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Case Report

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Brain MRI Manifestation in Two Patients with East Syndrome

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Abstract

EAST Syndrome is a rare channelopathy caused by KCNJ10 mutations. It has four cardinal signs, including epilepsy, ataxia, sensorineural deafness, and tubulopathy. Dentate nucleus abnormalities and/or mild cerebellar atrophy have been reported as important neuroimaging findings in these patients. Additionally, restricted diffusion of globus pallidus, thalami, brainstem, dentate nuclei, and cervical spinal cord have been observed in some case reports [1].

Method

This study analyzes two unrelated Iranian children with epilepsy, ataxia, renal salt-losing tubulopathy, and normotensive hypokalemia metabolic alkalosis with age growth. Whole-genome linkage analysis confirmed EAST syndrome. The first patient's genotyping showed homozygote KCNJ10 (NM_002241.5 c.595C>T p.Arg199), and the second patient showed homozygote KCNJ10 gene (NM_002241. c.556delG:p.V186Lfs*11). Both patients underwent 1.5 Tesla Brain MRI due to seizures and neurological symptoms.*

Results: Brain MRI examinations at 5 years old in Patient 1 and at 10 years old in Patient 2 revealed distinctive brain involvement characterized by true restricted diffusion of thalami, brain stem (especially midbrain and pons), dentate nuclei, tegmental tracts, and pulvinar. More severe symptoms correlated with more extensive and intense imaging findings

Keywords: Case Report, East Syndrome, Whole-Exome Sequencing, Brain Mri, True Restriction, Dentate Nucleus

1. Introduction

EAST syndrome (epilepsy, ataxia, Sensorineural hearing loss, Tubulopathy) or sesame syndrome (Seizures, Sensorineural deafness, Ataxia, Mental disability, and Electrolyte imbalance) is a rare genetic disease resulting from a mutation in the KCNJ10 gene (kir4.1), which is located on chromosome 1 and has an autosomal recessive mode of inheritance [2]. Kir4.1 is crucial for potassium channel function in the central nervous system, kidneys, and ears, impacting potassium buffering and homeostasis. Loss of function due to gene mutation highlights the importance of this regulating mechanism [3]. The highest kir4.1 levels are found in the central nervous system in astrocyte processes close to the synaptic cleft [4]. They are also found in peripheral tissues throughout the renal tubular system and the inner ear. They are found in the basolateral membrane of the distal convoluted tubule, cortical collecting duct, and thick ascending limb of Henle [5]. Because of the distribution of rectifying potassium channels, Symptoms of the disease include seizures, ataxia, and renal, and auditory problems, which will be explained in detail below. Although the prevalence of this syndrome is low, due to its autosomal recessive nature, it is effective for the genetic examination of other family members. As well as the effect of timely diagnosis and familiarization with MRI manifestations leads to more appropriate treatment and prevention of ineffective treatments.

1.1 Epilepsy

Seizures occur in 0 / 5% of affected patients [6]. Kir4.1 and a much lesser degree kir5.1 are dominant in astrocytes. These cells volute in a potassium buffering by absorbing potassium, at the junction of oligodendrocytes for excitation jump from node to node. Mutation in kcnj10 directly affects Na, K channel malfunction, and neuronal excitability, leading to seizures [7]. Seizures are typically infantile in onset, with the first attack usually occurring between 3 to 9 months of age, a possible episode in the neonatal period has been reported [8].

1.2 Ataxia

Bergman glial cells, crucial for migrating neurons, cerebral and cerebellar cortex [9]. These cells modulate Purkinje cell proliferation by regulating K+ homeostasis [10]. The proximity of Bergman glial cells to Purkinje cells and the high expression of Kir4.1 indicate that Kir4.1 may be involved in this function. Most of the Children who are old enough to assess cerebellar function had varying degrees of cerebellar dysfunction that affected daily activities, including intention tremor, dysdiadochokinesia, dysmetria, trunk ataxia, titubation, speech problems, and nystagmus [11].

1.3 Sensorineural Hearing Loss

Kir4.1 is essential for the endocochlear potential, playing a critical role in passive K+ transmission on both sides of the cell. It is likely to be critical for high dynamic range hearing [12]. The severity of hearing loss varies, ranging from mild cases that may go undiagnosed until formal testing is conducted as part of a study, to severe cases that necessitate bilateral hearing aids.

