ISSN: 2692-5206
AMERICAN ACADEMIC PUBLISHER
INTERNATIONAL JOURNAL OF MEDICAL SCIENCES

CLINICAL AND BIOCHEMICAL TRACES OF HEREDITARY METABOLIC DISEASES. ON THE EXAMPLE OF DRUG-RESISTANT EPILEPSY

Yodgorov Jasurbek Jo'rayevich

Bukhara State Medical Institute named after Abu Ali ibn Sino. Bukhara, Uzbekistan.

e-mail: yodgorov.jasurbek@bsmi.uz

Annotation: In this article, we will provide information after studying hereditary metabolic diseases (HMD) where epilepsy manifests prominently. In the process of analyzing the database, we identified IMD associated with various types of epilepsy, which we classified according to the IMD classification based on classical pathophysiology and classified according to the factors associated with the selected seizure (neonatal seizures, infantile spasms, myoclonic seizures, and characteristic EEG patterns) and the possibility of treating the underlying metabolic defect. In addition, we analyzed the clinical severity level to compare the phenotype with biochemical characteristics, genotype, and delayed initiation of pyridoxine. As a result, we classified according to the clinical severity scale as follows: 1) global developmental delay/intellectual disability; 2) age of seizure onset before pyridoxine treatment; 3) current seizures during treatment. An expanded list of IMD, an overview of the main clinical signs, and the recommended diagnostic and therapeutic approaches may be useful for epileptologists and healthcare professionals assisting patients with metabolic disorders.

Keywords: Seizures, Epilepsy, Metabolic, Drug-resistant epilepsy, Neurometabolic, Diagnosis, Treatment.

Аннотация: В этой статье мы изучим и предоставим информацию о наследственных метаболических заболеваниях (НМЗ), где эпилепсия проявляется наиболее ярко. В процессе анализа базы данных были выявлены ИМД, ассоциированные с различными вариантами эпилепсии, которые мы классифицировали по классификации ИМД, основанной на классической патофизиологии, и классифицировали по факторам, связанным с выбранными судорогами (неонатальные судороги, инфантильные спазмы, миоклонические судороги и характерные ЭЭГ-образцы) и возможности лечения основного метаболического дефекта. Для сравнения фенотипа с биохимическими особенностями, генотипом и задержкой инициации пиридоксина мы изучили и проанализировали степень клинической тяжести. В результате мы классифицировали по шкале клинической тяжести следующим образом: 1) глобальная задержка развития/ умственная отсталость; 2) возраст начала судорог до пиридоксина; 3) текущие приступы при лечении. Расширенный список ИМД, обзор основных клинических симптомов и рекомендуемые диагностические и терапевтические подходы могут быть полезны для эпилептологов и медицинских работников, оказывающих помощь пациентам с метаболическими нарушениями.

Ключевые слова: Приступы, Эпилепсия, Метаболическая, Лекарственная эпилепсия, Нейрометаболическая, Диагностика, Лечение.

ISSN: 2692-5206
AMERICAN ACADEMIC PUBLISHER
INTERNATIONAL JOURNAL OF MEDICAL SCIENCES

Аннотация: Мақоламида эпилепсия яққол намоён бўладиган ирсий метаболик касалликлар (ИМК) ҳақида маълумот ўрганиб чиқиб маълумотлар берамиз. Маълумотлар базасини таҳлил қилиш жараёнида эпилепсиянинг турли хиллари билан боғлиқ ИМДни аниқлади, уларни классик патофизиологияга асосланган ИМД таснифига кўра таснифладик ва танланган тутқаноқ билан боғлиқ омиллар (неонатал тутқаноқлар, инфантил спазмлар, миоклоник тутқаноқлар ва характерли ЭЭГ намуналари) ва асосий метаболик нуқсонни даволаш имкониятига кўра таснифладик. Шу қаторда фенотипни биокимёвий хусусиятлар, генотип ва пиридоксин инициациясининг кечикиши билан таққослаш учун клиник оғирлик даражасини ўргиним чиқиб таҳлил қилдик. Нитижада клиник оғирлик шкаласи бўйича қуйидагича классификацияладик: 1) глобал ривожланиш кечикиши/ ақлий заифлик; 2) пиридоксингача бўлган тутқаноқ бошланиш ёши; 3) даволанишдаги жорий тутқаноқлар. ИМДнинг кенгайтирилган рўйхати, асосий клиник белгилар шарҳи ҳамда тавсия этилган диагностик ва терапевтик ёндашувлар метаболик бузилишлари бўлган беморларга ёрдам кўрсатувчи эпилептологлар ва тиббиёт ходимлари учун фойдали бўлиши мумкин.

