Seizure: European Journal of Epilepsy 99 (2022) 12–15

Contents lists available at ScienceDirect

Seizure: European Journal of Epilepsy

journal homepage: www.elsevier.com/locate/seizure

Neurological phenomenology of the IRF2BPL mutation syndrome: Analysis of a new case and systematic review of the literature

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ARTICLE INFO

Keywords:
IRF2BPL gene
Epilepsy

ABSTRACT

Background: IRF2BPL is an intronless gene that was mapped to 14q24.3 chromosome in 2000 and codes for the interferon regulatory factor 2 binding like protein.
Objective: To analyses the clinical characteristics of the patients reported in the literature and of an additional patient we observed in order to better delineate the phenomenological spectrum of the disease and provide indications to improve clinical recognition and facilitate diagnosis.
Methods: We reported on 28 patients carrying the IRF2BPL mutation who were identified in 10 papers (n.27), using PUBMED as the search engine, and in our hospital (n. 1).
Results: All patients shared developmental delay/regression. Additional neurological symptoms were present in a large proportion of patients and reflected the involvement of five main neurological domains, i.e. epilepsy, dystonia, ataxia, spasticity, and ocular disturbances. Correlation analysis suggested a significant positive correlation between the number of affected neurological domains and the presence of MRI abnormalities (rho = 0.45, p = 0.02), while no significant correlation emerged between the number of affected clinical domains and age at disease onset (rho = 0.18, p = 0.35) or variant type (rho = 0.30, p = 0.12).
Conclusions: Our analysis highlights that the IRF2BPL mutation syndrome is highly specific to the central nervous system. Diagnostic work-up should consider the clinical picture of the IRF2BPL mutation syndrome herein delineated and the existence of conditions that share developmental delay/regression and result from acquired/genetic or unidentifiable underlying etiology.

1. Introduction

IRF2BPL is an intronless gene (also known as EAP1 or c14orf4) that was mapped in the 2000 on chromosome 14q24.3 [1]. This gene codes for the 796 amino acids-long interferon regulatory factor 2 binding-like protein, which is expressed in multiple human tissues, including the brain. Albeit its functions are largely unknown, several preclinical and clinical studies have suggested a possible role in neuronal development and homeostasis [2], transcription of the gonadotropin-releasing hormone [3], modulation of the ubiquitin-proteasome pathway (UPS) [4] and ubiquitination and degradation of β-catenin in gastric cancer [5]. To date, 27 patients with *IRF2BPL* mutations have been described in the literature [2],[6–14]. Here we present a patient carrying a novel pathogenetic variant of the *IRF2BPL* gene showing mild development delay, speech disturbances, myoclonic epilepsy and multifocal dystonia. We analyzed this patient and the previously reported *IRF2BPL* mutation carriers, in order to better delineate the phenotypical spectrum of the disease and provide indications to improve clinical recognition and facilitate diagnosis.

2. Case Report

A 24-year-old woman came to clinical observation for a neurodevelopmental disorder with regression, memory lapses and seizures. She was born to healthy unrelated parents after a normal birth. Psychomotor development appears to have been normal until school age, when a mild learning disability starting at 7 years of age with dyslexia and dyscalculia was detected. She attended both primary and secondary school, but was unable to complete the high school. She gave birth to a healthy baby at the age of 20, after a normal pregnancy.

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https://doi.org/10.1016/j.seizure.2022.04.010
Received 30 November 2021; Received in revised form 1 April 2022; Accepted 16 April 2022
Available online 18 April 2022
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In 2018, when she was 22, a tonic-clonic seizure occurred during sleep. The patient was first given Lamotrigine, subsequently switched to Carbamazepine because of drug-related side effects (cutaneous rash). There was no recurrence of tonic-clonic seizure for the following three years. In 2019, twelve months after seizure occurrence, the patient progressively developed bradyphrenia, forgetfulness, depressed mood, and irritability. Since January 2020, the patient has reported myoclonic jerks and unsteady gait with frequent falls.