1.4 Renal Tubulopathy

From a nephrological point of view, EAST syndrome is very similar to Gitelman syndrome, because of the same mechanism of defective electrolyte transport in the distal convoluted tubule [13]. Inactivation of K ir4.1 leads to a drastic reduction in basolateral K+ conductance and coupling of Na+/K+-ATPase activity and reducing the export of Na+. In addition, potential-dependent transport processes for the efflux of Mg2+ Ca2+ and Cl− reduced. Decreased salt reabsorption leads to urinary salt loss, extracellular volume depletion, and compensatory increases in renin and aldosterone. The increase in aldosterone increases Na + reabsorption through epithelial Na + channels in the distal nephron and partially compensates for urinary salt loss. At the same time, high aldosterone levels increase K+ secretion, which contributes to hypokalemia [14].

1.5 MRI Findings

MRI of the brain detected pathological findings in most cases of EAST Syndrome, although normal brain MRI were reported in some cases. The majority showed abnormalities of the cerebellum, the cerebellar dentate nuclei, and cerebellar hypoplasia. These ranged from subtle signal changes to more obvious changes in both deep cerebellar nuclei and hilar white matter. [8] Due to the rarity of the syndrome, this article introduces the MRI manifestations of two patients to serve as a guide for other colleagues.

Magnetic resonance imaging (MRI) was performed using a 1.5T Siemens magneto Avanto, brain sequences obtained included axial coronal, and sagittal T1/T2-weighted turbo spin echo (TSE) images (slice thickness 5 mm) and fluid-attenuated inversion recovery (FLAIR) and apparent diffusion coefficient (ADC)/ diffusion-weighted imaging (DWI) images.

2. Case Examination

2.1 First Patient

The patient was a 5-year-old boy born at term after an uncomplicated pregnancy with a birth weight of 3 kilograms by cesarean section because of a previous cesarean section. He had no history of icterus and NICU admission in the neonatal period. His parents were cousins from Mashhad City Iran. He first presented at 3 months of age with 4 attacks of generalized tonic clinic seizure (most of them in the morning). ECG revealed long QTC. Biochemical testing at that time revealed mild hypocalcemia and hypokalemia but other parameters were normal. Treatment with phenobarbital was done and continues. He was seizure-free for one year. He started walking with his hand at 1.5 years old. He spoke his first meaningful words at 15 months and his speech was slurred with delayed development to the same age. He was hyperactive and had some degree of ADHD. The parent noticed ataxia and mildly delayed development in all activities to the same age. He was admitted at 3 years old again, with seizures without fever, intermittent hypokalemia, intellectual disability, and delayed development. EEG showed normal findings. An audiology assessment was not done. He was admitted to the hospital several times, because of severe intermittent hypokalemia, alkalosis, hypomagnesemia, and seizure attack.

2.1. 1 Methods

Due to these symptoms, delayed development disorder history of seizure attacks, and ataxia, complete gene sequencing was done at 4 years old. A homozygote pathogenic variant was identified in the KCNJ10 gene. The genetic diagnosis of Sesame syndrome was confirmed. In his recent admission, he had multiple seizure attacks after an upper respiratory infection. LP was normal. EEG had normal findings. Lab tests show mild hypokalemia. Brain MRI was done for the first time, it showed high signal intensity in T2 sequences and low signal intensity in T1 in the pons, midbrain especially superior and inferior colliculus, medial thalamus, and dentate nucleus on both sides. as well as scattered foci in the left cerebral hemisphere in different parts of Deep and subcortical white matter was seen. Diffusion-weighted imaging revealed restricted diffusion with ADC correlation in all affected areas. Figure (1,2,3)

