Clinical commentary

Epileptic Disord 2020; 22 (5): 659-63

Description of a peculiar alternating ictal electroclinical pattern in a young boy with a novel *SPATA5* mutation*

Caterina Zanus [1,a], Paola Costa [1,a], Flavio Faletra [1], Luciana Musante [1], Angelo Russo [2], Luisa Grazian [3], Marco Carrozzi [1]

[1] Institute for Maternal and Child Health, IRCCS "Burlo Garofolo", Trieste
[2] Child Neurology and Psychiatry Unit, IRCCS Institute of Neurological Sciences, Bologna,
[3] Unit of Pediatric, Ca' Foncello Hospital, Treviso, Italy
[a] These authors contributed equally.

Received January 30, 2020; Accepted July 03, 2020

ABSTRACT – Heterozygous variants in the *SPATA5* gene have recently been described to be associated with epileptic encephalopathy. As of 2019, 37 patients have been described in the published literature. We report a patient with a novel autosomal recessive pathogenic variant in *SPATA5* and a clinical phenotype consistent with SPATA5 syndrome, including severe neurological impairment, intellectual disability (ID), generalized intractable epilepsy, microcephaly, abnormal muscle tone, and sensorineural hearing loss. The epileptic clinical features were characterized by infantile spasms associated with seizures with a complex ocular movement; a predominant involvement of the posterior cerebral area and cortical visual impairment were also noticed. This phenotype is highlighted with a review of the literature showing other patients with SPATA5-related disease. This report aims to contribute to further understanding phenotype/genotype correlations, which are fundamental for the interpretation of data made available by exome sequencing for the diagnosis of epileptic encephalopathies. [*Published with video sequence*].

Key words: *SPATA5*, epileptic encephalopathy, SPATA5 syndrome, phenotype

VIDEO ONLINE

Correspondence:
Paola Costa
Neuropsichiatria Infantile,
Institute for Maternal and Child Health
IRCCS "Burlo Garofolo" Via dell'Istria 65/1
34011 Trieste
<paola.costa@burlo.trieste.it>

doi:10.1684/epd.2020.1204

SPATA5 is an 892-amino acid protein, first identified in mouse testes as a spermatogenesis associated factor (SPAF) (Liu *et al*., 2000). SPATA5 has been proposed to have a role in mitochondrial integrity during morphogenesis, with an important influence on synaptic development and plasticity, and is developmentally expressed throughout the brain (Puusepp *et al*., 2018a).

*The case was presented at the last "Riunione Policentrica, Lega Italiana Contro l'Epilessia" (January 2020).

In 2015, Tanaka and colleagues (Tanaka *et al*., 2015) described 14 patients with a clinical phenotype characterized by severe neurological impairment including intellectual disability (ID), generalized intractable epilepsy, microcephaly, abnormal muscle tone, and sensorineural hearing loss due to autosomal recessive pathogenic variants in *SPATA5* (MIM 613940).

More recently, additional 23 cases have been reported (Tanaka *et al*., 2015; Kurata *et al*., 2016; Buchert *et al*., 2016; Szczaluba *et al*., 2017; Puusepp *et al*., 2018a; Khurana *et al*., 2019) and the known clinical features of *SPATA5*-related early-onset encephalopathy have been classified as epilepsy, hearing loss, and mental retardation syndrome (EHLMRS, OMIM: 616577).

Papuc *et al*. (2019) found *SPATA5* homozygous or compound heterozygous mutations in as many as 3% of their cohort which was selected in order to assess the role of recessive inheritance in early-onset epileptic encephalopathies, indicating that *SPATA5*-related early-onset encephalopathy may have been underdiagnosed in previous studies.

The 37 patients with mutation in *SPATA5* reported so far share very similar clinical features, confirming the phenotype delineated by Tanaka *et al*. (2015). In particular, the association with sensorineural hearing loss suggests a mitochondrial disease. Epilepsy was present in 28 of the 37 patients. The most common seizures types reported were infantile spasms and tonic, myoclonic-tonic seizures. Seizures with eye deviation, paroxysmal episodes of eye blinking, upward gaze, convergent strabismus, eyeball tremor and a predominance of occipital involvement of paroxysmal activity on EEG were reported in more detail by some authors (Tanaka *et al*., 2015; Kurata *et al*., 2016; Szczaluba *et al*., 2017).