Калит сўзлар: Хуружлар, Эпилепсия, Метаболик, Дориларга чидамли эпилепси, Нейрометаболик, Диагностикаси, Даволаш.

Epilepsy is a widespread serious neurological disorder that currently affects more than 70 million people worldwide. People with epilepsy have recurrent causeless seizures, which can be focal or generalized. To control seizures, several anticonvulsant drugs with different mechanisms of action and targets can be used, which are beneficial for most patients. However, it does not significantly change the overall seizure-free outcome of some patients. Due to drug resistance, some patients still experience uncontrolled seizures. In 2010, the International League Against Epilepsy defined drug-resistant epilepsy (DCHE) as the failure of sufficient trials of two resistant, appropriately selected and applied drug schedules with high resistance (as monotherapy or in combination) to achieve sustained seizure freedom.

The "Categories of Metabolic Traces" aims to provide a complete list of hereditary metabolic diseases (HIMD) associated with specific medical conditions. The articles published so far in this series cover the relationship of IMACs with motor disorders, liver diseases, cardiovascular diseases, changes in mental state, phenotypes of cerebral palsy, skin diseases, gastrointestinal symptoms, myopathies, tumors, eye phenotypes, kidney and ear diseases. The 15th review of the series is devoted to hereditary metabolic epilepsy (HME), in which metabolic disorders become one of the main symptoms of epilepsy. First of all, we will dwell on the classification of metabolic pathological mechanisms leading to epilepsy and epileptogenesis. The clinical presentation, methods of diagnosis, and treatment of IME are described. Our results show that hereditary metabolic epilepsy is more common in the neonatal period, with infantile spasms or myoclonic seizures. In addition, ~20% of hereditary metabolic epilepsy that were found to be treated as a result of our search were mainly associated with the IMD groups "cofactor and mineral metabolism" and "intermediate metabolism of nutrients." The data provided by this study were differentiated, including by age, type of seizure, and characteristics of epilepsy patients.

The prognostic effect of the initial age for DRE persisted throughout the entire age range and was positively correlated with its prognosis; at the onset, older age led to a better

ISSN: 2692-5206
AMERICAN ACADEMIC PUBLISHER
INTERNATIONAL JOURNAL OF MEDICAL SCIENCES

prognosis. Based on the analyzed data, we witnessed that many studies were focused on pediatric patients aged 0-18. Among the studies included in this article, most subgroup analyses were conducted in children with DRE up to 1 year of age. According to the study, the prognosis of DRE occurrence is presented in newborns and young children aged 0-24 months and 0-30 months, respectively, and in the subsequent study - in both children and adults. Several studies have shown that the age of onset of the disease is especially common in children under 1 year of age.

Drug resistance is a major problem in the treatment of epilepsy. Drug-resistant epilepsy (DRSE) accounts for 30% of all epileptic cases and is a major concern due to uncontrollability and high workload, mortality rate, and level of involvement. Currently, numerous studies are being conducted aimed at developing predictors that contribute to the early detection of DRE in order to facilitate the early initiation of individual treatment. Although many predictors and risk factors have been identified, currently there are no standard predictors that can be used to manage the clinical management of DRE. In this review, we will discuss several potential DRE predictors and related factors that may become predictors in the future, and analyze the evidence ranking to identify reliable potential predictors. We report on the treatment outcomes of eleven patients with pyridoxine-induced epilepsy due to pathogenic variants of ALDH7A1 (PDE-ALDH7A1). In eight patients with a phenotype from mild to severe (there is no lysine-restricted diet in the infantile period), the level of α-AASA in urine or plasma increased more than 10 times. The phenotype ranged from mild to moderate in patients with homozygous cutting variants, and from moderate to severe in patients with homozygous messenger variants. There was no correlation between the severity of the phenotype and the degree of proliferation of α-AASA in urine or genotype. All patients were on a restricted diet with pyridoxine, nine patients with arginine, and five patients with lysine. Free seizures with pyridoxine occurred in 73% of patients. In 25% of patients, a mild phenotype was observed during monotherapy with pyridoxine. 100% of patients on a lysine-restricted diet, which began in the first 7 months of life, had a mild phenotype. Early onset of a lysine-restricted diet and/or arginine therapy may have improved neurodevelopmental outcomes in young patients with PDE-ALDH7A1.

RESULT

In this study, we provide comprehensive information about hereditary metabolic disorders, which are one of the main manifestations of epilepsy. Although the frequency of each of the individual cases identified in this study is rare, their overall prevalence is significant. In addition, our results showed that the high probability of IMS in infancy, manifested by infantile spasms or myoclonic seizures, encourages the study of metabolic etiology in the applied clinical scenarios. Along with this, we focused on the clinical features and biochemical signs that can predict DRE. Our analysis of the evidence rating showed that the mixed type of seizure, SE, absence or poor response to the first ASM, neonatal seizure, abnormal neuroimaging results, and abnormal neurological examination results, along with HMGB1 and SCN1A, are reliable predictors of DRE.