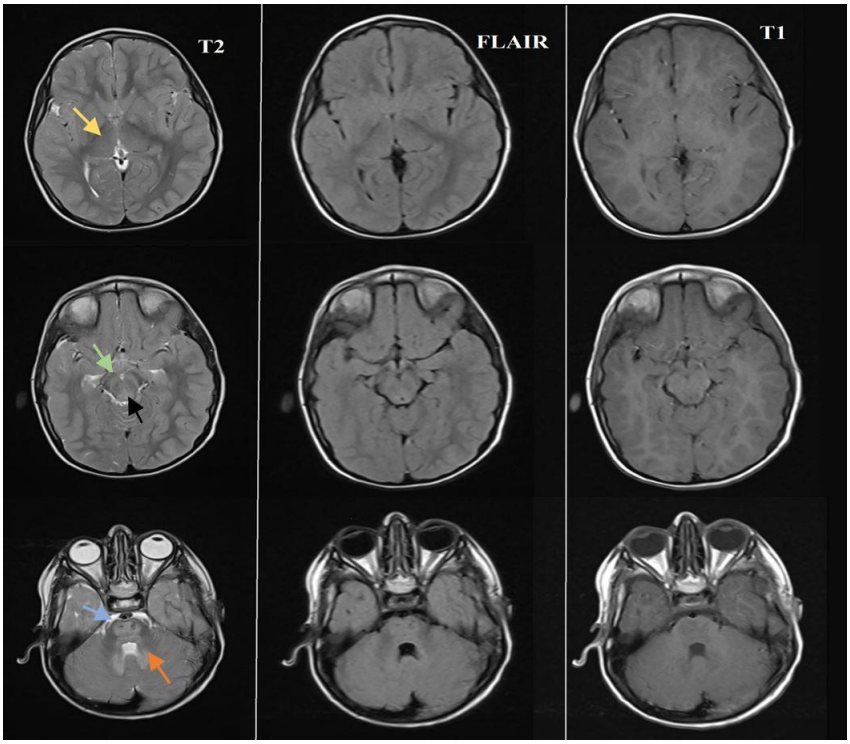

Figure 1: Brain MRI of the Patient at the Age of Five Years. Axial T2 Weighted and Flair Images Reveal Symmetrical Hyper Intensity Of Medial Thalami (Yellow Arrow), Periventricular Matter of Third Ventricle and Pulvinar, With Sparing of the Mammillary Bodies, Phornics, Internal Capsule, and Corpus Striatum. The signal Abnormality Extends to the Midbrain (Green Arrow) and Pons (Blue Arrow), with Involvement of Red Nucleus and Substantial Nigra and Periaqueductal Gray Matter and Tegmental Tract (Black Arrow) and Dentate Nucleus (Orange Arrow) with Sparing of Most of the Corticospinal Tract and Middle Cerebellar Peduncle. In this region, the T1 Sequence Showed a Faint Decreased Signal Intensity

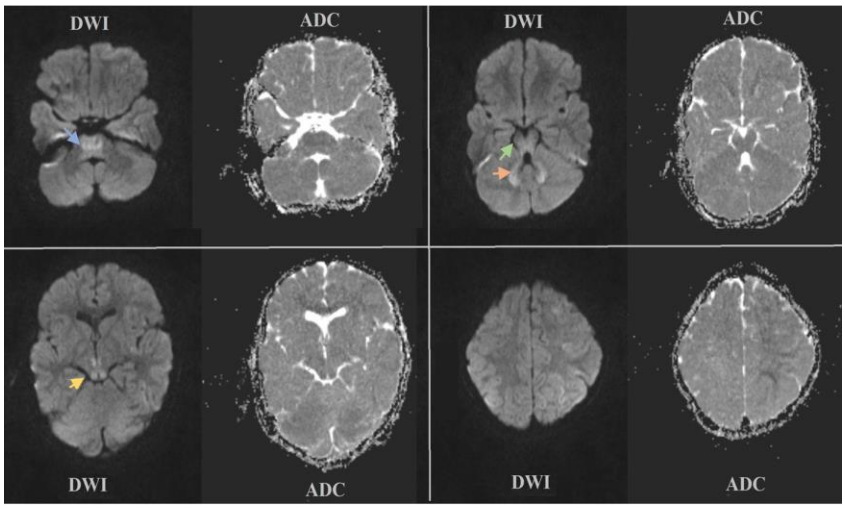

Figure 2: Diffusion-Weighted Imaging Reveals Restriction with ADC Correlation in the Affected Area. Also, the Scattered Focal True Restriction was Shown in Subcortical and Deep with the Matter in the Left Front Parietal

