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Epileptic encephalopathy refractory to treatment and heredodegenerative disease of unknown etiology

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Epileptic encephalopathies are severe brain disorders in which epileptic electrical discharges are presumed to contribute to progressive psychomotor dysfunction. They are related to young age, thus creating progressive dysfunction of the developing neurologic system. Depending on the age at onset, the child loses learned skills, or never even acquires them. First noticeable behavior changes in our patient born from a normal pregnancy occurred while attending kindergarten at the age of 3.5 years. Generalized tonic-clonic seizures with loss of consciousness started at the age of 4 years and 10 months. Computed tomography showed atrophy of the brain. Magnetic resonance imaging of the brain showed cerebellar and brain stem atrophy with leukodystrophy. He further became atactic, with choreo-atetotic movements, hypertonus, incomprehensive speech, upper gaze palsy and nystagmus. Psychomotor deterioration developed gradually. No myopathy or neuropathy was shown on electromyoneurography, and no lesion on visual evoked potentials. Wide range laboratory and microbiological investigations were undertaken with normal results. Skin biopsy EM analyses were negative as well as mtDNA, tRNA Leu or Lys. Now, he is aged 13 years and 9 months and his EEG is without pathology with beta waves. He is tetraparetic, with heavy psychomotor retardation, incontinent, obstipated, often vomits and produces a lot of saliva. His current therapy is levetiracetam and his last seizure was 9 months ago. As of now, we were not able to find the causative factor for this progressive heredodegenerative disease with brain atrophy and epileptic encephalopathy refractory to treatment.

Keywords: heredodegenerative disorders, nervous system; epileptic encephalopathy, early infantile

INTRODUCTION

Epileptic encephalopathy is a severe brain disorder with presumed epileptic electrical discharges that contribute to progressive psychomotor dysfunction. Such encephalopathy is often related to young age, thus creating progressive dysfunction of the developing neurologic system. Paroxysmal EEG activity recorded in these cases is often aggressive; seizures are often multi-form and refractory to treatment. This progressive deterioration may lead to early death. Sometimes first and only manifestations are cognitive deficits and behavioral disturbances coupled with electrographic epileptic discharges.

Depending on the age at onset, the child loses learned skills, or never even acquires them. Epileptic activity during brain maturation is the underlying cause of this cognitive and neurologic regression. The onset of seizures may not coincide with the onset of epileptic activity, hence the damage may advance until the first symptoms are noticed as delayed development and then progressive decline. Decreased neurogenesis and reduced distribution of excitatory glutamatergic receptors irreversibly disable normal cognitive and behavioral development. Excessive neocortical excitability to idiopathic causes becomes deleterious in its semiology and resembles reactions of very immature brain. These reactions can be traced in very specific epileptic patterns such as burst-suppression, hypsarrhythmia and slow

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generalized spike-wave discharges. Even in cases where epileptic bursts diminish in adolescence, the damage to the developing brain can never be substituted and normal function restored.

CASE REPORT

Our patient was born in January 1999, in the village of Zaton near Šibenik in Croatia. His parents are in consanguinity in 6th generation, and his brother born in 1993 is healthy. The boy was born after a normal pregnancy and normal delivery. His psychomotor development in the first year of life was uneventful. At the age of 2 years, he was able to pronounce the first few syllables (ma, ta), and his hearing was considered normal. Speech development was also thought normal. First noticeable behavior changes were noticed while attending kindergarten at the age of 3.5 years. He became aggressive against other children. He was referred to psychologist and psychological tests revealed moderate psychomotor and speech retardation, i.e. the attention deficit hyperactivity disorder (ADHD) syndrome. At the age of 4 years and 4 months, he fell from a slide on his stomach with absences, astatic attacks and myoclonias of hands, which started 2 months later. Interictal EEG finding was diffusely dysrhythmic. Computerized tomography (CT) of the brain showed enlarged subarachnoid space around the brain stem; therapy with lamotrigine was started. Generalized tonic-clonic seizures with loss of consciousness of 2 minutes started at the age of 4 years and 10 months, when valproate was added. Magnetic resonance (MR) of the brain showed cerebellar and brain stem atrophy with leukodystrophy. At the age of 5 years and 5 months, the patient was atactic, with choreo-athetotic movements, incomprehensive speech, upper gaze palsy and nystagmus. Hypertonus was present with intense tendon reflexes and positive Babinski's sign. EEG background was slow; spike-waves were seen bilaterally. Fundus of the eyes was normal. At the age of 6 years and 5 months, the boy had balance problems with slow unstable gate at lateral part of the feet, and pronounced salivation. At the age of 6 years and 7 months, the patient could not walk independently, he was able to swim with hand-balloons and drive bicycle with additional wheels. He received 700 to 800 mg of valproic acid daily. At the age of 7 years and 8 months, he presented myoclonias of hands and astatic attacks without loss of consciousness, generalized tonic-clonic fits and pseudoabsences. He was unable to walk supported, had tetraparesis, without control of urine and stools, psychomotor deterioration developed gradually. EEG showed paroxysms of the spikes and spike and wave complexes of 2 Hz, then low voltage slow waves 3.5 Hz. No myopathy or neuropathy was shown on electromyoneurography (EMNG) and no lesion on visual evoked potentials (VEP). Dysfunction of auditory potentials at olivary complex of the brain stem was found. CT showed atrophy of the brain. Psychomotor functioning was adequate for 2 years of age. He received valproate, topiramate, tetracosactide, mannitol, dexamethasone, clonazepam and diazepam. Following this treatment, myoclonias of hands and a few tonic fits were seen, the boy was able to stand supported and pronounced a few sounds. At the age of 7 years and 11 months, somatic status and phenotype were normal, with severe psychomotor retardation, unable to change body position, able to stand supported at the point of his feet, hypertonic, followed persons with his eyes; the sound of a few consonants was heard. He sometimes smiled. EEG showed normal background with slow waves frontally. MR of the brain showed progression of the brain, cerebella and corpus callosum atrophy. Ultrasonography of the liver, spleen, kidneys and heart was normal.

