Neurologic, Neuropsychologic, and Neuroradiologic Features of EBF3-Related Syndrome

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Abstract

Background and Objectives
Heterozygous mutations or deletions of the EBF3 gene are known to cause a syndrome characterized by intellectual disability, neurodevelopmental disorders, facial dysmorphisms, hypotonia, and ataxia; the latter is quite common despite in most patients brain MRI is reported to be normal. Despite the predominant neurologic involvement of EBF3-related syndrome, a systematic definition of neurologic, cognitive/behavioral, and neuroradiologic features is lacking.

Methods
We report on 6 patients (2 females and 4 males, age range 2–12 years), of whom 4 carrying a heterozygous point mutation of the EBF3 gene and 2 with 10q26 deletion encompassing the gene, diagnosed at Carlo Besta Neurologic Institute of Milan, Italy. Clinical evaluation was performed by a pediatric neurologist and pediatric dysmorphologist; ataxia severity was rated by Scale for the Assessment and Rating of Ataxia (SARA); brain MRIs were reviewed by expert neuroradiologists; general quotient levels were obtained through standardized Griffiths Mental Development Scales. Patients carrying a 10q26.3 deletion were diagnosed by array-CGH, whereas EBF3 variants were detected by whole exome sequencing.

Results
Phenotype was consistent in all patients, but with wide variability in severity. Developmental milestones were invariably delayed and resulted in an extremely variable cognitive impairment. All patients showed ataxic signs, as confirmed by SARA scores, often associated with hypotonia. Brain MRI revealed in all children a cerebellar malformation with vermis hypoplasia and a peculiar foliation anomaly characterized by a radial disposition of cerebellar folia (dandelion sign). Neurophysiologic examinations were unremarkable.

Discussion
EBF3-related syndrome has been so far described as a neurodevelopmental condition with dysmorphic traits, with limited emphasis on the neurologic features; we highlight the predominant neurologic involvement of these patients, which can be explained at least in part by the underlying cerebellar malformation. We therefore propose that EBF3-related syndrome should be classified and treated as a congenital, nonprogressive ataxia.
Early B cell factor 3 (EBF3) is a gene located on chromosome 10q26.3 that encodes for a member of a superfamily of highly homologous transcription factors (collier/olfactory-1/EBF; COE family), which drives cellular development and differentiation in various species across evolution.1,2 Early studies about EBF3 function come from molecular oncology: Zardo et al.3 first reported this gene to be aberrantly methylated and silenced or deleted in grade IV brain tumors, and loss of expression of the gene (because of epigenetic silencing, deletion, or somatic point mutations) was later discovered in several types of cancer. EBF3 was found to induce cellular cycle arrest and apoptosis, acting as a tumor suppressor, but was also implicated in regulation of neurogenesis and differentiation, and it is thought to play a role in the lamination of the cerebral cortex.1,4,5

EBF3 involvement in neurodevelopment was first hypothesized from studies on patients with 10q terminal deletions encompassing the gene, and later confirmed in 2017, when 3 independent groups demonstrated that EBF3 de novo pathogenic variants cause a syndromic neurodevelopmental disorder.2,5,6 After this, several reports of patients with EBF3 loss-of-function variants have been reported, sharing similar clinical features with those carrying terminal 10q26 deletions (summarized by Lopes et al. and Narayanan et al.7,8).

In the last years, the phenotype of EBF3-related syndrome has been therefore defined: the core feature of the condition is intellectual disability (ID), always present albeit with variable severity; in addition, a large proportion of patients present other neurodevelopmental issues, mostly attention deficit/hyperactivity disorder (ADHD), autism spectrum disorder (ASD), or nonspecific behavioral problems.5,9 Several participants show hypotonia, at least in infancy and early childhood, and ataxia is frequent, although only less than half patients present cerebellar vermis hypoplasia and/or dysplasia on brain MRI, whereas in the remaining cases, neuroimaging is reported as normal.2,4,6,9,11 Additional features include strabismus; congenital malformations involving genitourinary, gastrointestinal, or musculoskeletal system; and facial dysmorphisms (long face, tall forehead, high nasal bridge, deep philtrum, straight eyebrows, short and broad chin, and mildly dysmorphic ears).5,8

Despite the predominant neurologic involvement of EBF3 syndrome, a systematic definition of neurologic, cognitive/behavioral, and neuroimaging features is lacking, and such aspects are usually discussed within a broader description of all the general issues of the syndrome.

