Case Report

Atypical benign partial epilepsy of childhood with acquired neurocognitive, lexical semantic, and autistic spectrum disorder

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Atypical benign partial epilepsy (ABPE) of childhood or pseudo-Lennox syndrome is a form of idiopathic focal epilepsy characterized by multiple seizure types, focal and/or generalized epileptiform discharges, continuous spike–wave during sleep (CSWS), and sometimes reversible neurocognitive deficits. There are few reported cases of ABPE describing detailed correlative longitudinal follow-up of the various associated neurocognitive, language, social communicative, or motor deficits, in parallel with the epilepsy. Furthermore, the molecular inheritance pattern for ABPE and the wider spectrum of epilepsy aphasia disorders have yet to be fully elucidated. We describe the phenotype–genotype study of a boy with ABPE with follow-up from ages 5 to 13 years showing acquired oromotor, language, social communicative, and neurocognitive manifestations (with stabilization and partial improvement upon seizure remission), followed longitudinally from ages 5 to 13 years. Exome sequencing revealed variants in SCN9A, CPA6, and SCNMI. A direct role of the epilepsy in the pathogenesis of the oromotor and neurocognitive deficits is apparent.

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1. Introduction

The idiopathic focal epilepsies of childhood represent a heterogeneous and presumed genetic group of epilepsies for which the underlying molecular mechanisms remain largely undetermined. Atypical benign partial epilepsy (ABPE) of childhood or pseudo-Lennox syndrome is a rare form of idiopathic focal epilepsy characterized by multiple seizure types including focal seizures, “generalized minor seizures” (atonic, absence, or myoclonic seizures), and occasional febrile seizures or status epilepticus [1]. The electroencephalogram (EEG) in ABPE shows focal or multifocal sharp waves, a tendency towards changing location, generalization, and pronounced activation during sleep often resulting in continuous spike-and-wave during slow-wave sleep (CSWS). As such, ABPE is part of the “epilepsy aphasia spectrum” of disorders where rolandic epilepsy occurs at one end and the Landau-Kleffner syndrome (LKS) occurs at the more severe end. ABPE is associated with reversible or residual deficits in language, motor function, and cognition. However, prospective studies describing in detail the epilepsy and specific motor, cognitive, social communicative, and language deficits are rarely reported. With advances in next generation DNA sequencing, efforts to correlate the molecular genetic architecture of these disorders could also be described in conjunction with uniquely insightful phenotypes.

This report describes the phenotype of a boy with ABPE who, following a very active seizure period, demonstrated acquired oromotor, language, social communicative, and neurocognitive manifestations (with stabilization and partial improvement upon seizure remission), followed longitudinally from ages 5 to 13 years. Exome sequencing revealed variants in SCN9A and two other epilepsy-associated genes, CPA6 and SCNMI.

2. Methods & results

2.1. Epilepsy, motor, language, cognitive, and social communicative disorder

2.1.1. Clinical summary

The proband, a boy, was born full term with an unremarkable perinatal history to nonconsanguineous Caucasian parents. There was no family history of seizure or autistic spectrum disorder; however, his younger sister presented at age 11 years with mild elective mutism, primary anxiety, and minor sensory processing difficulties (EEG and genetic characterization were not possible in his sister). When the boy was...
first seen at seizure presentation at age 23 months, his developmental milestones were normal including hearing, speech, and language (he had 3- to 4-word sentences and understood 3-stage commands), and physical examination was normal. Brain magnetic resonance imaging, routine biochemistry, hematological indices and chromosomal microarray CGH were normal. Later, emergence of left hand preference was assumed familial (maternal aunt and first cousin).

Following initial seizure presentation, he went to preschool (kindergarten) and continued to acquire new skills. His preschool teacher noted occasional (intermittent) mild speech slurring and pronunciation difficulty, although these were not noted by his parents. He made accelerated progress with reading acquisition and, at age 4 years, was reported by the preschool teacher to have significantly advanced word reading (hyperlexia). Prior to first formal neuropsychological assessment (age 5 years), a retrospective review identified subtle intermittent aberrations in play pattern (specific interests) and repetitive behaviors, after initial seizure onset. During the most active epilepsy period, deterioration in learning and social communication was observed. In addition, at age 6.2 years, following the onset of the most active epileptic period (including CSWS and prominent bilateral centrotemporal discharges), language also became severely impaired. Receptive language declined below expressive language; however, verbal auditory agnosia (LKS) was not a feature. As seizure control and EEG abnormalities improved, there was recovery in language skills (more in expressive than receptive), but an overall residual specific disorder of lexical semantics affecting both receptive and expressive vocabulary occurred.

