International Journal of Science and Healthcare Research
Vol. 8; Issue: 4; Oct.-Dec. 2023
Website: ijshr.com
Case Report *ISSN: 2455-7587*

Solute Carrier Transport Disease - A Rare Case Report

Dr. Akshita Kansal[1], Dr. Abhijit Shinde[2], Dr. Suresh Waydande[3], Dr. Sunil Natha Mhaske[4]

[1]Junior Resident, Department of Paediatrics, DVVPF'S Medical College and Hospital, Ahmednagar, India
[2]Associate Professor, Department of Paediatrics, DVVPF'S Medical College and Hospital, Ahmednagar, India
[3]Professor and HOD, DVVPF'S Medical College and Hospital, Ahmednagar, India
[4]Dean and Professor in Department of Paediatrics, DVVPF'S Medical College and Hospital, Ahmednagar, India

Corresponding Author: Dr. Akshita Kansal

DOI: https://doi.org/10.52403/ijshr.20230432

ABSTRACT

The International Society for the Prevention of Epilepsy revised the classification in 2017, changing "encephalic encephalitis" to "encephalic developmental encephalitis". With the advancement of genetic technology, the number of genes that cause brain damage and the development of epileptic brain disease is increasing. Among these, the failure of the carrier to function is part of the etiology of developmental and mental diseases. Solute transporters play important physiological functions in the human body, and their dysfunction is associated with many human diseases. Therefore, in-depth studies of the development of infectious diseases and brain damage may help develop new therapies to improve the treatment of refractory epileptics and improve the patient's prognosis. In this article, the concept of transport chain is introduced for the first time and 9 brain development and brain diseases that occur as a result of malfunction of the transport chain are explained in terms of etiology, clinical features, diagnosis and correct treatment.

Keywords: Transport disease, epileptic encephalopathy, developmental encephalopathy, transporter protein, epilepsy

INTRODUCTION

The concept of brain diseases was widely accepted and used in the early years, but later scientists realized that many diseases, in addition to the direct effect of epilepsy on mass growth, can also cause slowing of growth (1). The International Association for the Prevention of Infectious Diseases (ILAE) introduced a new developmental stage of epilepsy (DEE) in 2017 (2). Most of the brain enlargements and epilepsies are genetic. Thanks to recent advances in genetic testing and neuroimaging, the causes of DEE are better understood, leading to further genetic discoveries. One of the main reasons for the development of osteoporosis is lack of bearing, of which heavy lifting (SLC) carriers are most common. Comprehensive screening of SLC carriers may help improve the treatment of patients with refractory epilepsy, as they are important for motor control and are the main targets of this pharmacology in humans. To date, nine DEEs linked to the SLC gene have been discovered. Both patient prognosis and treatment goals will benefit from examining the physiology of the nine DEEs. There are 458 different transmembrane SLCs divided into 65 groups in humans (3). SLC transporters are one of the major proteins found in mammalian cell membranes and perform various transport functions between different organelles. SLC transporters are considered secondary transporters because they rely on electrochemical or ionic

gradients created by pumps to transport substrates (4). This transporter plays an important role in maintaining normal brain function, and dysfunction of the SLC transporter can lead to various neurological diseases such as Huntington's disease, Parkinson's disease, and seizures (5, 6) As a solute carrier (SLC) transporter, transporters mediate. Important physiological processes in many neurological diseases. In this review, we focus on current knowledge about metal ion transporters, glucose transporters, and amino acid transporters because they are important in maintaining cell homeostasis in many types of diseases.

CASE REPORT

An 11-month-old male child born to a G2P1L1 mother via normal vaginal delivery cried immediately after birth with a birth weight of 2.9 kg product of non-consanguineous marriage presented with clinical indications of global developmental delay, truncal hypotonia, poor eye contact, spastic quadriplegia, diminished deep tendon reflexes, has been brought to the hospital with complains of seizures involving left leg and arm with uprolling of eyes. The patient also complained of fever, cough, and cold and was diagnosed with bronchopneumonia so was taken on continuous positive airway pressure mode of ventilation. The patient was kept nil by mouth and IV fluids and IV antibiotics were started. The child has a similar previous history, i.e., at 4 months of age, the child had high-grade fever which was sudden in onset and not relieved by taking oral medications. Followed after 2 days, the child had first episode of seizure involving the left side of the body and uprolling of eyes.

The child is on three antiepileptics. The patient's family history is suggestive of a sister having similar complaints of delayed developmental milestones. There is no significant antenatal history. The child's immunization is completed up to date.

The child is unable to crawl or sit without support but can sit with support. The pincer grasp is absent but the child can fix and follow objects through 180 degrees by turning his head, the child is unable to speak syllables but can speak monosyllables, the child does not wave bye-bye but can hold the bottle for feeding.

Patients' families belong to lower middle-class families according to the Kuppuswamy scale.

The child was shown to a pediatric neurologist for the same who he advised various investigations because the patient's sister had similar complaints and had a case of cerebral palsy.

MRI brain shows cerebral atrophy & urine tms shows raised levels of pyruvate and lactate.

The nerve conduction study was not suggestive of any neuropathy.