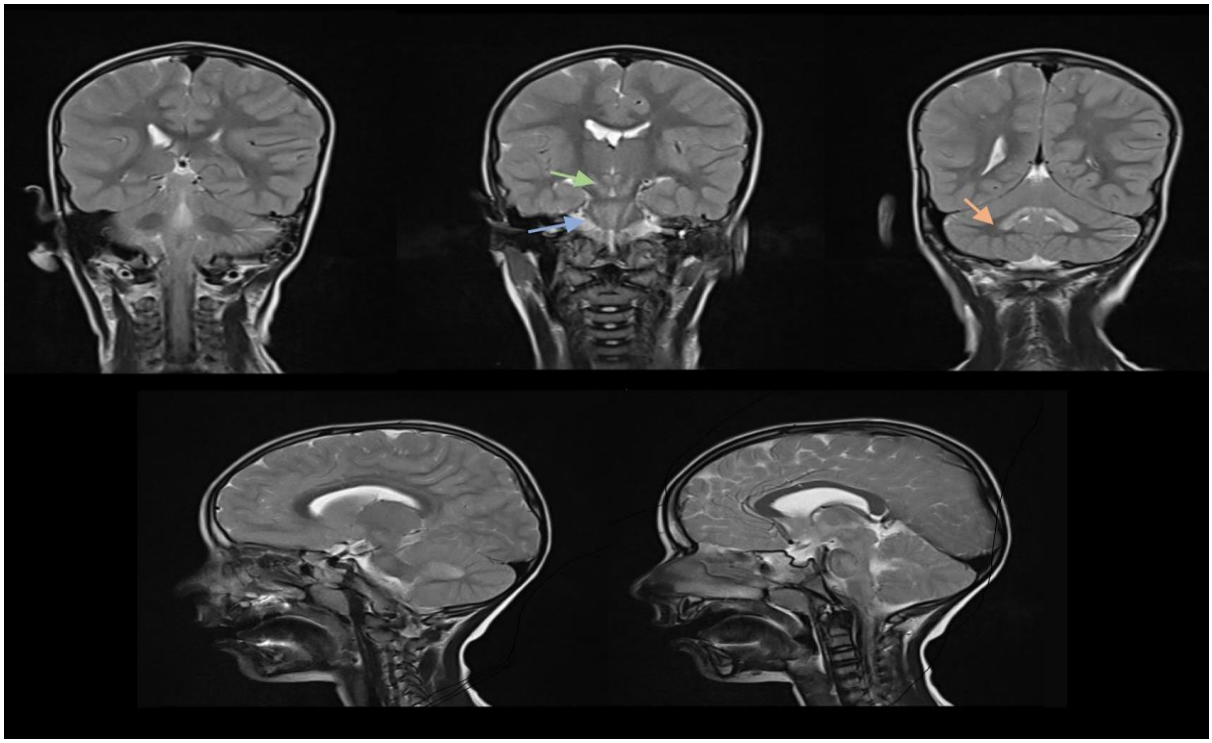

Figure 3: T2 Weighted Coronal and Sagittal Images with the Same Brain Involvement and Some Faint Signal Abnormality in the Medulla with Extension to the Cord

2.2 Second Patient

She is a 14-year-old girl who had a natural fetal period and was born by cesarean section. The birth weight was 3.5 kg. The Apgar at birth was determined as 9 out of 10. The patient is the second child of the related parents (cousins). Her sister had a history of death due to intermittent seizure attacks and electrolyte imbalance at the age of 4 years. Her mother had a history of an abortion in the first three months. She was hospitalized due to severe vomiting and hypokalemia at birth. On average, she was hospitalized due to intermittent hypokalemia and hypomagnesemia, and seizures every 4 months. During this time, the patient with the diagnosis of Gitelman syndrome was treated with spironolactone, calcium, magnesium, and potassium. Due to the developmental disorder and the addition of symptoms such as vision loss and hearing loss, a close assessment was done. In the hearing examination, due to hearing impairment, aids were prescribed to improve the symptoms. Glasses were prescribed to improve her visual acuity. Speech problem and developmental delay becomes more visible as she grows up. EEG showed normal findings. According to the patient's symptoms and the death of her sister with similar symptoms, whole sequence genotyping was done. A homozygous likely pathogenic variant was identified in the KCNJ10 gene. The genetic diagnosis of autosomal recessive sesame syndrome was approved.

