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FBLN1 P. (HIS695ARG) VARIANT IN A GIRL WITH LATE ONSET EPILEPTIC SPASMS (LOS) AND DISTINCT DYSMORPHIC FEATURES: CLINICAL REPORT

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ВАРИАНТ FBLN1 P. (HIS695ARG) У ДЕВОЧКИ С ПОЗДНИМ НАЧАЛОМ ЭПИЛЕПТИЧЕСКИХ СПАЗМОВ (LOS) И ОТЧЕТЛИВЫМИ ДИСМОРФИЧЕСКИМИ ПРИЗНАКАМИ: КЛИНИЧЕСКИЙ СЛУЧАЙ

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FBLN1 P. (HIS695ARG) VARIANTI KECH BOSHLANGAN EPILEPTIK SPAZMLAR (LOS) VA ANIQ DISMORFIK BELGILAR BILAN NAMOYON BO'LISHI: KLINIK HOLAT

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Эпилептические спазмы с поздним началом (LOS) – это тип спазмов, возникающих после первого года жизни. Мы сообщаем о пациентке с ЛОС, задержкой развития и дисморфическими признаками, у которого была обнаружена мутация FBLN1 c.2048A> G (p.His695Arg) наряду с другими генетическими состояниями. Согласно OMIM, ген # 608180 FBLN1 может быть связан с 3 / 3›4 синполидактилией, а также с пястными и плюсневыми синостозами, но указанный выше вариант помечен как доброкачественный в базе данных ClinVar. В литературе сообщалось о связи между мутацией FBLN1 и эпилепсией с общей задержкой развития и отчетливыми дисморфическими признаками. Необходимы дальнейшие исследования, чтобы определить роль FBLN1 в развитии центральной нервной системы и соединительной ткани.

Ключевые слова: *эпилептический спазм, позднее начало, общая задержка развития, дисморфические признаки.*

Kech boshlangan epileptik spazmlar (LOS) - hayotning birinchi yilidan keyin yuzaga keladigan spazmlar turi. Biz LOS, rivojlanish kechikishi va dismorfik xususiyatlarga ega bo'lgan, boshqa genetik holatlar bilan bir qatorda FBLN1 c.2048A> G (p. His695Arg) mutatsiyasiga ega bo'lgan bemor haqida hisobot beramiz. OMIM ma'lumotlariga ko'ra, # 608180 FBLN1 geni 3 / 3'4 sinpolidaktiliya, metakarpal va metatarsal sinostozlar bilan bog'liq bo'lishi mumkin, ammo yuqorida keltirilgan variant ClinVar ma'lumotlar bazasida yaxshi deb belgilangan. FBLN1 mutatsiyasi va epilepsiya, global rivojlanish kechikishi va aniq dismorfik xususiyatlar o'rtasidagi bog'liqlik ilmiy adabiyotlarida keltirilgan. FBLN1 ning markaziy asab tizimi va biriktiruvchi to'qima rivojlanishidagi rolini aniqlash uchun qo'shimcha tadqiqotlar zarur.

Kalit so'zlar: *kech boshlangan epileptik spazmlar, LOS, FBLN1, dismorfik belgilar.*

Epileptic spasms are characterized by brief and sudden movements of flexion, extension, or both, predominantly localized to the head, proximal limbs, and axial muscles, that are usually more sustained than myoclonic seizures but less so than tonic seizures [2,5,8]. Epileptic spasms typically occur in infancy, as part of the West syndrome or other forms of epilepsy, but can also appear after the first year - late-onset epileptic spasms - in 2%to 8% of cases [2-4]. The clinical course of infantile spasms has been described in detail, particularly in relation to the diverse etiologic conditions [2,9-11]. On the other hand, clinical characteristics, management and prognostic issues related to late-onset epileptic spasms, and their link with etiology, remain unsettled because of the relative rarity and heterogeneity of this clinical condition [3,4,7,9]. The association with structural abnormalities, genetic disorders, or inborn errors of metabolism is also not well explained.