We report on 6 patients, of whom 4 presented with an EBF3 point mutation and 2 with a small 10q26 deletion involving the gene. We focus on a detailed characterization of neurologic features, some of which are unique and may turn to represent “diagnostic handles” for easy disease recognition, which will help addressing patients to the appropriate genetic testing.

Methods
The children were 2 females and 4 males, aged between 2 and 12 years, referred to the Carlo Besta Neurologic Institute of Milan, Italy, for clinical assessment and diagnosis. Clinical evaluation was performed by a pediatric neurologist and pediatric dysmorphologist; ataxia severity was rated by the Scale for the Assessment and Rating of Ataxia (SARA).12 Brain MRIs were reviewed by expert neuroradiologists and EEG recordings were all reassessed by a pediatric epileptologist. The general quotient/intelligence quotient (GQ/IQ) level was obtained through standardized scales: Griffiths Mental Development Scales (GMDS) or Wechsler Intelligence Scale for Children (WISC).

Array-CGH was performed with CytoSure oligo ISCA180K platform (average resolution: 40 Kb). Genomic coordinates are given according to GRCh37/hg19 (genes included in the deletions are listed in eTable 1, links.lww.com/NXG/A579). EBF3 genomic variants were detected by whole exome sequencing (WES); WES data were analyzed using the VarGenius pipeline13 and validated with Sanger sequencing; variants were classified according to the American College of Medical Genetics guidelines14 with the help of VarSome tool15 (detailed classification criteria are listed in eTable 2, links.lww.com/NXG/A579). Previously unreported variants were submitted to ClinVar database. Patient 3 brain MRI has been previously reported by our research group.16

Patient Consent
Written informed consent was obtained from all guardians of participants in the study for data publication and for the disclosure of brain MRIs. For the patient shown in pictures, the parents signed an additional consent for recognizable picture publication.

Data Availability
All patient data have been anonymously published in the article. Raw data of the WES sequencing may be shared, deidentified, on request of any qualified investigator for the purposes of replicating procedures and results; all data will be made available up to years after publication of this article.

Glossary
ADHD = attention deficit/hyperactivity disorder; ASD = autism spectrum disorder; EBF3 = early B cell factor 3; GMDS = Griffiths Mental Development Scales; GQ/IQ = general quotient/intelligence quotient; ID = intellectual disability; SARA = Scale for the Assessment and Rating of Ataxia; WES = whole exome sequencing.
Results

The 6 children globally presented the same phenotype but with significative differences in severity expression of the disease. No sex-related discrepancies were detectable.

Genetic results, clinical and neuropsychologic data, and MRI/EEG findings are summarized in Table 1.

Three children carried missense variants, including the recurrent variant p.Gly171Asp, already reported in literature4 (rs10575194379) found in 2; one had a novel frameshift variant (submitted to ClinVar, submission ID: SUB10872282). The 2 heterozygous 10q26.2q26.3 deletions spanned 6.6 and 7.8 Mb, respectively, and were comparable with other reported cases.11 No genotype-phenotype correlations are evident because the 2 patients with the same EBF3 missense variant show different severity with one of them (P3) presenting the worst cognitive performance and the highest SARA score.

Developmental milestones are reported to be invariably delayed for both motor and language skills in all patients with the mutation; looking at mean scores, head control was reached after 5 months, trunk control at approximately 1 year, and autonomous walking at approximately 4 years. Expressive language skills were more severely affected than receptive language, with all children having good competences in following easy verbal requests but a delay in first words development. In the 2 patients with EBF3 deletion instead, no significant delay in developmental skills is seen.

Cognitive outcome seemed to be extremely variable, with 2 patients presenting moderate developmental delay (P1 and P3, both carrying the same variant) and 2 showing mild developmental delay (P2 and P4). Of the 2 deleted patients, one showed a mild developmental delay with a subsequent positive course (GQ 83 at the age of 3 years 8 months) and the other one had normal developmental stages and also has a normal IQ level scored by WISC at the age of 6 years 10 months (P5 and P6). None of the patient was diagnosed with a behavior disorder (e.g., ASD or ADHD, both reported in the condition), but some mild problems, particularly anxiety, attention deficit, or low tolerance to frustration, were reported.