In parallel with recurrent perisylvian seizures at age 5 years, transient motor difficulties emerged in the form of right-sided limb and facial weakness, slurred speech, drooling of saliva, and oromotor difficulties. While general motor improvement occurred following seizure remission, difficulties with fine oromotor gestures persist at age 14 years.

Details of the epilepsy as well as language, cognitive, and social communication disorders follow (summarized in Fig. 1 and Supplemental Table 1).

2.1.2. Epilepsy course
At age 23 months, the boy presented with a seizure characterized by jerking of the right arm and leg, eye-rolling, drooling, and unconsciousness. EEG showed left centrotemporal spikes. Over the following 2 years, while treated with carbamazepine, clusters of brief perisylvian seizures occurred characterized by right (sometimes left) arm jerking/hand clenching, facial twitching, and frothing at the mouth. From the age of 4 years, multiple seizure types were seen, affecting either side of the body while various antiepileptic drugs (AEDs) were ineffective (Supplementary Table 1). EEGs showed high amplitude spike–wave discharges predominantly in the left parietocentral/centrotemporal regions. At the age of almost 5 years, subtle drop attacks developed. Ongoing seizures included episodes of blinking, facial twitching, and drooling. EEG continued to show mainly left parietocentral spikes (Fig. 2A). A course of betamethasone (2 mg/day for 7 weeks) led to seizure remission, but one week after weaning, seizures recurred. A second course of betamethasone after 5 weeks achieved seizure freedom, but relapse occurred with attempted weaning. Following dose adjustment, milder breakthrough seizures continued. Vigabatrin was added, and steroids weaned after a total of 4 months. At this stage, awake and sleep EEG showed high-amplitude spike–wave discharges predominantly in the left parietocentral/centrotemporal regions. At the age of 6.4 years, sulthiame and a course of adrenocorticotrophic hormone (ACTH) significantly improved drop attacks; however, following ACTH withdrawal, seizures worsened, and EEG evolved to CSWS (Fig. 2B). A course of daily prednisolone combined with ethosuximide achieved seizure freedom for weeks.
with only sporadic drop attacks and focal seizures. At 6.8 years when prednisolone was switched to a pulsed regimen (25 mg twice weekly), complete remission of seizures occurred. At follow up, EEGs showed marked improvement (centrotemporal discharges without CSWS). At age 14 years, he remains seizure-free (3 years after steroid withdrawal; see Supplemental Table 1 for epilepsy course and treatment).

2.1.3. Language regression & assessments

Language skills were formally tested from ages 5 to 13 years. These focused on receptive and expressive language using the Clinical Evaluation of Language Fundamentals (CELF) Preschool Ed. (Editions 3 and 4). Other assessments included the British Picture Vocabulary Scale (BPVS), Test for Reception of Grammar (TROG), and Expressive Vocabulary Test (2nd Ed.). The first language assessment at age 5 years was normal, prior to the most severe epilepsy phase (including the emergence of CSWS) and associated cognitive deterioration. Soon after, his parents reported unclear speech and less verbal output. Language deterioration was first documented during assessment at age 6.2 years with persistent disordered language profiles in subsequent assessments (focusing on CELF-3 and CELF-4 assessments; Table 1). In particular, receptive language abilities declined (moderate to severe range) more than expressive abilities, an atypical pattern. Receptive language scores demonstrated little variation across the years compared with expressive language scores which demonstrated greater variation and improvements. The lowest scores in both receptive and expressive language abilities occurred at age 7.3 years (during which he appeared anxious and responded slowly).

Additional language tests confirmed particular patterns. The British Picture Vocabulary Scale (BPVS, a test of receptive vocabulary) revealed a score within the severe impairment range at last follow-up (age 13 years). Additional expressive language assessments included the Expressive Vocabulary Test (EVT, 2nd Ed., a test of naming ability and expressive vocabulary) with scores within the moderate impairment range. These tests indicate impairments in the area of lexical semantics in both the receptive and expressive language domains. The Test for Reception of Grammar (TROG) (Syntax) (for receptive grammar) scored in the average range (standard score: 88; age 13 years). Thus, language structure (syntax and morphology) was identified as an area of relative strength for receptive language along with the ability to produce grammatically correct sentences (“formulated sentences” subtest score: 7; CELF-4). Working memory as seen in “recalling sentences” subtest (score: 11; CELF-4) was also relatively strong.