Electromyography shows abnormal findings suggestive of evidence of electrophysiological dysfunction of the visual tract from either side.

Whole exome sequencing shows –

Gene	Location	Variant	Zygosity	Disease	Inheritance	Classification
SLC25A12	Exon 5	c.400C>T	Homozygous	Developmental and epileptic encephlopathy	Autosomal recessive	Likely pathogenic (PVS1, PM2)

DISCUSSION

In this report, we present the concept of virus transport for the first time. There are 9 types of DEE phenotypes, we will discuss DEE type 39 in detail from its pathogenesis, clinical features, diagnosis and treatment features. All nine types of DEE suffer from early onset, insidious diabetes, and slow global progression, but their presentation may vary. New antiepileptic drugs targeting the pathophysiology of each specific condition may be developed to help treat epilepsy. For example, increased EAAT2 expression protects neurons from excitatory

neurotransmitter damage and increases glutamate uptake by glial cells (7, 8). LDN/OSU-0212320, ceftriaxone, Parawixin 10, and recombinant interleukin-1 receptor antagonists all work by upregulating EAAT2 expression (8 – 10). Pathogenesis-SLC25A12 is located on chromosome 2q31.1 and encodes the mitochondrial aspartate/glutamate transporter (AGC) (11). SLC25A12 is expressed primarily in neurons and skeletal muscle and is an important component of the malate/aspartate shuttle (11, 12). It ensures the exchange of aspartate into glutamate and protons in the mitochondria and the transfer of the cytosolic reductant balance to the mitochondria (12). When the AGC is dysfunctional, aspartate cannot be transported to the cytoplasm, resulting in decreased N-acetylglutamate in the cytoplasm, resulting in poor myelin production (12, 13). However, the exact mechanism by which SLC25A12 variants cause epilepsy remains unclear. It is suggested that this may be related to intracellular glutamate accumulation and cell damage. SLC25A12 variants are associated with developmental epileptic encephalopathy type 39 (DEE39, OMIM 612949), which is considered a somatic recessive disease. Four cases were reported in previous studies, and their main clinical features were early-onset epilepsy, psychomotor retardation, hypotonia, short stature, and microcephaly (13-15). Brain MRI shows characteristic dysmyelination and brain atrophy (14). Proton magnetic resonance wave analysis will show decreased N-acetyl aspartate peaks indicating neuronal damage (). Treatment Options: Ketogenic diet reduces weight loss in AGC1 deficiency, suggesting a possible link between the pathophysiology of AGC1 deficiency and the ketogenic diet. The ketogenic diet alleviates neuronal energy deficits because it directly supplies acetyl-CoA to the mitochondrial Krebs cycle (16). Since malate dehydrogenase is a NADH-dependent dehydrogenase and the ketogenic diet will reduce NADH produced by cellular glycolysis, oxaloacetic acid will be converted to aspartic acid instead of malic acid, thus promoting the utilization of aspartate and N-acetylglutamic acid from myelin producing neurons. In a previous study, a decrease in seizures and improvement in mental functions were observed when the ketogenic diet was applied in two patients carrying the SLC25A12 gene mutation (16, 17).

CONCLUSION

The brain contains hundreds of transporters important for the distribution of various substrates. Studying SLCs helps understand the function of substrates in the brain and the function of transporters in maintaining brain homeostasis. SLCs may facilitate the distribution of drugs across the BBB and into the brain or act as drug targets. Although we have made efforts to unravel SLC transport in the brain, we still do not fully understand the transport mechanism. More research is still needed on the physiological role, disease modification, and drug release of most SLCs expressed in the brain. Understanding SLC in a chemical and physiological context will help advance drug discovery. Using mammalian host cell lines overexpressing SLC transporters, Pardridge (2015) demonstrated a high-throughput screening of a small neurodrug library to find drugs that interfere with SLC expression at the blood-brain barrier [18]. Tashima reviewed the drug user model for effective drug absorption, distribution, excretion and chemistry, specifically referring to the recognition of nitrogen-containing groups from carriers to the substrate [2]. Demonstrations based on transportation, drug screening, and drug discovery will lead to the discovery and delivery of new drugs to the brain to improve the quality of life of cancer patients.

Declaration by Authors

Acknowledgement: None
Source of Funding: None

Conflict of Interest: The authors declare no conflict of interest.