We describe an eight-year follow-up of a boy with a novel mutation in *SPATA5* who presented with a typical phenotype and a pattern of complex eye movements in association with epileptic spasms. The aim of this report is to contribute to further understanding the phenotype/genotype correlations which are becoming increasingly important for the interpretation of countless data made available by exome sequencing for the diagnosis of epileptic encephalopathies.

Case study

The boy was the only child of non-consanguineous parents. He was born at 40 + 1 gestational weeks. Apgar score was 10 after one and five minutes. Head circumference was 36.5 cm (85^{th}-97^{th} percentile). No congenital anomalies or dysmorphic features were noted. Perinatal hearing was normal. After the third month of life, impairment of social interaction, irritability and hypotonia were observed. Microcephalia (head circumference within the 25^{th}-50^{th} percentile) and sensorineural bilateral hypoacusia were detected. From the six month of life, symmetrical flexor spasms with upward eye deviation and repetitive sucking movements, lasting several minutes, were described. The interictal EEG showed a global disorganization of the activity with slow multifocal spikes and waves of high-amplitude discharge prevailing on the posterior regions, with sleep increment.

Treatment with ACTH controlled more intense and prolonged flexor spasms but subtle seizures with nystagmus, staring, and hyporeactivity persisted in daily clusters. At 11 months of age, valproate was started but a further regression with severe visual inattention and absence of any communicative intentionality was observed. Interictal EEG showed a global disorganization with slow multifocal spikes prevailing on the posterior regions. Ictal EEG was characterized by the interruption of background slow and paroxysmal activity and by the emergence of a prolonged condition, characterized by the appearance of short sequences of low-voltage beta activity, moving from one hemisphere to the other in concomitance with subtle seizures with ocular movements (*figures 1, 2 and video sequence*).

Zonisamide, vigabatrin, topiramate, lamotrigine, phenobarbital and the ketogenic diet were prescribed with no results. At eight years of age, the clinical picture was characterized by severe developmental delay, dystonic-dyskinetic tetraparesis, sensorineural bilateral hypoacusia and cortical visual impairment. Daily seizures with ocular movements, spasms with head deviation and slight shoulder elevation, and brief tonic generalized seizures persisted. The antiepileptic treatment was perampanel.

The diagnostic evaluation at onset showed normal brain MRI, cardiological assessment, abdominal ecography, ocular fundus. The metabolic work-up (lactic acid, vitamin B6, orotic acid, plasma amino acids, liquor neurotransmitters, copper and ceruloplasmin) was normal.

The clinical picture led to investigation with MRI spectroscopy based on a suspicion of a mitochondrial disorder at four years of age. Structural MRI showed a slight decrease in white matter thickness, most evident at the periventricular and subcortical bilateral occipital level, and a thin corpus callosum. No elevated lactate peaks were detected on white matter spectroscopy, nor altered metabolite ratios. CGH- array, including *FOXG1*, *CDKL5* and a comprehensive gene panel of 96 genes for epileptic encephalopathy, was negative.

Genetic study

The patient was investigated at the Neuropediatrics Department at IRCCS Burlo, (Trieste, Italy) as part of a cohort study with the aim of identifying new disease