Subtests pertaining to “understanding spoken paragraphs” or “semantic relationships” showed weaknesses (understanding and interpretation). The greatest area of difficulty was in the area of lexical semantics, with both receptive and expressive vocabulary impairment. Scores in the receptive and expressive “word classes” subtests in the CELF-4 were statistically lower than in other areas of language development.

2.1.4. Oral motor and speech disorder

The boy’s parents reported normal early oromotor development prior to the onset of seizures. His preschool teacher reported occasional slurring of speech and pronunciation errors. Primarily,
language assessment (age 5 years) was normal, but he subsequently developed oromotor difficulties, characterized at follow-up assessments (Table 1). These did not significantly impact on speech, which was intelligible; however, eating was messy, and oral hygiene was challenging. He was noted to have difficulties with muscles of the lips, cheek, and tongue. These included a reduced range of movement of the lips (unable to round lips/blow out cheeks, with clumsy tongue movements; unable to move tongue towards the right, to lick lips to clear food residue). These movements were subsequently achieved during speech, eating, and drinking at follow-up, but residual difficulties are seen. As the epileptic activity started in the anterior sylvian region (facial weakness, slurring of speech), it correlated with residual nonlinguistic oromotor problems (feeding, fine oromotor gestures) but not at the speech programming level (no features of verbal dyspraxia) (Table 1).

### 2.1.5. Cognitive development & neuropsychological assessments

In association with exacerbation of seizures, there was deterioration in language, oromotor, learning (cognitive), and social communication skills and increased anxiety. Cognitive developmental trajectory was monitored with serial neuropsychological assessments. Initial assessment at almost 5 years indicated overall functioning within the average range of ability (WPPSI-R; Table 2). Follow-up assessments between ages 6–12 years indicated a continued downward shift across cognitive domains (WISC-IV; Table 3) correlating initially with the active epilepsy period. The most recent assessment indicates residual cognitive functioning overall in the extremely low range (IQ range: 55–69) with minimal improvement in working memory and processing speed (Table 3). He attended a mainstream primary (junior) school with learning support and currently attends a mainstream secondary (senior) school in a class for students with learning disabilities. Therefore, cognitive deterioration occurred between 5 and 7 years of age during the most active epilepsy period (including CSWS). Thereafter, the global IQ scores remained relatively stable with little “recovery”.

Assessment of memory skills also revealed impaired functioning across both visual and verbal memory tasks with fall-off in verbal memory capacity as noted at the most recent assessment (Table 4). However, school attainment testing indicates a reverse trend to that found on cognitive assessment with evidence of continued gain in the acquisition of basic academic skills over the period of ages 7 to 12 years, progress correlating with good seizure control (Table 5).

### Table 1

Summary of pattern of score totals regarding receptive and expressive language assessments, as well as oromotor observations.

| Age          | Receptive | Expressive | Oromotor skills                          | General comment                          |
|--------------|-----------|------------|------------------------------------------|------------------------------------------|
| 5 years 1 month | Preschool CELF: 91 (average range) | Preschool CELF: 104 (average range) | Poor tongue movements; reduced elevation, depression and lateral movements, particularly to the right side. Reduced lip rounding | Excellent attention and concentration. Mild to moderate unintelligibility. Poor articulation. Hoarse breathy vocal quality. Hypernasal speech |
| 6 years 2 months | CELF-3: 71 (moderate deficit) | CELF-3: 65 (severe deficit) | Poor tongue movements; reduced elevation, depression and lateral movements, particularly to the right side. Reduced lip rounding | Lethargic during assessment. Hypernasal, mild dysarthria. |
| 6 years 7 months | Preschool CELF: 65 (severe deficit) | Preschool CELF: 89 (average range) | Not available | Developmental speech sound errors. Mild dysarthria (slow labored speech). |
| 7 years 3 months | CELF-3: 64 (severe deficit) | CELF-3: 75 (moderate deficit) | Not available | Breathy voice quality. Highly anxious during assessment. Mild word finding difficulties. |
| 8 years 10 months | CELF-3: 66 (severe deficit) | CELF-3: 92 (average range) | Not available | Dysphonic voice quality. Mild dysarthria. Quiet with little spontaneous speech. Slow processing of verbal information. Nasal speech with oral motor difficulties. Speech intelligible |
| 10 years 4 months | CELF-4: 76 (moderate deficit) | CELF-4: 80 (mild deficit) | Reduced lip rounding, clumsy tongue movements, reduced movement to the right | Quiet with little spontaneous speech. |
| 13 years 1 month | CELF-4: 68 (severe deficit) | CELF-4: 77 (moderate deficit) | Reduced lip rounding, reduced tongue tip elevation and reduced movement of tongue to the right | Speech intelligible |
|               | TROG: 88 (average range) | EVT: 73 (moderate deficit) | Speech intelligible | Good interaction with therapist |