CLINICAL REPORT

The patient presented at 2 years and 7 months of age with a history of global developmental delay, generalized hypotonia and recent onset of seizures. She was the second child of young and healthy, non-consanguineous parents. Pregnancy had been uneventful although birth at 39 weeks of gestation was by cesarean section due to pelvic presentation. At birth, she weighed 2200 gr and measured 44 cm, with head circumference 31 cm and APGAR score of 9. Despite developmental delay and generalized hypotonia at age 12 months, she made slow and steady progress. At 2 years, she developed epileptic spasms in the form of head nods. Subtle nods weren't considered as seizures although parents noticed worsening of hypotonia and developmental arrest. An MRI of the brain revealed cortical atrophy. At 2 years 7 months full blown spasms developed – sudden flexor movements, localized to axial muscles and both upper limbs, grouped in clusters (2-4), mainly on awakening.

On initial evaluation we noticed dysmorphic features including epicanthus, wide and depressed nasal bridge, Brushfield spots in eyes, right hand clinodactyly, single transverse palmar crest on the right hand, floppiness and hypotonia of the right side of the body, lower limb malformation consisting of 2nd and 3rd toe syndactyly and metatarsal synostosis (Figure).

In addition to 21 chromosome trisomy (clinically mildly manifested mosaic type) and the partial duplication of 10 chromosome q arm distal fragment, exome sequencing disclosed a mutation of FBLN1 gene: c.2084A>G / p.His 695Arg.

EEG showed diffuse slow wave transients, maximal in frontal areas. They were followed by fast rhythm/ or polyspike burst of low amplitude and electrodecrement. Interictal recording did not show hypsarrhythmia – which is usual in LOS.

Hydrocortisone therapy was administered and 2 months later seizures had ceased and the child had recovered lost skills. EEG after 6 months follow-up showed no epileptic activity.

DISCUSSION

Late onset spasms were described as epileptic seizures consisting of a series of flexor or extensor movements, predominating in axial and/or proximal limb muscles, occurring with a noticeable periodicity, after the usual age of infantile spasms [9].

Infantile spasms and various aspects of epilepsy in Down syndrome have been fairly described in literature [1,11,12]. Yet no cases with late-onset epileptic spasms have been reported, and the case we present differs from those previously described in the literature (characteristics such as mean age, EEG features, association with West syndrome)

The combination of FBLN1 mutation with epileptic spasms was had been reported by Bohlega et al. [6]. In 3 sibs from consanguineous parents, with a unique syndrome comprising variable syndactyly, undescended testes, delayed motor milestones, mild mental retardation, and brain atrophy, Bohlega et al. [6] identified a homozygous c.1190G-T transversion in exon 10 of the FBLN1 gene, resulting in a cys397-to-phe (C397F) substitution at a highly conserved residue. The eldest of 3 sibs, a girl exhibited a clinical course similar to that of our patient although she presented with syndactyly in her left hand unlike in our case – thus, suggesting that dysmorphism may affect upper or lower limb. Additional reports will be important to confirm this association.

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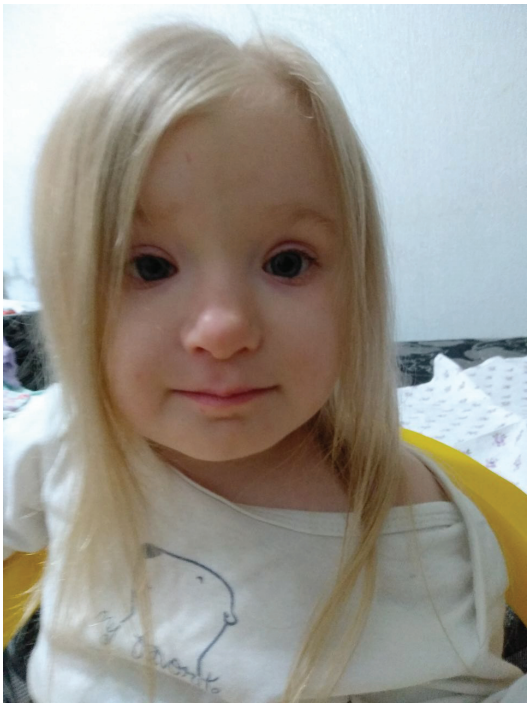
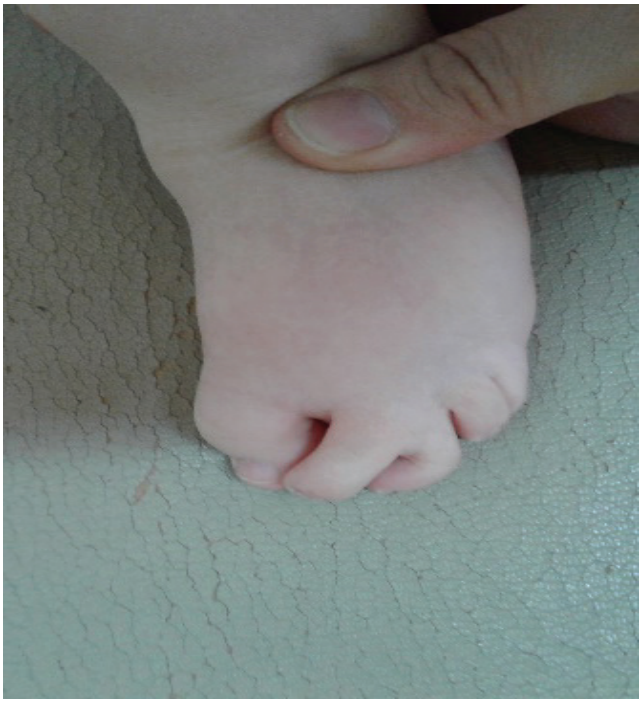
We would like to kindly thank our patient and her family for allowing us to participate in her care and share her case with others.