3. Methods

Due to the severity of seizures and developmental disorders, a brain MRI was performed at the age of 10 years. It showed a signal increase in T2 and FLAIR sequences and a signal decrease in T1 sequences in the thalamus, globi pallidi, midbrain, and pons symmetrically (with sparing of fornices and putamen and internal capsule) and dentate nucleus on both sides. They sowed restrictions on DWI images with ADC correlation in affected cites. Brain MRI was done again 4 months later because of a severe seizure attack, same finding was shown. Evidence of atrophy was not seen in the cerebellum, dentate nucleus, and corpus callusom. (Figure 4,5,6)

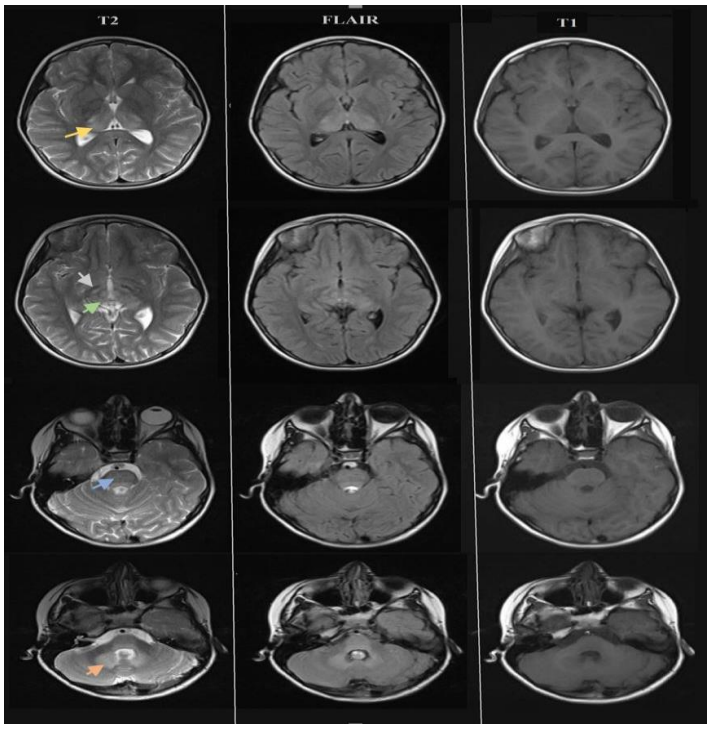

Figure 4: The Brain MRI of the Patient at the Age of 10 Years. Axial T2 Weighted and Flair Images Reveal Symmetrical Hyper Intensity of Thalami (yellow arrow), Globi Pallidi (White Arrow), Periventricular Matter of Third Ventricle and Subthalamic Nuclei and Pulvinar, With Sparing of the Mamillary Bodies, Phornics, Internal Capsule, and Putamen. The Signal Abnormality Extends to the Midbrain (Green Arrow), Pons (Blue Arrow), Medulla (Black Arrow), and Upper Segment of the Cord, With Involvement of Red Nucleus and Substantial Nigra and Periaqueductal Grey Matter and Tegmental Tract and Dentate Nucleus (Orange Arrow) with Sparing of Most of the Corticospinal Tract and Middle Cerebellar Peduncle

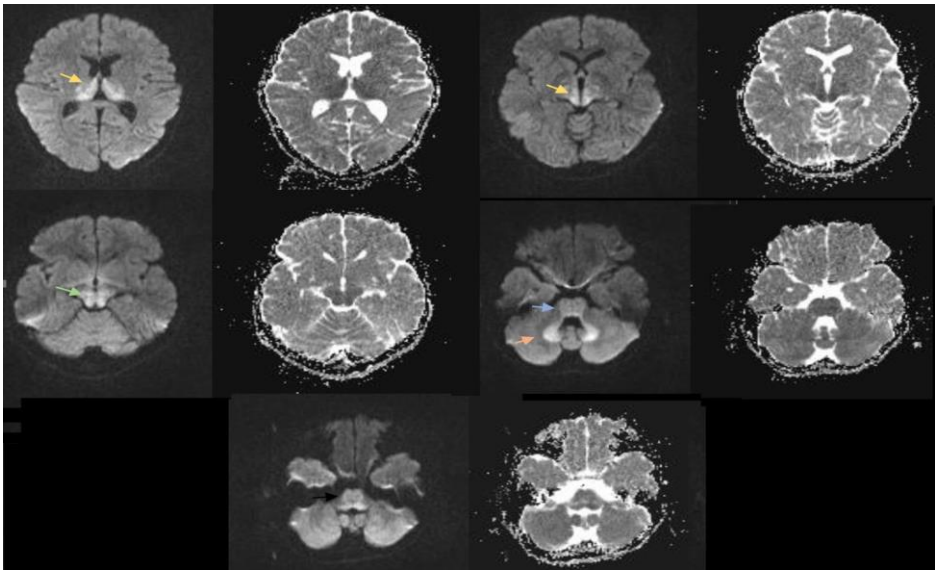

Figure 5: Diffusion-Weighted Imaging Reveals Restriction with ADC Correlation in Deep Gray Matter with Extension to the Brain Stem