**Abbreviations:** Preschool CELF = Preschool Clinical Evaluation of Language Fundamentals; CELF-3 = 3rd Ed.; CELF-4 = 4th Ed.; BPVS = British Picture Vocabulary Scale; TROG = Test for Reception of Grammar; EVT = Expressive Vocabulary Test (2nd Ed.); Scores: Clinical Evaluation of Language Fundamentals, CELF (average range: 86–115), EVT (standard score reported), TROG (average range: 86–115).

### Table 2

Early cognitive profile.

| WPPSI-R (4.11 years) | Performance score | Verbal score | Full scale score | Percentile rank |
|----------------------|-------------------|--------------|------------------|----------------|
| 97 (average)         | 88 (low average) | 91 (average) | 42               |
| 97 (average)         | 88 (low average) | 91 (average) | 21               |
| 97 (average)         | 88 (low average) | 91 (average) | 27               |

**Abbreviations:** WPPSI-R, Wechsler Preschool and Primary Scale of Intelligence — Revised; WPPSI-III, Wechsler Preschool and Primary Scale of Intelligence — 3rd Edition (UK).

### Table 3

Primary (mainstream) school cognitive profile.

| WISC-IV | Age 7.7 years | Age 8.5 years | Age 9.11 years | Age 12.10 years |
|---------|---------------|--------------|---------------|----------------|
| Verbal comprehension | 83 (low average) | 87 (low average) | 79 (borderline) | 73 (borderline) |
| Perceptual reasoning | 82 (low average) | 77 (borderline) | 67 (extremely low) | 69 (extremely low) |
| Working memory | 62 (extremely low) | 77 (borderline) | 74 (borderline) | 74 (borderline) |
| Processing speed | 68 (extremely low) | 85 (low average) | 83 (low average) | 78 (borderline) |
| Full scale IQ | 70 (borderline) | 77 (borderline) | 70 (borderline) | 68 (extremely low) |

**Abbreviation:** WISC-IV, Wechsler Intelligence Scale for Children — 4th Edition (UK).
2.2. Genetics

2.2.1. Exome sequencing methods

Ethics committee approval from Temple St. Children’s University Hospital, Dublin, Ireland and informed parental consent were obtained to collect clinical data and perform whole exome sequencing on the proband’s extracted DNA. Whole exome sequencing was performed using the Agilent SureSelectXT All Exon V4 + UTR enrichment kit (Agilent Technologies, Santa Clara, USA) and sequenced on an Illumina HiSeq platform (Illumina Inc., San Diego, California, USA). Data cleaning and variant calling were performed using standard methods (see Supplemental Data). As this is a very rare disorder, all variants with a minor allele frequency of >1% were excluded as candidate disease variants. Variants present in previously reported epilepsy genes were noted. Primers were designed to validate variants of interest, and inheritance was assessed by Sanger sequencing.

2.2.2. Exome sequence results

Variants with a MAF of <1% were found in 2 genes previously associated with epilepsy; SCN9A (A1964G) and CPA6 (C46A). A novel variant was also identified in SCN1 (C521T), a known epilepsy-modifier gene (Table 6). All variants were confirmed by Sanger sequencing and inheritance tested. The variants in SCN9A and CPA6 were maternally inherited while the variant in SCN1 was paternally inherited (see Supplemental Data for further results of these variants).

3. Discussion

ABPE is considered within the spectrum of the idiopathic focal epilepsies with CSWS now increasingly referred to as the “epilepsy aphasia spectrum” [2]. This longitudinal study of a patient with ABPE (seizure/EEG/pharmacotherapy) and detailed correlative neuropsychological follow-up over several years has not, to our knowledge, been previously reported, although various degrees of intellectual disability have been described in this epilepsy “syndrome” (also now known as pseudo-Lennox syndrome) since Aicardi and Chevrie’s [3] initial reports.