Neurologic examination revealed signs of cerebellar involvement in all patients, confirmed by the SARA scores. Strabismus was present in all (2 showing exotropia, 4 esotropia) and was invariably associated with dyspraxic ocularmotor functions; oro-buccal dyspraxia and/or dysarthria was also frequent (5 of 6 patients). Hypotonia is common: all patients had infantile hypotonia, with subsequent resolution in 2, whereas 4 showed persistent hypotonia, affecting the trunk, limbs, or generalized.

Tremor and/or dysmetria were noted in all but one patient when performing the nose-finger or heel-shin test. Finally, all children showed an ataxic gait, even if in some of them it was only detectable in direction turning or tandem walking. The SARA has been administered to 5 patients (P4 being too young) and confirmed the presence of ataxic signs (SARA score range: 9–20 out of 40 points).

Brain MRI revealed in all children a cerebellar malformation with foliation anomaly (wavy and blurred folia boundaries plus flattened course of folia white matter stems) and vermis hypoplasia. Patients with EBF3 mutations present a peculiar radial disposition of cerebellar folia that in sagittal images assumes a dandelion appearance (dandelion sign) (Figure 1).

Regarding neurophysiologic studies, all the mutated patients had a normal EEG. Of note, some abnormalities were found in the 2 patients with EBF3 deletion and in particular the EEG recording of Patient 5 was poorly organized; however, it did not show epileptic abnormalities, whereas the recording of Patient 6 showed few spikes during drowsiness and sleep compatible with the pattern of benign idiopathic epilepsy, occurring probably random (the child never had any episode of possible epileptic origin) (Figure 2). Evoked potentials were normal in the 4 patients who underwent the examination and so were the EMGs and ENGs.

Finally, on general examination, all patients showed an overall dysmorphic appearance with some common facial traits (in particular deep set eyes and thin upper lip). Figure 3 shows the phenotype evolution of Patient 3, with features becoming more apparent over the years. In 2 cases, growth is below −2 SD and all children have a height below the mean value (maximum height in P1: −0.2 SD). Some minor malformations were present, mainly flat feet, and constipation was reported in half patients. However, all children were globally in good general health.

Discussion

Most of the articles published so far about EBF3-related syndrome describe the condition mainly as a neurodevelopmental disease with dysmorphic traits, giving poor—and sometimes none—relevance to its neurologic features. However, the cerebellar signs, at least in our cohort, dominate the overall presentation and many of the clinical issues reported in children mutated in EBF3, including the cognitive impairment but also hypotonia, may be ascribed to the cerebellar dysfunction typical of the syndrome.

Syndromic features include facial dysmorphisms and malformations. Previous studies have deeply described the typical facial appearance of this condition, characterized by a long or triangular face, tall forehead, straight eyebrows, strabismus, high nasal bridge, bulbous nasal tip, deep philtrum, short and broad chin, and dysmorphic ears.5,7,17 These were also present in our cohort, confirming that EBF3-related syndrome, and other congenital malformative ataxias, may be characterized by prominent and recognizable facial dysmorphisms. Congenital malformations reported in the literature involve
### Table 1 Overview of Clinical, Neuroradiologic, Neurophysiologic, and Genetic Findings of the Patients