Wide range laboratory investigations were undertaken with normal results: chromosomes, Fragile-X, basic laboratory tests, ammonia, acid-base status, lactate (plasma, cerebrospinal fluid), urinary ketones, uric acid, total plasma proteins with electrophoresis, immunoglobulins (IgG, IgM, IgA), plasma lipoproteins (cholesterol, HDL, LDL, triglycerides, ApoE), Fe, UIBC, TIBC, Fe saturation, transferrin, ferritin, copper, ceruloplasmin, ACTH, cortisol, amino acids (plasma, urine, cerebrospinal fluid), organic acids (urine), analysis of glycosylation pattern of transferrin, very long chain fatty acids (VLCFA), homocysteine, vitamine B12, folic acid, beta-hexosaminidases A and B, arylsulphatase A, beta-galactocerebrosidase, chitotriosidase, and anti-streptococcal antibody titer. Skin biopsy (electron microscopy) analyses were negative (for neuronal ceroid lipofuscinoses and progressive myoclonus epilepsy with Lafora bodies). No deletion, no mitochondrial myopathy, encelopathy, lactic acidosis, and stroke (MELAS) (A3243G), no myoclonic epilepsy with ragged red fibers (MERRF) (A8344G) or no neuropathy, ataxia and retinitis pigmentosa (NARP) (T8993C/G) mutation was found in blood mtDNA. No mutation in tRNA Leu or Lys was seen with polymerase chain reaction-denaturing gradient gel electrophoresis (PCR-DGGE) techniques in blood mtDNA. No vacuolated lymphocytes were found. The CSF blood-brain barrier was normal, oligoclonal bands were not found. Serologic tests for neurotropic viruses (including *Borrelia burgendorferi, Bartonella quintana* and *Bartonella henselae*) in CSF were negative, as well as the detection of specific antibodies and reverse transcription-PCR for measles, rubella and mumps viruses. Serologic tests in blood showed a status after vaccination against measles, rubella and mumps. There was no acute infection with Epstein Barr virus (EBV).

At the age of 8 years and 3 months, the patient had the somatic status appropriate for his age. He was in wheelchair, tetraparetic, followed with his eyes persons around him, swallowed chopped food, did not speak, and suffered from insomnia. He had no epileptic fits; his EEG had a few isolated spike and wave complexes over the central temporal region bilaterally. MR of the brain (with many movement artifacts) showed cerebellar, brain and brain stem atrophy. He was taking valproate, topiramate and clonazepam, and received kinesiotherapy at home. Now he is 13 years and 9 months old and his EEG is without pathology with beta waves. He is tetraparetic, with heavy psychomotor retardation, incontinent, obstipated, often vomits and produces a lot of saliva. His current therapy is levetiracetam and his last seizure was 9 months ago. As of now, we could not find the causative factor for this progressive heredodegenerative disease with brain atrophy and epileptic encephalopathy refractory to treatment.

DISCUSSION

Progressive encephalopathy is a type of brain injury resulting in central nervous system dysfunction with quite a long list of possible causes. In approaching cases where such progressive deterioration is noticeable, it is necessary to consider metabolic, neurodegenerative, infectious and toxic etiologies. A history of parental consanguinity is also associated with a marked increase in the risk of progressive encephalopathy, and can be an important clue suggesting metabolic or neurodegenerative disease. We were able to exclude brain anomalies, intracranial hemorrhage and infections, known genetic disorders, maternal toxins, or other diseases that might have impaired oxygenation to the fetus. Our patient did not show clinical picture that would resemble any of the progressive myoclonic epilepsies such as Unverricht-Lundborg disease, mitochondrial encephalopathy with ragged-red fibers, Lafora body disease, neuronal ceroid lipofuscinosis, and sialidosis cherry-red spot myoclonus syndrome. We were able to exclude lysosomal diseases, neuronal ceroid lypofuscinosis. There were no EMNG signs of peripheral neuropathy or myopathy. We were also able to exclude disorders of amino acid metabolism, hyperammonemia, organic acidemias and mitochondrial diseases.