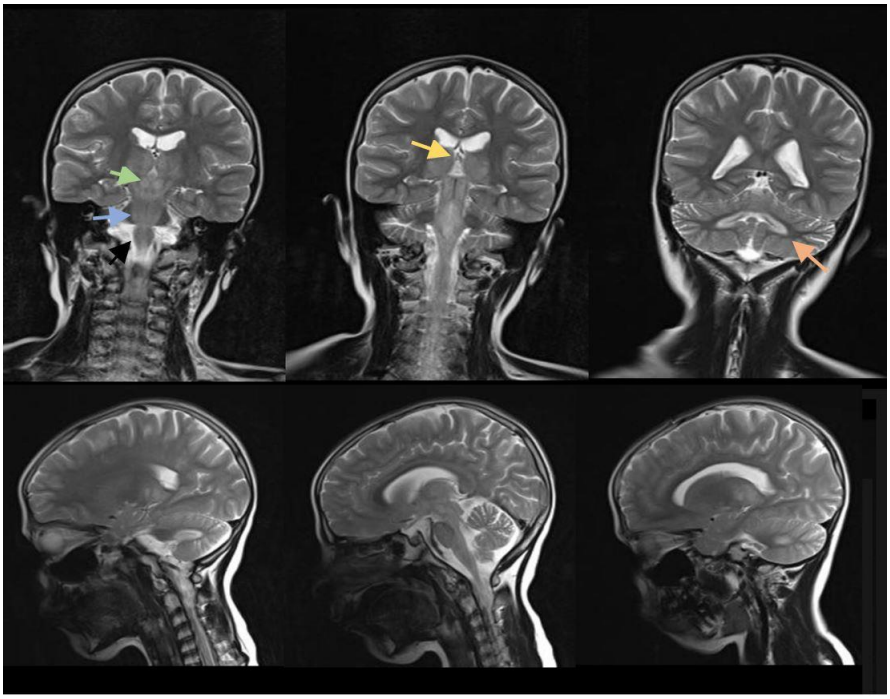

Figure 6: T2 Weighted Coronal and Sagittal Images with the Same Brain Involvement as Shown above and Signal Abnormality in the Medulla with Extension to the Cord

4. Conclusion

Brain image analysis revealed a characteristic pattern of morphological change. It showed restricted diffusion in deep gray matter and ascending and descending pathways in the brain stem with extension to the spinal cord in one patient. These findings help to better diagnose the EAST Syndrome.

5. Discussion

EAST syndrome a clinical syndrome characterized by epilepsy, ataxia, sensorineural deafness, and tubulopathy, has been associated with recessive mutations in the KCNJ10 gene. We described in more detail the brain MRI findings of the two children. Both patients were from the same city in Iran. Their parents were relatives. The mutation in first patient was homozygote KCNJ10 (OMIM 602208), NM_002241. 5 c.595C>T (p.Arg199*). American College of Medical Genetics (ACMG) classification was pathogenic. We detected a homozygote variant in exon2 of the KCNJ10 gene (NM_002241. c.556delG: p.V186Lfs*11), autosomal recessive (phenotype number 612780) in the second patient. ACMG classification was likely pathogenic. The genome sequence also revealed homozygote ITGA7 (OMIM600536) in the second patient, while ACMG classification was a variant of unknown significance. The symptoms of the disease were more severe in the second patient than in the first patient. The number and frequency of convulsions and the severity of ataxia and developmental disorder were higher in the second patient. Also, there was a documented vision and hearing disorder only in the second patient. Most patients with East syndrome have brain MRI Changes. This imaging phenotype includes dentate nucleus signal abnormality as well as cerebellar hemispheric/vermian hypoplasia, callosal, and spinal changes [15]. Brain MRI involvement was more significant in patients with more severe symptoms.

6. Key Clinical Message

Brain MRI findings revealed distinct abnormalities including restricted diffusion in thalami, brainstem, dentate nuclei, tegmental tracts, and pulvinar, which expand the spectrum of neuroimaging manifestations associated with EAST syndrome. This emphasizes more diffuse MRI findings may be associated with increased severity of symptoms in EAST syndrome.