<table>
<thead>
<tr>
<th>Patient #</th>
<th>Genotype</th>
<th>Sex</th>
<th>Age</th>
<th>Developmental milestones</th>
<th>Behavior</th>
<th>Neurologic examination</th>
<th>SARA scale</th>
<th>Brain MRI</th>
<th>Neurophysiology tests</th>
<th>Growth parameters</th>
<th>Facial dysmorphisms</th>
<th>Malformations</th>
<th>Clinical issues</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patient 1</td>
<td>EBF3:c.512G&gt;A (p.Gly171Asp) dn</td>
<td>M</td>
<td>11 y</td>
<td>Head control: 6 mo Trunk control: 1 y 1 mo walking: 5 y first words: 2 y 6 mo</td>
<td>Attention deficit and mild delay in following rules and occasional repetitive conduct. Bruxism during stressful situations. Friendly behavior, good social and communication skills</td>
<td>Exotropia, oculomotor and orobuccal dyspraxia, and dysarthria. Lower limbs hypotonia. Terminal tremor, dysmetria, truncal, and gait ataxia</td>
<td>16 (4 + 3 + 1 + 3 + 1 + 1 + 1 + 2)</td>
<td>Radial folia (dandelion sign), blurred wavy folia boundaries, vermis hypoplasia + lack of vermis subdivision; facing cerebellar hemispheres + flattened course of folia white matter stem</td>
<td>EEG: Normal Evoked potentials (BAEP, VEP, ERG): Normal</td>
<td>H 25–50° (−0.2 SD) W 25° (−0.7 SD) HC 25° (−0.6 SD)</td>
<td>Deep set eyes, broad and depressed nasal bridge, thin upper lip, anteverted ears</td>
<td>Kidney asymmetry and mild pylectasia, pectus excavatum</td>
<td>Infantile hypotonia, bruxism, constipation</td>
</tr>
<tr>
<td>Patient 2</td>
<td>EBF3:c.481delT (p.Cys161Alafs*21) dn</td>
<td>F</td>
<td>6 y 1 mo</td>
<td>Head control: 4 mo Trunk control: 10 mo Walking: 2 y first words: 3 y</td>
<td>No behavioral problems, good social and communication skills</td>
<td>Exotropia, nystagmus, oculomotor and orobuccal dyspraxia, dysarthria. Limbs hypotonia. Tremor, dysmetria, mild truncal and gait ataxia</td>
<td>14 (2 + 3 + 1 + 1 + 2 + 1 + 2 + 2)</td>
<td>Radial folia (dandelion sign); blurred wavy folia boundaries; vermis hypoplasia + lack of vermis subdivision; facing cerebellar hemispheres + flattened course of folia white matter stem</td>
<td>EEG: Normal Evoked potentials (BAEP, VEP, ERG): Normal</td>
<td>H &lt; 3° (−2.3 SD) W 3° (−1.9 SD) HC 3–10° (−1.7 SD)</td>
<td>Deep set eyes</td>
<td>Flat feet</td>
<td>Infantile hypotonia, constipation</td>
</tr>
<tr>
<td>Patient 3</td>
<td>EBF3:c.512G&gt;A (p.Gly171Asp) dn</td>
<td>M</td>
<td>12 y 2 mo</td>
<td>Head control: 5 mo Trunk control: 2 y walking: 4 y 6 mo First words: 2 y</td>
<td>No behavioral problems, good social and communication skills</td>
<td>Exotropia, oculomotor and orobuccal dyspraxia, dysarthria. Generalized hypotonia, reduced tendon reflexes. Tremor, dysmetria, truncal and gait ataxia</td>
<td>20 (3 + 3 + 1 + 5 + 2 + 2 + 2 + 2)</td>
<td>Radial folia (dandelion sign); blurred wavy folia boundaries; vermis hypoplasia + lack of vermis subdivision; facing cerebellar hemispheres + flattened course of folia white matter stem</td>
<td>EEG: Normal Evoked potentials (BAEP, VEP, ERG): Normal</td>
<td>H 10–25° (−1.1 SD) W 25–50° (−0.5 SD) HC 75–90° (1.0 SD)</td>
<td>Infraorbital creases, large and bulbous nasal ridge, flat philtrum, thin upper lip, retrognathia, low-set ears, auricular pit</td>
<td>Infante hypotonia, constipation</td>
<td></td>
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Table 1  Overview of Clinical, Neuroradiologic, Neurophysiologic, and Genetic Findings of the Patients (continued)