The therapy he had been receiving included topiramate, valproate, phenobarbitone, phemitone, B6 vitamin, corticosteroids, oxcarbazepine, clonazepam, levetiracetam, and lamotrigine.

Using numerous advances in molecular biology, we have been able to distinguish between metabolic disorders and heredodegenerative diseases for the most part. Nevertheless, some critical differences remain. Using functional cloning we have been able to identify genes responsible for basic biochemical defects as in phenylketonuria or maple syrup urine disease. Unfortunately, many of presumed metabolic diseases do not yet have an identifiable biochemical substrate leading to the development of reverse genetics, where it was possible to identify the gene but still without the specific known protein product (1). For this identification, it is necessary to include whole families using linkage studies presumably affected by a certain disease (2). Use of candidate genes responsible for coding of proteins and enzymes responsible for certain brain functions have been mapped and sequenced. Assigning a gene locus for a certain heredodegenerative disease using linkage studies, candidate genes from this region are assessed and compared with features of the particular disease. Using the reverse process when a new gene is assigned to chromosomal region, candidate diseases are analyzed by analogous process (3). From the clinical point of view, heredodegenerative diseases are grouped by their clinical presentation and by the brain region that seems to be most affected. Combining the knowledge gained from genetic testing, we see that many common neurologic phenotypes have multiple genetic etiologies as well as single genes resulting in different clinical expressions. As we have witnessed in the past decades, the effect of environmental factors has been increasing and our knowledge and certainty of causative relationships between genotype and phenotype has become vaguer. Selective cell death as well as mitochondrial dysfunction as seen in heredodegenerative diseases of basal ganglia still perplexes the scientists and clinicians.

The features of epileptic encephalopathies can become interchangeable and overlap thus making it difficult to distinguish among them (4). Sometimes it is possible to set age limits and presume one over the other based on the age at onset, while it is to be expected that one may evolve into the other as well. Eluding from what we know now defining the etiopathology of these syndromes is not quite possible as it may be multiple and overlapping.

It has been known for decades that the risk of epilepsy increases in consanguineous marriages. The risk is decreasing as the degree of consanguinity increases, meaning further apart the relatives are the risk is lower. It is known that idiopathic epilepsy has a higher familial clustering of epilepsy, and the same is true for cryptogenic epilepsy, especially for generalized seizures and younger onset of epilepsy. With regards to symptomatic epilepsy such as temporal lobe epilepsy and hippocampal sclerosis, there seems to be a family history of seizures or epilepsy. Even though in Croatia consanguineous marriages are not frequent, the environmental circumstances such as living on small islands or rural poorly connected areas may increase the risk of consan-

guinity among parents, as it was in this case. Still no clear connection to any of the currently known diseases has been made, and the etiology of this heredodegenerative disease with epilepsy refractory to treatment remains unknown.

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SAŽETAK

Epileptična encefalopatija refraktorna na liječenje i heredodegenerativna bolest nepoznate etiologije

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Epileptičke encefalopatije su teška oštećenja mozga kod kojih se smatra da epileptička električka izbijanja pridonose progresivnom psihomotornom propadanju. Budući da su vezane za pojavnost u mladoj dobi, dolazi do progresivnog propadanja neurološkog sustava u razvoju. Ovisno o dobi početka dijete gubi dotad usvojena znanja i vještine ili ih nikad i ne usvoji. Prve promjene u ponašanju kod našeg bolesnika, koji je rođen iz uredne trudnoće, javile su se u dobi od 3,5 godine, dok je bio u vrtiću. Generalizirani toničko-klonički napadaji s gubitkom svijesti počeli su u dobi od 4 godine i 10 mjeseci. Morfološke promjene mozga prema CT-u govorile su u prilog atrofije mozga, dok je MR mozga upućivao na atrofiju malog mozga i moždanog debla s leukodistrofijom. Bolesnik je postao ataktičan s koreo-atetotičnim pokretima, naznačenog hipertonusa, nerazumljivog govora, parezom pogleda prema gore i nistagmusom. Psihomotorno propadanje razvijalo se postupno. Nije nađeno miopatije ni neuropatije na elektromioneurografiji kao niti lezija na vidnim evociranim potencijalima. Obavljeni široki spektar laboratorijskih i mikrobioloških pretraga bio je u granicama normale. Biopsija kože, gledana elektronskim mikroskopom, bila je negativna kao i mtDNK, tRNK Leu i Lys. Dječaku je sad 13 godina i 9 mjeseci a njegov EEG je u granicama normale s beta-valovima. Ima tetraparezu, s teškom psihomotornom retardacijom, inkontinentan je i opstipiran, često povraća i jako slini. Njegova trenutačna terapija je levetiracetam, a njegov posljednji cerebralni napadaj bio je prije 9 mjeseci. Dosad nismo uspjeli naći uzročni čimbenik za ovu progresivnu heredodegenerativnu bolest s atrofijom mozga i epileptičkom encefalopatijom otpornom na lijekove.

Ključne riječi: heredodegenerativna bolest, živčani sustav; epileptička encefalopatija, rana dječja