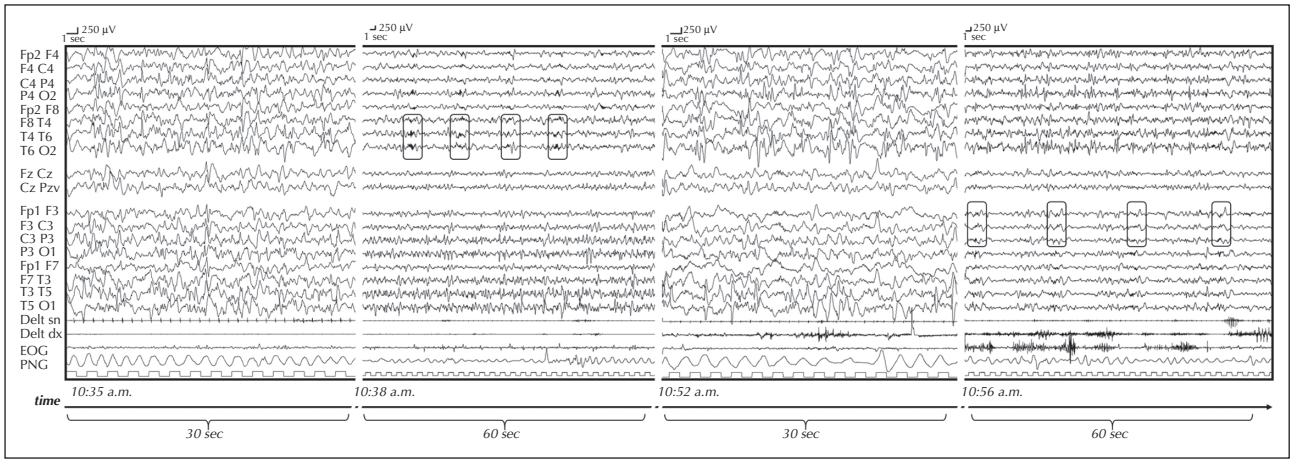

Figure 1. (A-D) EEG of a prolonged event on awakening at the age of 11 months, showing the main changes on EEG (the time from onset of the episode is reported below each image); note the progressive asynchronous and asymmetric involvement of the two hemispheres. (B, D) Lateralized interruption of the multifocal interictal activity and the appearance of fast activities in ipsilateral focal regions in a pseudoperiodic pattern (a longer time period is presented in order to highlight the pseudoperiodicity of the focal fast activity associated with eye movements, alternating between the two hemispheres).