<table>
<thead>
<tr>
<th>Patient #</th>
<th>Genotype</th>
<th>Sex</th>
<th>Age</th>
<th>Developmental milestones</th>
<th>GQ/IQ (scale)</th>
<th>Behavior</th>
<th>Neurologic examination</th>
<th>SARA scale</th>
<th>Brain MRI</th>
<th>Neurophysiology tests</th>
<th>Growth parameters</th>
<th>Facial dysmorphisms</th>
<th>Malformations</th>
<th>Clinical issues</th>
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<tr>
<td>Patient 4</td>
<td>EBF3:c.422A&gt;G (p.Tyr141Cys) dn</td>
<td>M</td>
<td>2 y</td>
<td>Head control: 6 m Trunk control: 1 y walking: – First words: –</td>
<td>GQ 60 (Griffiths)</td>
<td>No behavioral problems, calm and obedient child</td>
<td>Esotropia, oculomotor dyspraxia, drooling, Truncal and lower limbs hypotonia, mild reduction of tendon reflexes. Mild dysmetria, truncal and gait ataxia</td>
<td>NP</td>
<td>Radial folia (dandelion sign); vermis hypoplasia + lack of vermis subdivision; facing cerebellar hemispheres + flattened course of folia white matter stem</td>
<td>EEG: Normal</td>
<td>H 10–25* (–0.8 SD) W 50–75* (+0.2 SD) HC 75–90* (+1.0 SD)</td>
<td>—</td>
<td>Infantile hypotonia</td>
<td></td>
</tr>
<tr>
<td>Patient 5</td>
<td>arr[GRCh37]10q26.2q26.3 (127,657,000_135434409)x1 dn</td>
<td>F</td>
<td>8 mo</td>
<td>Head control: 6 mo Trunk control: 10 mo Walking: 2 y first words: 1 y 6 mo</td>
<td>GQ 83 (Griffiths)</td>
<td>Impulsive and aggressive behavior, emotional dysregulation, Low frustration tolerance, constantly asking for attention, repetitive conducts. Sufficiently adequate social abilities</td>
<td>Esotropia, mild oculomotor dyspraxia. Mild gait ataxia</td>
<td>9 (1 + 1 + 0 + 2 + 0 + 2 + 0 + 2 + 1)</td>
<td>Blurred wavy folia boundaries; facing cerebellar hemispheres + flattened course of folia white matter stem</td>
<td>EEG: Slow background activity, poorly organized sleep pattern</td>
<td>H 10–25* (–1.0 SD) W 10* (–1.3 SD) HC 3–10* (–1.4 SD)</td>
<td>Deep set eyes, epicanthus, tented upper lip</td>
<td>—</td>
<td>Axial hypotonia/ lower limbs hypotonia in first infancy</td>
</tr>
<tr>
<td>Patient 6</td>
<td>arr[GRCh37]10q26.2q26.3 (128,939,462_135506781)x1 dn</td>
<td>M</td>
<td>6 y 10 mo</td>
<td>Head control: 3 mo Trunk control: 7 mo Walking: 1 y 4 mo First words: 1 y</td>
<td>GQ 98 (Griffiths) IQ 93 (WISC)</td>
<td>Attention deficit, low frustration tolerance, food selectivity. Friendly behavior, good social and communication skills. Mild anxiety signs</td>
<td>Esotropia. Oculomotor dyspraxia. Orbuculocerebral dyspraxia and dysarthria. Slight terminal tremor, dysmetria, mild gait ataxia</td>
<td>11 (1 + 1 + 0 + 2 + 1 + 2 + 2 + 2 + 2)</td>
<td>Vermis hypoplasia; facing cerebellar hemispheres + flattened course of folia white matter stem</td>
<td>EEG: Well organized; during drowsiness and sleep, spikes on vertex and centroparietal regions reminiscent of benign idiopathic epilepsy Evoked potentials (BAEP, VEP, ERG): Normal</td>
<td>EMG/ENG: Normal</td>
<td>H &lt; 3* (–2.8 SD) W &lt; 3* (–2.6 SD) HC &lt; 3* (–2.2 SD)</td>
<td>Triangular face, thin and mildly upslanting palpebral fissures, narrow nasal ridge, thin lips with tented upper lip, large ears</td>
<td>Valgus and flat feet, V toe clinodactyly</td>
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Abbreviations: BAEP = brainstem auditory evoked potentials; ENG = electroneuronography; ERG = electroretinogram; FRI = fluid reasoning index; GERD = gastroesophageal reflux disease; GQ = general quotient; H = height; HC = head circumference; IQ = performance IQ; PSI = processing speed index; SARA = Scale for Assessment and Rating of Ataxia; VCI = verbal comprehension index; VEP = visual evoked potentials; vIQ = verbal IQ; VSI = visual spatial index; W = weight; WMI = working memory index.
genitourinary system (kidney dysplasia, vesicoureteric reflux, undescended testes, and bicornuate uterus) or skeletal system (scoliosis, pectus excavatum, syndactyly, hip and knee contractures, and flat feet). Gastroesophageal reflux or constipation are also frequent. Such manifestations, only found in a subset of our patients, are overall rare and mild; even if only one adult patient has been reported so far, we can infer that general health is good in most patients and life expectancy is not impaired by the syndrome.