Upon admission to our inpatient clinic in October 2020, neurological examination showed multifocal myoclonic jerks, intention tremor in the four limbs and gait ataxia. A comprehensive neuropsychological test battery showed impairment in long-term verbal memory. A standard electroencephalographic recording revealed diffuse epileptiform abnormalities and a photoparoxysmal response at 8-10 Hz photic stimulation. A magnetic resonance imaging (MRI) scan disclosed six small T2/Flair-hyperintense supratentorial, bilateral gliotic lesions. Metabolic (ceruloplasmin blood level, blood and urinary copper) and genetic (SCA1, 2, 3, 6, 7, 17 and HTT genes) investigations resulted normal. She was therefore diagnosed with myoclonic epilepsy and Carbamazepine was switched to Levetiracetam and Clonazepam. In the following months, the new drug regimen consistently reduced the frequency of the myoclonic jerks, that occurred only during wakefulness. Whole exome sequencing (WES) followed by Sanger sequencing revealed a *de novo* heterozygous pathogenetic variant (c.364C> T, p.Gln122Ter) in the *IRF2BPL* gene. This variant was found in a relatively preserved position (phyloP-vertebrate = phyloP-Primate = 0.2/0.65; PhastCons = 1.00/1.00) and caused premature insertion of a stop codon at the level of the aminoacid number 122 /2391 (ref Seq NM_024496.3, nonsense loss of function). WES was also performed in the parents of the patient but results did not reveal any mutation. The patient refused to perform genetic assessment in her child. There was no family history of epilepsy or other neurological diseases.

3. Review of the literature

A review of the literature was performed using Pubmed as the search engine and the following key words: *IRFBPL* gene; *EAP1* gene; *c14orf4* gene. Our search identified 10 papers, published in English from 2018 to 2021 that provided clinical details of 27 patients carrying *IRF2BPL* mutations. We also identified a further recent paper written in Chinese [15] that reported six new patients; however, since we had no means to access the information contained in the latter, it was excluded by our review.

The patient sample included 14 men and 14 women aged 19.8 ± 16.6 years (median, 13.5; range, 2 – 54). There was no firm evidence suggesting early mortality associated with the gene: a man died at 15 years [2] a women died at 12 years [6], and a men died at 54 years [11] were described up to now. Owing to the retrospective assessment, age at onset of clinical manifestations could not be determined in several cases. Nevertheless, the available information pointed to a disease onset of one year of age or less in 6 cases, between 1 and 3 years of age in 5 cases, between 4 and 5 years of age in 9 cases, between 6 and 10 years of age in 3 cases, and more 10 to 23 years of age (median, 11) in 5 cases.

Developmental delay and/or motor/speech regression of variable severity were present in all 28 patients (100%). Developmental delay was reported to be mild to moderate in 12 patients, severe in 16 patients. We could not find any correlation between age at onset and severity of regression on examination (age at onset > 6 years: 4/16 patients with severe regression vs. 4/12 patients with mild to moderate regression; Fisher's exact test, 0.7). In the five patients who reported disease onset at 10 years of age or more, regression was particularly severe in the two with the later onset (15 and 23 years), slight to moderate in the remaining three patients.

Additional neurological symptoms were present in a large proportion of patients and reflected the involvement of five main neurological domains, including epilepsy (21/28 patients) [2,6,7,8,10,11,13], dystonia (12/28 patients) [2,6,7,9,11,12], ataxia (10/28 patients) [6,7,10,12], spasticity (14/28 patients) [2,6–9,12] and a variety of ocular disturbances (12/28) [2,6-9,11,12]. Non-neurological problems were rare and included mild dysmorphic features (facial weakness, wider inter-nipple distance, joint laxity, etc.) in 5/28 patients (17.9%) and cardiomyopathy in 1/28 patients (3.6%) [2,6,8,11].

Epilepsy manifested with multiple types of seizures, including myoclonic, infantile spasms, absences, generalized tonic-clonic, and focal seizures. Epileptic manifestations were associated with EEG abnormalities in 16/21 patients, and eight of them also showed a photoparoxysmal response. We could not observe any correlation between age of onset of epilepsy and seizures type. Several drugs have been used to treat the wide spectrum of epileptic manifestations that characterized the IRF2BPL gene mutation syndrome, including lamotrigine, carbamazepine, oxcarbazepine, topiramate, valproic acid, clonazepam, etc. In our case, for example, we obtained good response with levetiracetam, as it would be expected in myoclonic seizures. Thus, treatment of epileptic seizures in subjects carrying the IRF2BPL gene mutation did not appear to differ from that of subjects with other syndromes, even in the occurrence of drug resistance. Generalized dystonia was observed in 5/12 patients, segmental/multifocal dystonia in 3/12 cases, whereas no information about dystonia distribution was available in 4/12 patients. Ocular disturbances included retinal abnormalities, keratoconus, ophthalmoplegia, nystagmus, slow or dysmetric saccades.