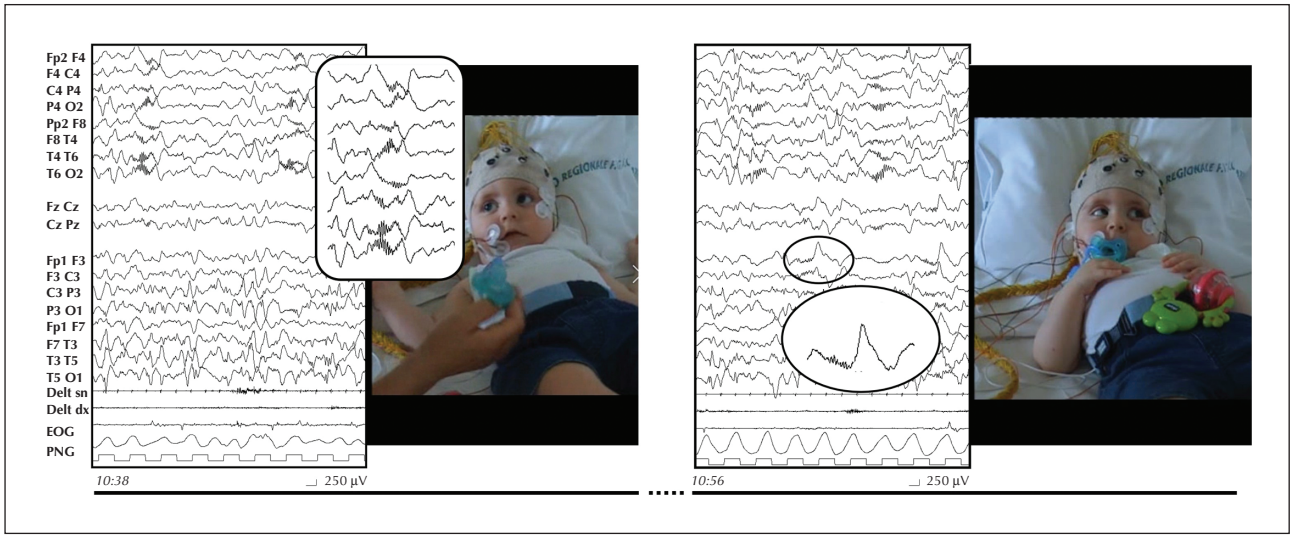

Figure 2. Details of the same prolonged episode reported in *figure 1*, showing the morphology of the focal modifications and the correlation with ocular movements. (A) Fast activity involving the right hemisphere, more evident on the posterior area, after a movement of the eyes towards the right. (B) Fast activity superimposed on the ascending side of a diphasic slow wave involves the centro-anterior regions of the left hemisphere concurrently with an upward gaze movement towards the left.

genes for epileptic encephalopathies through exome sequencing ("whole-exome sequencing" [WES]) in order to support clinical/diagnostic pathways and genetic analysis methods within the IRCCS network (EPI IDEA network). SNP array analysis revealed a normal karyotype 46 XY. WES (Personal Genomics, Verona, Italy) performed on samples from both the patient and his parents led to the identification of a homozygous missense candidate variant in *SPATA5* at chr4:123028258A>G (GRCh38/hg38; NM_145207: c.A1942G; p.Lys648Glu), located within a region of homozygosity of about 6.7 Mb on chromosome 4 (GRCh38/hg38; chr4:121980929-128717969), which was detected via a study of contiguous regions of runs of homozygosity (ROH). The novel mutation located on exon 13 of *SPATA5* was validated by Sanger sequencing. The variant is predicted to be damaging based on several *in silico* prediction tools. In addition, the project HOPE (Venselaar *et al*., 2010) was used to perform 3D modelling of the identified missense change. The results corroborate previous findings supporting a deleterious impact of the mutation on SPATA5 protein.

Discussion

The *SPATA5* gene and the protein encoded by it were first described by Liu as a spermatogenesis- associated factor (SPAF). The SPAF protein is involved in a variety of cellular processes, including protein unfolding and degradation, microtubule motor movement, DNA replication, membrane fusion and regulation of the structural integrity of mitochondria during spermatogenesis (Liu *et al*., 2000). SPATA5 is developmentally expressed throughout the brain, including the cerebral cortex and hippocampus and may play a critical role in neuronal development and growth (Tanaka *et al*., 2015).

The recent study of Puusepp on functional studies of SPATA5 deficiency shows that SPATA5 protein is required to sustain mitochondrial morphology, dynamics and ATP production in neurons, and its deficiency leads to impaired axogenesis of rat cortical neurons. Therefore, in the authors' opinion, SPATA5-related diseases can be indirectly categorized under mitochondrial disorders (Puusepp *et al*., 2018b).

Epilepsy is present in 28/37 *SPATA5* mutated patients but electroclinical reports at present are sparse in the literature.

In our case, a sequence of symptoms involving eye movements and epileptic spams (ES) were observed during single prolonged events, mostly appearing on awakening.

The presence of ES is reported in six of the 14 cases in the original paper and in 11 of the 28 cases in the literature so far. A predominance of paroxysmal activity on posterior regions is described by some authors (Tanaka *et al*., 2015; Kurata *et al*., 2016; Szczaluba *et al*., 2017). According to Kurata *et al*. (2016), the electrophysiological features and expression of the posterior cortical hyperexcitability underlying cortical visual impairment and epileptogenesis could enhance early recognition of the disorder.

Based on the International League Against Epilepsy (ILAE) 2017 classification, epileptic spasms (ES) can be focal or generalized, depending on both clinical and electrographic correlates, or of unknown onset in the absence of distinguishing features (Fisher *et al*., 2017). Gobbi *et al*. (1987) described a pseudoperiodic EEG and clinical phenomenon, called "periodic spasms" (PE), considered as a unique focal epileptic seizure, consisting of a series of spasms occurring in almost periodic sequence, with complex EEG modification. The occurrence of ES and partial seizures as a single ictal event is a described phenomenon and is considered to be indicative of structural brain abnormalities (Pachatz *et al*., 2003).