Of note, when assessing intellective functions, our patients with whole gene deletion (10q26 deletion syndrome) seem to lack cognitive impairment, whereas this is always present in patients with EBF3 point mutations. Data from our study differ from what previously reported by Nishi et al., who found no significant differences in total GQ/IQ, adaptation, and language or social skills between the 2 groups but a more significant neurologic impairment in the EBF3 deletion group. In our cohort, otherwise, the global presentation is milder in deleted patients and among the mutated ones, the missense p.Gly171Asp variant is associated with the most severe phenotype (worse than the frameshift variant). The EBF3:c.512G > A (p.Gly171Asp) variant has already been reported in other studies, always associated with phenotypes showing a
moderate to severe ID, neurologic involvement with definite ataxic syndrome and hypotonia, facial dysmorphisms, and genitourinary malformations.\textsuperscript{4,18,19} Our cohort demonstrate that the phenotypic spectrum could be largely variable, still such data must be confirmed by broader studies.

In addition to cognitive impairment, several neuropsychologic and behavioral disturbances have been reported in \textit{EBF3} children, including behavioral problems, stereotypic behaviors, ASD features, oppositional defiant behavior, short attention span, and ADHD traits\textsuperscript{2,6,8,19,20}; moreover, self-injurious behavior and aggression were reported mainly in patients carrying the deletion.\textsuperscript{7,21} Half of the children in our cohort did not show any behavioral concern, whereas the other half presented signs mostly related to attention deficit or poor tolerance of stressful events.

Beyond such features, that are common to many neurodevelopmental syndromes, neurologic signs make the difference and represent a hallmark of this condition. Ataxia is present in all patients and may manifest with the whole spectrum of cerebellar impairment: oculomotor anomalies (e.g., oculomotor apraxia, nystagmus, and strabismus), dysarthria, gait unbalance, truncal and appendicular ataxia, a/dysdiadochokinesia, and tremor. A recent article by Ignatius et al.\textsuperscript{22} investigated the cerebellar signs in patients with \textit{EBF3}-related ataxia and found that all patients showed signs of cerebellar involvement, although the SARA score of the reported participants was overall lower than in our cohort: the patient with the most severe presentation reached a score of 15, whereas in our cohort, the ataxic features are prominently expressed (SARA scores 9–20). Hypotonia is also often present and should also be considered of cerebellar origin because it was already reported in some previous cases.\textsuperscript{22,23} Cerebellar features have been underestimated in a number of articles discussing \textit{EBF3}-related syndrome as a neurodevelopmental disorder; here, we underline that ataxia must be considered a cardinal sign of the syndrome and taken into full consideration when planning management because children would greatly benefit from a rehabilitation program including exercises to improve gross and fine motor skills.

Ataxic signs are also directly related to the cerebellar malformations evident at brain imaging. The review by Jiménez de la Peña et al.\textsuperscript{5} states that structural brain abnormalities are infrequent, with vermis hypoplasia, delayed myelination, and subtle migration disorders rarely reported, and with half patients showing a normal brain MRI. In addition, in the article by Ignatius et al., 5 of 9 patients seemed to have no neuroradiologic alteration. However, in our cohort, not only cerebellar neuroradiologic abnormalities were always present but, at least in the \textit{EBF3} mutated group, they shared a peculiar pattern (“dandelion sign”) which could represent a pathognomonic and well-recognizable sign able to guide the diagnostic suspicion. In this light, a careful assessment of brain imaging by expert pediatric neuroradiologists could help improve the diagnostic sensitivity to detect such neuroradiologic signs.

In conclusion, this study shows how \textit{EBF3} alterations determine a disease with predominant neurologic involvement, where even the neurocognitive aspects are, at least in part, attributable to cerebellar dysfunction. It is widely known that the cerebellum plays an important role in behavior and cognition, as confirmed by studies on general nervous system functioning or works on other congenital or acquired ataxias.\textsuperscript{24} Our findings indicate that \textit{EBF3} may also be part of that categorization, and we therefore advocate that \textit{EBF3}-related syndrome be classified and treated as a congenital ataxia.
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Disclosure
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<th>Location</th>
<th>Contribution</th>
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Appendix (continued)

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<td>Major role in the acquisition of data, study concept, or design</td>
</tr>
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References