The frequency of most of the aforementioned neurological abnormalities did not differ between men and women (data not shown), apart from spasticity, that was present in 10/14 men and 4/14 women (hi-square test, p = 0.023). Similarly, patients with and without epilepsy were similar in gender, age of onset, and number of neurological domains involved (Table 1).

Magnetic resonance imaging (MRI) abnormalities were detected in 16/24 patients and mainly consisted in focal or diffuse cortical/subcortical atrophy (n.11/16), cerebellar atrophy (n.5/16), and thinning of the corpus callosum (n.5/16). Other less frequent features were supratentorial T2/Flair hyperintensities (n. 4/16), subarachnoid hemorrhage (n. 1/16), putaminal atrophy (n. 1/16), increased iron deposits in basal ganglia (n.1/16), thickening of corpus callosum (n.1/16). Among clinical findings, only epilepsy was significantly associated with MRI abnormalities (Table 2).

In general, the pathogenetic mutations associated with the described clinical phenotype were *de novo* (not present in the ExAC/gnomAD databases) loss of function variants (LoF): nonsense (# 18), missense (# 2) and frameshift (# 8). Nonsense mutations frequently occur early in the transcript, before the predicted PEST sequences, whereas the two missense mutations occur in the central part of the protein. Only one case of nonsense pathogenetic variant with autosomal dominant

Table 1
Demographic and clinical features in patients who did (n. 21) or did not (n.7) had epilepsy.

	Patients who reported epilepsy (n. 21)	Patients who did not report epilepsy (n.7)	P (by two-tailed chi-square/ Fisher test)
Men/women	10/11	4/3	1.0
Age at onset (n. pts.)	5	1	
One year or less	3	3	
1 to 3 years	6	2	0.5
4 to 5 years	3	0	
6 to 10 years	4	1	
> 10 years			
Dystonia (n. pts.)	9	3	0.66
Ataxia (n. pts.)	9	1	0.36
Spasticity (n. pts.)	11	3	1.0
Ocular disturbances (n. pts.)	9	3	1.0

Table 2
Distribution of clinical symptoms in patients with (n. 16) or without (n. 12) magnetic resonance imaging abnormalities.

Clinical feature	Presence of MRI abnormalities (n. 16)	Lack of MRI abnormalities (n.12)	P (by two-tailed chi-square/ Fisher test)
Epilepsy (n. pts.)	15	6	0.023
Dystonia (n. pts.)	8	4	0.46
Ataxia (n. pts.)	8	2	0.11
Spasticity (n. pts.)	10	3	0.25
Ocular disturbances (n. pts.)	9	4	0.14

inheritance (maternal transmission to a child with a similar dystonic syndrome) has been reported. *IRF2BPL* is highly constrained based on the lack of LoF variants in ExAC [16], resulting in high probability LoF intolerance score (pLI) and missense constraint Z score. The only LoF variants present in ExAC and gnomAD are the frameshift ones, which either do not pass the quality filter or appear to be called as artefacts in repetitive regions, if the browser view tool is used. Neither the presence of additional neurological features nor the detection of MRI abnormalities were significantly associated with mutation type (Table 3). We also did not observe any relationship between developmental disability (severe to mild/moderate) on examination and mutation type (missense, frameshift, and nonsense mutation). However, the sample may be too small to draw definite conclusions.

In the 28 patients, Spearman correlation analysis did not yielded any significant positive correlation between age at symptom onset and presence of epilepsy (rho = 0.14, p = 0.48), dystonia (rho = 0.31, p = 0.11), ataxia (rho = 0.25, p = 0.19), spasticity (rho = -0.04, p = 0.82), ocular symptoms (rho = 0.04, p = 0.82), or MRI abnormalities (rho = 0.32, p = 0.1).

Since the available information did not allow the assessment of neurological symptoms severity, we referred to the number of neurological domains (epilepsy, dystonia, ataxia, spasticity, and ocular disturbances) that were associated with developmental delay/regression as a surrogate of the clinical severity of *IRF2BP*L-related disorders. Spearman correlation analysis suggested a significant positive correlation between the number of affected neurological domains and the presence of MRI abnormalities (rho = 0.45, p = 0.02), while no significant correlation emerged between the number of affected clinical domains and age at disease onset (rho = 0.18, p = 0.35) or variant type (rho = 0.30, p = 0.12).