More recent studies focus on scalp EEG ictal gamma and beta activity, as indicators of local dysfunction in infants who fail to respond to early treatment (Panzica *et al*., 2007), in order to identify a localized seizure onset (Nariai *et al*., 2017). A surgical approach is recommended in selected patients who manifest with focal findings on neuroimaging and EEG (Barba *et al*., 2016). Conversely, in the context of developmental and epileptic encephalopathies, ES are often related to widespread epileptogenicity or diffuse lesions.

The pathophysiology of ES is still debated. The condition is proposed to be related to a widely disrupted network at a particular stage of development, a process implicit in the associated encephalopathy (Wilmshurst, 2017). The earliest studies suggested brainstem dysfunction as a trigger for spasms. Based on PET studies showing focal cortical hypometabolism, abnormal functional interactions between the brainstem and a focal cortical abnormality were hypothesized (Chugani *et al*., 1990). Most authors agree on the role of cortical-subcortical circuitry and a defective interaction that leads to the facilitation or induction of epileptiform activity (Vigevano *et al*., 2001; Lado and Moshe, 2002; Pachtaz *et al*., 2003).

A complex involvement of cortical areas and networks has been recently hypothesized by Garcia Tarodo *et al*. (2018) to explain a triad of clinical manifestations during a single ictal event, comprising a cluster of ES, vertical binocular nystagmus, and focal tonic seizures. In our case, the ictal pattern showed a sudden modification of EEG with a lateralized interruption of multifocal spikes with occipital right predominance and the appearance of focal fast activities in ipsilateral posterior regions in an almost periodic pattern, accompanying a slow conjugate eye movement towards the right. During the same prolonged episode, after some minutes, the other hemisphere was independently, globally involved and a stereotyped ipsilateral transient with the morphology of a focal spasm, anteriorly localized, corresponding to a tonic upward eye movement towards the left, appeared. These two bilateral asynchronous, almost periodic, patterns recurred, alternating with each other. The different phenomenology and temporal trend of the two events during a single prolonged episode suggests an initially posterior cortical activation but then a complex dysfunction of different cortical areas and subcortical networks.

Keeping in mind the proposed early influence of SPATA5 on synaptic development and plasticity and its diffuse expression throughout the brain, this may indicate the possibility of a predisposing genotype. Further investigation and other detailed clinical reports are needed to establish whether specific electroclinical characteristics may enhance the recognition of SPATA5-related encephalopathy. □

Legend for video sequence

The ictal EEG shows the interruption of interictal slow and paroxysmal activity and the appearance of clusters of short sequences of low-voltage fast activity initially on the posterior regions of the right hemisphere, then moving from one hemisphere to the other in almost a periodical and alternating trend. At first, fast activity involves the right hemisphere and is more evident on the posterior areas after a slow movement of the eyes towards the right. The fast activity is then bilateral, superimposed on a biphasic slow wave, and followed by an electrodecrement, with the occurrence of a subtle spasm. Lastly, fast activity superimposed on the ascending side of a diphasic slow wave involves the centro anterior regions of the left hemisphere concurrently with an upward gaze movement towards the left. At four years of age, the ocular movements still appeared in clusters but assumed the clinical characteristics of vertical nystagmus. The ictal EEG was characterized by a sequence of bilateral and synchronous fast activity.

Key words for video research on www.epilepticdisorders.com

Phenomenology: spasm (epileptic), eye deviation, epileptic nystagmus
Localisation: not applicable
Syndrome: epileptic encephalopathy not otherwise classified
Aetiology: genetic disorder

Disclosures.
None of the authors have any conflict of interest to declare.

References

Barba C, Mai R, Grisotto L, *et al*. Unilobar surgery for symptomatic epileptic spasms. *Ann Clin Transl Neurol* 2016; 4: 36-45.