With the appearance of these prognoses, drug resistance can be detected early during treatment, and the diagnosis of DRE may not depend only on the response to drug therapy, which can allow patients with drug-resistant epilepsy to receive early individualized and optimized treatment to improve clinical outcomes. However, the use of these predictors in

ISSN: 2692-5206
AMERICAN ACADEMIC PUBLISHER
INTERNATIONAL JOURNAL OF MEDICAL SCIENCES

clinical practice is hindered by various problems, such as inaccurate reports on the predictive abilities of some factors. In addition, recent studies of drug-resistant epilepsy included patients with various confusing factors such as age, sex, and race differences, which led to a limited generalization of the results for most patients.

LITERATURE:

1. Aaberg, K.M., Bakken, I.J., Lossius, M.I., Lund Søraas, C., Tallur, K.K., Stoltenberg, C., Chin, R., Sur´en, P., 2018. Short-term seizure outcomes in childhood epilepsy. Pediatrics 141.
2. Almannai M, Al Mahmoud RA, Mekki M, El-Hattab AW, Metabolic seizures, Front. Neurol 12 (2021), 640371.
3. Abo El Fotoh, W.M., Abd El Naby, S.A., Habib, M.S., Lrefai, A., Kasemy, Z.A., 2016. The potential implication of SCN1A and CYP3A5 genetic variants on antiepileptic drug resistance among Egyptian epileptic children. Seizure 41, 75–80.
4. Berg, A.T., Shinnar, S., Levy, S.R., Testa, F.M., Smith-Rapaport, S., Beckerman, B., 2001. Early development of intractable epilepsy in children: a prospective study. Neurology 56, 1445–1452.
5. Jain-Ghai S, Mishra N, Hahn C, Blaser S, Mercimek-Mahmutoglu S (2014) Fetal onset ventriculomegaly and subependymal cysts in a pyridoxine dependent epilepsy patient. Pediatrics 133:e1092–e1096.
6. Gallagher RC, Van Hove JL, Scharer G et al (2009) Folinic acidresponsive seizures are identical to pyridoxine-dependent epilepsy. Ann Neurol 65:550–556.
7. Denton, A., Thorpe, L., Carter, A., Angarita-Fonseca, A., Waterhouse, K., Hernandez Ronquillo, L., 2021. Definitions and risk factors for drug-resistant epilepsy in an adult cohort. Front. Neurol. 12, 777888.
8. Leontariti, M., Avgeris, M., Katsarou, M.S., Drakoulis, N., Siatouni, A., Verentzioti, A., Alexoudi, A., Fytraki, A., Patrikelis, P., Vassilacopoulou, D., Gatzonis, S., Sideris, D. C., 2020. Circulating miR-146a and miR-134 in predicting drug-resistant epilepsy in patients with focal impaired awareness seizures. Epilepsia 61, 959–970.
9. Mills PB, Struys E, Jakobs C et al (2006) Mutations in antiquitin in individuals with pyridoxine-dependent seizures. Nat Med 12:307– 309.
10. Van Karnebeek CD, Hartmann H, Jaggumantri S et al (2012) Lysine restricted diet for pyridoxine-dependent epilepsy: first evidence and future trials. Mol Genet Metab 107:335–344.
11. Nikodijevic, D., Baneva-Dolnenec, N., Petrovska-Cvetkovska, D., Caparoska, D., 2016. Refractory epilepsy-MRI, EEG and CT scan, a correlative clinical study. Open Access Maced J Med Sci 4, 98–101.
12. Sultana, B., Panzini, M.A., Veilleux Carpentier, A., Comtois, J., Rioux, B., Gore, G., Bauer, P.R., Kwon, C.S., Jett´e, N., Josephson, C.B., Keezer, M.R., 2021. Incidence and prevalence of drug-resistant epilepsy: a systematic review and meta-analysis. Neurology 96, 805–817.
13. .Riney K, Bogacz A, Somerville E, Hirsch E, Nabbout R, Scheffer IE, Zuberi SM, Alsaadi T, Jain S, French J, Specchio N, Trinka E, Wiebe S, Auvin S, Cabral-Lim L, Naidoo A, Perucca E, Moshé SL, Wirrell EC, Tinuper P, International League Against Epilepsy classification and definition of epilepsy syndromes with onset at a variable age: position statement by the ILAE Task Force on Nosology and Definitions, Epilepsia 63 (2022) 1443–1474.