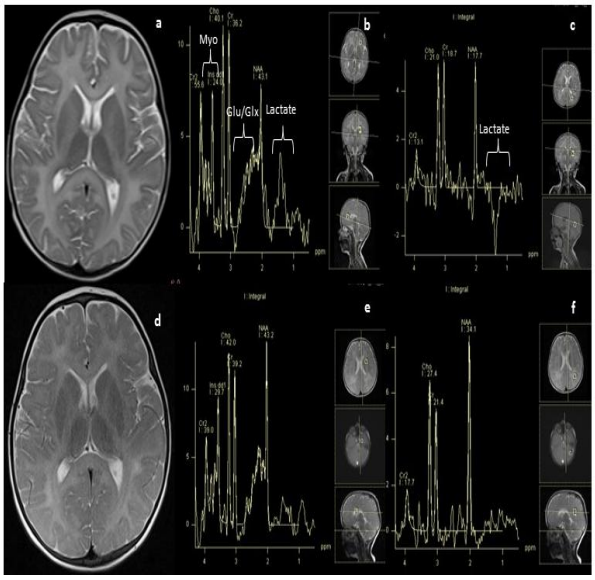

Figure 1: (a) Diffuse dysmyelination throughout supratentorial white matter during acute attack, short (b) and long echo MRS (c) shows increased myoinositol peak, increased glutamine/glutamate peak and increased lactate peak. (d) Controlled MRI and MRS performed one year later, decrease in T2 signal changes in supratentorial white matter, short (e) and long echo MRS (f) shows decrease in lactate and glutamine-glutamate peaks, unchanged myoinositol and choline peaks. Glu/Glx: Glutamine/glutamate. Myo:myoinositol

Patient's ataxia and truncal hypotonia recovered within 2 weeks. However, after 10 months during summer time, he developed severe sunburns over his face which was treated with topical cortisone (Figure 2). After genetic diagnosis; patient was interned and reevaluated at the age of 46 months. The patient had no signs of onychodystrophy, brittle hair or facial dimorphisms. The control MRI/MRS showed that, dysmyelination signal changes in supratentorial white matter had decreased. At short and long echo MRS, compared to previous spectra which were taken one year ago, marked neither lactate nor glutamine-glutamate peaks

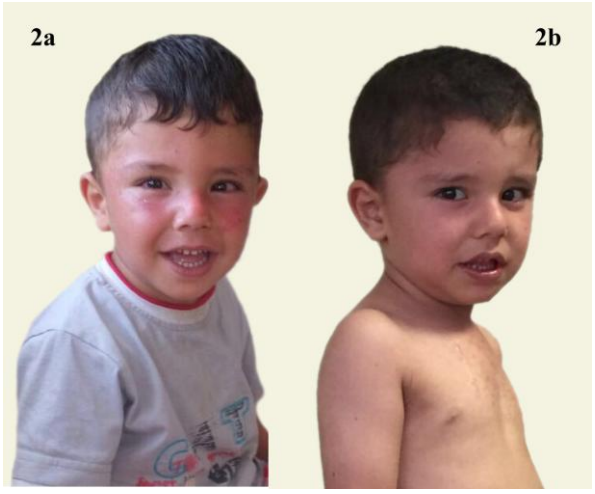

Figure 2a: Patient showing facial lesions after sun exposure 2b: Recovery of sunburn after 2 weeks of topical cortisone treatment.

DISCUSSION

In the last twenty years, studies have shown that XP, TTD and CS are in a close relationship even though they have phenotypic heterogeneity. Despite highly different clinical characteristics of the XP and TTD, these syndromes have been shown to overlap in several cases [12-15]. Diagnosing cases with ERCC2 gene mutation indicates mild phenotypic features which are challenging. Presence of relatively occult findings like the absence of severe intellectual deficiency, initial UV sensitivity, nail dystrophy and facial dysmorphism makes this case difficult to name. The presented patients mostly show features that resemble XP-Neurological disease, however, in those patients myelin destruction has not been reported [13, 16]. This raises two possibilities; lack of a triggering effect like an infection in previous XP-Neurological patients that may cover up a potential white matter change; or the boundaries of NER syndromes are so obscure and constitute a wide spectrum of disorders (makes them difficult to distinguish compare to distinct diseases) that are difficult to distinguish rather than distinct diseases.

In this case, the patient admitted with complaint of acute gastroenteritis which was re-admitted after two weeks with symptoms of gait disturbance and the MRI images showed destruction of cerebral white matter. The association with Leukodystrophy and infection has been a popular field of study, however, has never been a well-known entity. White matter disease that is triggered by a minor trauma or infection may be seen in acquired or inherited leukodystrophies such as; Multiple Sclerosis and Vanishing White Matter (VWM) disease [17, 18]. Endoplasmic reticulum (ER) stress is just known to be a triggering factor [19]. It was proposed that in case of exceeding the capacity of the ER provokes ER stress and triggers the unfolded protein response (UPR) that leads to the apoptotic death of the stressed cell. The UPR is a coordinator for decreasing protein folding load, increasing folding capacity of the ER, and inducing cytoprotective genes like ERCC2 [20].

We have identified a homozygous missense mutation on exon 5 [NM_000400; 334C>T; p.R112C] in the ERCC2 gene. This mutation was previously reported at a compound heterozygous state in an 11-year-old boy who had an obvious phenotype of TTD. The patient had dystrophic hair, diffuse cerebral hypomyelination, developmental delay, microcephaly, ichthyosis, cataract and recurrent infections. He also had mild, diffuse central osteosclerosis [12]. Clinical findings of our patient were mild compared to that previous case in the literature. White matter change was the only finding in common with TTD present in our patient. It could be attributed to the young age of the child who is only 46 months of age since according to another case-report; onychodystrophy or mental retardation may be a late onset feature in TTD [14].

Our patient had also high cholesterol levels compared to his age group. A 27 year-old patient with XP/TTD had also high lipid profile [14]. Hypercholesterolemia is not a common feature of XP or TTD patients however it is reported in other NER disorders such as Ataxia Oculomotor Apraxia and Spinocerebellar ataxia with axonal neuropathy (SCAN1) [21]. Physicians should be aware of high lipid profiles and liver/kidney failures beginning from early ages.

CONCLUSION

Diagnosing cases with ERCC2 mutation shows mild phenotypic features are challenging. Exome sequencing allows an earlier diagnosis of mild cases before the appearance of clear symptoms. Our patient had an acute leukodystrophy as an initial finding however developed UV sensitivity after causative mutation was found. Unlike TTD, the patient has neither severe intellectual disability and onychothiodystrophy nor brittle hair. Besides, he did have leukodystrophy, which is not a feature of XP. This report is unique as it presents an acute initiation of leukodystrophy followed by recovery and development of XP neurological phenotype afterwards. We recommend physicians to be aware of mild manifestations of ERCC2

mutations and to investigate DNA repair genes in leukodystrophy before UV sensitivity presents.

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