DECLARATION OF INTEREST

The authors report no conflicts of interest. The authors alone are responsible for the content and writing of this article.





Figure

References

1. Arya R., Kabra M., Gulati S. Epilepsy in children with Down syndrome // Epileptic Dis. – 2011. – Vol. 13, №1. – P. 1-7.
2. Arzimanoglou A., Guerrini R., Aicardi J. Aicardi's Epilepsy in Children. – 3rd ed. – Philadelphia, PA: Lippincott Williams & Wilkins, 2004.
3. Auvin S., Lamblin M.-D., Pandit F. et al. Infantile epileptic encephalopathy with late-onset spasms: report of 19 patients // Epilepsia. – 2010. – Vol. 51. – P. 1290-1296.
4. Bednarek N., Motte J., Soufflet C. et al. Evidence of late-onset infantile spasms // Epilepsia. – 1998. – Vol. 39. – P. 55-60.
5. Blume W.T., Luders H.O., Mirzahi E. et al. Glossary of descriptive terminology for ictal semiology: report of the ILAE Task Force on Classification and Terminology // Epilepsia. – 2011. – Vol. 42. – P. 1212-1218.
6. Bohlega S., Al-Ajlan H., Al-Saif A. Mutation of fibulin-1 causes novel syndrome involving the central nervous system and connective tissues // Europ. J. Hum. Gen. – 2014. – Vol. 22. – P. 640-643.
7. Eisermann M.M., Ville D., Soufflet C. et al. Cryptogenic late-onset epileptic spasms: an overlooked syndrome of early childhood? // Epilepsia. – 2006. – Vol. 47. – P. 1035-1042.
8. Engel J. A proposed diagnostic scheme for people with epileptic seizures and with epilepsy. Report of the ILAE task force on classification and terminology // Epilepsia. – 2001. – Vol. 42. – P. 796-803.
9. Goldstein J., Slomski J. Epileptic spasms: a variety of etiologiesand associated syndromes // J. Child Neurol. – 2008. – Vol. 23– P. 407-414.
10. Pellock J.M., Hrachovy R., Shinnar S. et al. Infantile spasms: a U.S.consensus report. // Epilepsia. 2010; Vol. 51: P. 2175-2189.
11. Silva M.L., Ciuetta C., Guerrini R. et al. Early Clinical and EEG Features of Infantile Spasms in Down Syndrome // Epilepsia. – 1996. – Vol. 37, №10. – P. 977-982.
12. Stafstrom C.E., Konkol R.J. Infantile spasms in children with Down syndrome // Development. Med. Child Neurol. – 1994. – Vol. 36. – P. 76-585.

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Late-onset epileptic spasms (LOS) are the type of spasms that occur after the first year of life. We report on a patient who presented with LOS, developmental delay and dysmorphic features and was found to have FBLN1 c.2048A>G (p.His695Arg) mutation alongside with other genetic conditions. According to OMIM, #608180 FBLN1 gene may be associated with 3/3'4 synpolydactyly, and metacarpal and metatarsal synostoses, but abovementioned variant is labeled as benign in ClinVar database. Association between FBLN1 mutation and epilepsy, global developmental delay and distinct dysmorphic features has been reported. Further studies are necessary to determine the role of FBLN1 in the development of central nervous system and connective tissue.

Key words: *late-onset epileptic spasms, LOS, FBLN1, dysmorphic features.*