REFERENCES

1. Berg AT, Berkovic SF, Brodie MJ, Buchhalter J, Cross JH, van Emde Boas W, et al. Revised terminology and concepts for organization of seizures and epilepsies: report of the ILAE Commission on Classification and Terminology, 2005-2009. *Epilepsia.* (2010) 51:676–85. 10.1111/j.1528-1167.2010.02522.x [PubMed] [CrossRef] [Google Scholar
2. Scheffer IE, Berkovic S, Capovilla G, Connolly MB, French J, Guilhoto L, Hirsch E, Jain S, Mathern GW, Moshé SL, Nordli DR. ILAE classification of the epilepsies: Position paper of the ILAE Commission for Classification and Terminology. Epilepsia. 2017 Apr;58(4):512-21.
3. Povey S, Lovering R, Bruford E, Wright M, Lush M, Wain H. The HUGO gene nomenclature committee (HGNC). Human genetics. 2001 Dec; 109:678-80.
4. Liu X, SLC. Family Transporters. *Adv Exp Med Biol.* (2019) 1141:101–202. 10.1007/978-981-13-7647-4_3 [PubMed] [CrossRef] [Google Scholar.
5. Aykaç A, Sehirli AO. The role of the SLC transporters protein in the neurodegenerative disorders. Clinical Psychopharmacology and Neuroscience. 2020 May 5;18(2):174.
6. Hu C, Tao L, Cao X, Chen L. The solute carrier transporters and the brain: Physiological and pharmacological implications. Asian journal of pharmaceutical sciences. 2020 Mar 1;15(2):131-44.
7. Colton CK, Kong Q, Lai L, Zhu MX, Seyb KI, Cuny GD, Xian J, Glicksman MA, Glenn Lin CL. Identification of translational activators of glial glutamate transporter EAAT2 through cell-based high-throughput screening: an approach to prevent excitotoxicity. Journal of biomolecular screening. 2010 Jul;15(6):653-62.
8. Green JL, Dos Santos WF, Fontana AC. Role of glutamate excitotoxicity and glutamate transporter EAAT2 in epilepsy: Opportunities for novel therapeutics development. Biochemical pharmacology. 2021 Nov 1; 193:114786
9. Dyomina AV, Zubareva OE, Smolensky IV, Vasilev DS, Zakharova MV, Kovalenko AA, Schwarz AP, Ischenko AM, Zaitsev AV. Anakinra Reduces Epileptogenesis, Provides Neuroprotection, and Attenuates Behavioral Impairments in Rats in the Lithium–Pilocarpine Model of Epilepsy. Pharmaceuticals. 2020 Oct 25;13(11):340.
10. Kong Q, Chang L-C, Takahashi K, Liu Q, Schulte DA, Lai L, et al. Small-molecule activator of glutamate transporter EAAT2 translation provides neuroprotection. *J Clin Invest.* (2014) 124:1255–67. doi: 10.1172/JCI66163
11. Sanz R, del Arco A, Ayuso C, Ramos C, Satrústegui J. Assignment of the calcium-binding mitochondrial carrier Aralar1 gene (SLC25A12) to human chromosome band 2q31 by in situ hybridization. Cytogenetics and cell genetics. 2000 Jul 1;89(3-4):143-4.
12. Jalil MA, Begum L, Contreras L, Pardo B, Iijima M, Li MX, Ramos M, Marmol P, Horiuchi M, Shimotsu K, Nakagawa S. Reduced N-acetylaspartate levels in mice lacking aralar, a brain-and muscle-type mitochondrial aspartate-glutamate carrier. Journal of Biological Chemistry. 2005 Sep 2;280(35):31333-9.
13. Wibom R, Lasorsa FM, Töhönen V, Barbaro M, Sterky FH, Kucinski T, Naess K, Jonsson M, Pierri CL, Palmieri F, Wedell A. AGC1 deficiency associated with global cerebral hypomyelination. New England Journal of Medicine. 2009 Jul 30;361(5):489-95.
14. Falk MJ, Li D, Gai X, McCormick E, Place E, Lasorsa FM, Otieno FG, Hou C, Kim CE, Abdel-Magid N, Vazquez L. AGC1 deficiency causes infantile epilepsy, abnormal myelination, and reduced N-acetylaspartate. JIMD Reports, Volume 14. 2014:77-85.
15. Kavanaugh BC, Warren EB, Baytas O, Schmidt M, Merck D, Buch K, Liu JS, Phornphutkul C, Caruso P, Morrow EM. Longitudinal MRI findings in patient with SLC25A12 pathogenic variants inform disease progression and classification. American Journal of Medical Genetics Part A. 2019 Nov;179(11):2284-91.
16. Pfeiffer B, Sen K, Kaur S, Pappas K. Expanding Phenotypic Spectrum of Cerebral Aspartate–Glutamate Carrier Isoform 1 (AGC1)

Deficiency. *Neuropediatrics.* (2020) 51:160–3. doi: 10.1055/s-0039-3400976.
17. Dahlin M, Martin DA, Hedlund Z, Jonsson M, von Döbeln U, Wedell A. The ketogenic diet compensates for AGC 1 deficiency and improves myelination. Epilepsia. 2015 Nov;56(11):e176-81.
18. Tashima T. Intriguing possibilities and beneficial aspects of transporter-conscious drug design. Bioorganic & Medicinal Chemistry. 2015 Aug 1;23(15):4119-31.
19. Pardridge WM. Blood–brain barrier endogenous transporters as therapeutic targets: a new model for small molecule CNS drug discovery. Expert opinion on therapeutic targets. 2015 Aug 3;19(8):1059-72

How to cite this article: Akshita Kansal, Abhijit Shinde, Suresh Waydande, Sunil Natha Mhaske. Solute carrier transport disease - a rare case report. *International Journal of Science & Healthcare Research.* 2023; 8(4): 226-230. DOI: *https://doi.org/10.52403/ijshr.20230432*

******