Table 3
Distribution of severity of developmental regression and of additional clinical symptoms in patients with missense (n. 2), frameshift (n. 8), and nonsense (n. 18) mutation in the IRF2BPL gene.

	Missense point mutation (n. 2)	Frameshift point mutation (n. 8)	Nonsense point mutation (n. 18)	P (by two-tailed Fisher test)
Developmental regression	1	2	9	0.48
Mild to moderate	1	6	9	
Severe				
Epilepsy (n. pts.)	2	4	15	0.13
Dystonia (n. pts.)	0	2	10	0.15
Ataxia (n. pts.)	0	2	8	0.34
Spasticity (n. pts.)	0	5	9	0.29
Ocular disturbances (n. pts.)	0	4	9	0.39
MRI abnormalities (n. pts)	0	5	11	0.24

4. Discussion

Variants in the *IRF2BPL* gene are responsible for a neurodevelopmental encephalopathy that is highly specific to the central nervous system. This is suggested by the consistent association with developmental delay/motor regression, the relatively high frequency of impairment in at least five main neurological domains (epilepsy, dystonia, ataxia, spasticity, and ocular disturbances), and the low frequency of involvement of other organs/systems. Our case report witnesses that the salient feature of the syndrome, that is developmental delay/ regression, may be of variable severity and may remain mild to moderate even in the adulthood, despite of childhood/juvenile onset. There was no correlation between severity of regression on examination and age at onset or the type (missense/frameshift/ nonsense) of the point mutation. As the great majority of previously reported probands diagnosed with *IRF2BPL*, our case patient had the disorder as the result of a de novo pathogenic variant, thus suggesting that the absence of a family history should not preclude diagnosis

The high frequency of epilepsy in in the *IRF2BPL* syndrome raises the possibility of an epileptic encephalopathy, a term implying that developmental delay and the other neurologic manifestations result from severe epilepsy. Owing to lack of information in the literature, however, it was not possible to check whether the severity of cognitive, motor and ocular manifestations was related to the severity and frequency of convulsive seizures. Although the significant relationship between epilepsy and presence of MRI abnormalities would provide some support to this view, the lack of epileptic manifestations in 25% of patients, and the observation that epilepsy did not cluster with any other neurological manifestations (Table 1), question the hypothesis of a pure epileptic encephalopathy.

There are a number of conditions resulting from acquired/genetic or unidentifiable underlying etiology (see supplemental tables 1 and 2) that share developmental delay/regression with the *IRF2BPL* variant syndrome. Since our analysis highlighted the phenotypical variability of the *IRF2BPL* variants and the lack of any combination of clinical/MRI signs that would make suggesting the diagnosis, then attribution of the clinical picture to the *IRF2BPL* variants may be difficult and a number of cases may be missed. Nevertheless, the relative high specificity to the CNS of the IRF2BPL variants herein reported may represent a diagnostic clue, particularly when facing with adult patients with childhood/juvenile onset syndrome that is likely to be defined and completed in the adulthood.

A stepwise diagnostic approach should therefore start with the exclusion of genetic/acquired conditions that may be misdiagnosed with the *IRF2BPL* variant syndrome (Supplemental Table 1), but are characterized by frequent multi-organ involvement, behavioural/psychiatric problems, or follow post-infective autoimmune encephalitis [17], perinatal HIV infection [18], or infantile spasms [19]. Since in our sample mean age on examination was about 20 years, and only three out of 28 patients died at 12, 15, and 54 years [2,6,11], differential diagnosis would pose no particular issues with conditions associated with high early mortality (such as asparagine synthetase deficiency) or which cannot reach adulthood (such as bi-allelic variants of CACNA1B gene). Thereafter, diagnostic work-up should focus on a panel of genetic conditions that present with only few extra-neurological manifestations and a clinical picture at least partially overlapping with that caused by *IRF2BPL* mutations. Among these conditions (summarized in the supplemental table 2) there are some known diseases (like Dravet and Leigh syndromes and neural ceroid lipofuscinosis) and several recently recognized genetic conditions for which information about phenomenology in the adulthood may be limited. Evaluation of these conditions with regard to inheritance modalities, age at onset and affected neurological domains in addition to developmental/delay regression may

provide insights into the genes to be included in the testing panel, leaving targeted next generation sequencing and whole exome sequencing as further line testing.

Declaration of Competing Interest

The authors declare that there is no conflict of interest

Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.seizure.2022.04.010.

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