References

1. Severino, M., Lualdi, S., Fiorillo, C., Striano, P., De Toni, T., Peluso, S., ... & Bruno, C. (2018). Unusual white matter involvement in EAST syndrome associated with novel KCNJ10 mutations. *Journal of neurology, 265*, 1419-1425.
2. Bockenhauer, D., Feather, S., Stanescu, H. C., Bandulik, S., Zdebik, A. A., Reichold, M., ... & Kleta, R. (2009). Epilepsy, ataxia, sensorineural deafness, tubulopathy, and KCNJ10 mutations. *New England Journal of Medicine, 360*(19), 1960-1970.
3. Abdelhadi, O., Iancu, D., Stanescu, H., Kleta, R., & Bockenhauer, D. (2016). EAST syndrome: Clinical, pathophysiological, and genetic aspects of mutations in KCNJ10. *Rare Diseases, 4*(1), e1195043.
4. Higashi, K., Fujita, A., Inanobe, A., Tanemoto, M., Doi, K., Kubo, T., & Kurachi, Y. (2001). An inwardly rectifying K+ channel, Kir4. 1, expressed in astrocytes surrounds synapses

and blood vessels in brain. *American Journal of Physiology-Cell Physiology, 281*(3), C922-C931.
5. Lourdel, S., Paulais, M., Cluzeaud, F., Bens, M., Tanemoto, M., Kurachi, Y., ... & Teulon, J. (2002). An inward rectifier K+ channel at the basolateral membrane of the mouse distal convoluted tubule: similarities with Kir4-Kir5. 1 heteromeric channels. *The Journal of physiology, 538*(2), 391-404.
6. Schultheis, P. J., Lorenz, J. N., Meneton, P., Nieman, M. L., Riddle, T. M., Flagella, M., ... & Shull, G. E. (1998). Phenotype resembling Gitelman's syndrome in mice lacking the apical Na+-Cl− cotransporter of the distal convoluted tubule. *Journal of Biological Chemistry, 273*(44), 29150-29155.
7. Orkand, R. K., Nicholls, J. G., & Kuffler, S. W. (1966). Effect of nerve impulses on the membrane potential of glial cells in the central nervous system of amphibia. *Journal of neurophysiology, 29*(4), 788-806.
8. Cross, J. H., Arora, R., Heckemann, R. A., Gunny, R., Chong, K., Carr, L., ... & Bockenhauer, D. (2013). Neurological features of epilepsy, ataxia, sensorineural deafness, tubulopathy syndrome. *Developmental Medicine & Child Neurology, 55*(9), 846-856.
9. Mori, T., Buffo, A., & Götz, M. (2005). The novel roles of glial cells revisited: the contribution of radial glia and astrocytes to neurogenesis. *Current topics in developmental biology, 69*, 67-99.
10. Wang, F., Xu, Q., Wang, W., Takano, T., & Nedergaard, M. (2012). Bergmann glia modulate cerebellar Purkinje cell bistability via Ca2+-dependent K+ uptake. *Proceedings of the National Academy of Sciences, 109*(20), 7911-7916.
11. Bockenhauer, D., Feather, S., Stanescu, H. C., Bandulik, S., Zdebik, A. A., Reichold, M., ... & Kleta, R. (2009). Epilepsy, ataxia, sensorineural deafness, tubulopathy, and KCNJ10 mutations. *New England Journal of Medicine, 360*(19), 1960-1970.
12. Zdebik, A. A., Wangemann, P., & Jentsch, T. J. (2009). Potassium ion movement in the inner ear: insights from genetic disease and mouse models. *Physiology, 24*(5), 307-316.
13. Maeoka, Y., & McCormick, J. A. (2020). NaCl cotransporter activity and Mg2+ handling by the distal convoluted tubule. *American Journal of Physiology-Renal Physiology, 319*(6), F1043-F1053.
14. Loffing, J., Vallon, V., Loffing-Cueni, D., Aregger, F., Richter, K., Pietri, L., ... & Kaissling, B. (2004). Altered renal distal tubule structure and renal Na+ and Ca2+ handling in a mouse model for Gitelman's syndrome. *Journal of the American Society of Nephrology, 15*(9), 2276-2288.
15. Stivaros, S. (2013). How the imaging investigation of EAST syndrome points towards the future of radiological multi-parametric phenotyping of a genetic disease. *Developmental Medicine & Child Neurology, 55*(9).