Buchert R, Nesbitt AI, Tawamie H, *et al*. *SPATA5* mutations cause a distinct autosomal recessive phenotype of intellectual disability, hypotonia and hearing loss. *Orph J Rare Dis* 2016; 11: 13.

Chugani HT, Shields WD, Shewmon DA, *et al*. Infantile spasms: I: PET identifies focal cortical dysgenesis in cryptogenic cases for surgical treatment. *Ann Neurol* 1990; 27: 406-13.

Fisher RS, Cross H, French JA, *et al*. Operational classification of seizure types by the International League Against Epilepsy. *Epilepsia* 2017; 58: 522-30.

Garcia Tarodo S, Nguyen T, Ranza E, *et al*. A triad of infantile spasms, nystagmus and a focal tonic seizure. *Epileptic Disord* 2018; 20: 295-300.

Gobbi G, Bruno L, Pini A, *et al*. Periodic spasms: an unclassified type of epileptic seizure in childhood. *Dev Med Child Neurol* 1987; 29: 766-75.

Khurana S, Weaver L, Miskin C, *et al*. Mitochondrial dysfunction: consider *SPATA5* mutations. *Neurology* 2019; 92(15S): P4.6-062.

Kurata H, Terashima H, Nakashima M, *et al*. Characterization of SPATA5-related encephalopathy in early childhood. *Clin Genet* 2016; 90: 437-44.

Lado FA, Moshe SL. Role of subcortical structures in the pathogenic of infantile spasms: what are possible subcortical mediators? *Int Rev Neurobiol* 2002; 49: 115-40.

Liu Y, Black J, Kisiel N, Kulesz-Martin MF. SPAF, a new AAA-protein specific to early spermatogenesis and malignant conversion. *Oncogene* 2000; 19: 1579-88.

Nariai H, Beal J, Galanopoulou AS, *et al*. Scalp EEG ictal gamma and beta activity during infantile spasms: evidence of focality. *Epilepsia* 2017; 58: 882-92.

Pachatz C, Fusco L, Vigevano F. Epileptic spasms and partial seizures as a single ictal event. *Epilepsia* 2003; 44(5): 693-700.

Panzica F, Binelli S, Canafoglia L, *et al*. Ictal EEG fast activity in West syndrome: from onset to outcome. *Epilepsia* 2007; 48: 2101-10.

Papuc SM, Abela L, Steindl K, Begemann A, *et al*. The role of recessive inheritance in early-onset epileptic encephalopathies: a combined whole-exome sequencing and copy number study. *Eur J Hum Genet* 2019; 27: 408-21.

Puusepp S, Kovacs-Nagy R, Alhadda B, *et al*. Compound heterozygous *SPATA5* variants in four families and functional studies of SPATA5 deficiency. *Eur J Hum Genet* 2018a; 26: 407-19.

Puusepp S, Reinson K, Pajusalu S, *et al*. Effectiveness of whole exome sequencing in unsolved patients with a clinical suspicion of a mitochondrial disorder in Estonia. *Mol Genet Metab Rep* 2018b; 15: 80-9.

Szczaluba K, Szymanska K, Kosinka J, *et al*. Isolated hearing impairment caused by SPATA5 mutations in a family with variable phenotypic expression. *Adv Exp Med Biol* 2017; 980: 59-66.

Tanaka AJ, Cho MT, Millan F, *et al*. Mutations in *SPATA5* are associated with microcephaly, intellectual disability, seizures, and hearing loss. *Am J HumGenet* 2015; 97: 457-64.

Venselaar H, Te Beek TA, Kuipers RK, *et al*. Protein structure analysis of mutations causing inheritable diseases. An e-Science approach with life scientist friendly interfaces. *BMC Bioinformatics* 2010; 11: 548.

Vigevano F, Fusco L, Pachatz C. Neurophysiology of spasms. *Brain Dev* 2001; 23: 467-72.

Wilmshurst JM, Ibekwe RC, O'Callaghan FJK. Epileptic spasms - 175 years on: trying to teach an old dog new tricks. *Seizure* 2017; 44: 81-6.