In this case, there was clear evidence of an acquired oromotor disorder (“epileptic anterior opercular syndrome”) followed by an acquired complex language disorder, characterized by lexical semantic deficits in both comprehension and expression but not the typical acquired verbal auditory agnosia of LKS. These problems could be localized initially to the anterior sylvian region with corresponding epileptiform activity and, later, to the posterior sylvian area, suggesting that different foci were active at successive periods of the epileptic process within the perisylvian region (Supplemental Table 1). A concomitant cognitive deterioration was also documented, as well as an apparently acquired autistic spectrum disorder. The cognitive deterioration occurred during the period of CSWS and then improved slightly over the subsequent years to a stable below-average IQ. In follow-up studies of children with CSWS, similar cognitive outcomes have been reported, but the specific language problems in this case appear unique [4]. While the cognitive and social communicative deficits may have contributed to the low language performances, neither can explain the specific, more severe language disorder which should be considered a separate manifestation of the epileptic disease involving other networks.
The apparent acquired “epileptic” nature of the social communicative deficit (autistic spectrum) is less clear than that of the other deficits observed in this case. However, early social communicative development before the epilepsy started (23 months) and in the subsequent 1 to 2 years preceding the marked worsening of the epilepsy did not arouse the clinical suspicion of a pervasive developmental disorder, although subtle features may have been present (hyperlexia, repetitive behavior, specific interests). It is possible therefore (as seen in some children with acquired epileptic aphasia who have preexisting developmental language deficit) that a mild pervasive developmental disorder was already present and unmasked further or exacerbated, as the epilepsy worsened. The borderland between specific language impairment (formerly “pragmatic language disorder”) and autistic disorders is not clearly defined, and features of either disorder can become more obvious over time or occasionally disappear [5], suggesting shared and overlapping networks that may be immature or deficient within this group of epilepsies. Further similar prospective case studies may clarify whether there are acquired, potentially drug responsive, and reversible epileptic “autistic regression” patterns and their context within the spectrum of language disorders [6].

While very few reports of children with ABPE or focal epilepsy with CSWS describe specific types of language impairment correlated with the active epilepsy, the contribution of inherited or genetic factors (besides the epileptic process per se) to such outcomes is even less well understood [22]. Recently, the identification of GRIN2A variants in a small subset of familial and sporadic cases of idiopathic focal epilepsy, particularly those with CSWS, has been a significant breakthrough [7,8,9]. The genotypic expression of most idiopathic focal epilepsies may reflect multiple genes and/or the presence of gene modifiers contributing to the various phenotypes, but for the most part, the molecular mechanisms have yet to be elucidated.

The proband was found to harbor variants in several important epilepsy genes. One variant (p.K655SR) occurred in SCN9A, a sodium channel gene causally associated with febrile seizures, afebrile seizures, and refractory focal epilepsy [10]. SCN9A variants may also play a role in Dravet syndrome [11], and the same p.K655SR variant identified in the proband has also been found in an individual with genetically generalized (formerly idiopathic generalized) epilepsy and febrile seizures and in two patients with Dravet syndrome, one of whom also harbored a de novo SCN1A variant [10]. While the role of sodium channelopathy genes is established in epilepsy, our understanding of the effects of modifier genes (including sodium channel genes themselves) is still evolving [10,11,12]. SCN1M (sodium channel modifier 1) is one of the few significant epilepsy-modifier genes known and has been shown to modify the splicing of SCN8A, a gene responsible for epileptic encephalopathy in humans [13]. In the proband, the SCN1M variant may have contributed to the biological effect of variant in SCN9A and/or CPA6 (carboxypeptidase A6), a nonion channel protein that displays a wide range of neuronal functions in the brain [14]. Variants in CPA6 have been identified in patients with temporal lobe epilepsy and febrile seizures [14,15] including the same variant (p.P16T) present in this proband. Other rare, novel, and previously reported variants in known epilepsy genes including those associated with “rolandic epilepsy”, CSWS, and ABPE (i.e., epilepsy aphasia spectrum) were not identified in the proband (Supplemental Data) [7,8,9,16–22].

Although already shown to play important pathogenic roles in epilepsy and predicted to significantly alter protein function, the p.K655SR and p.P16T variants were both detected in the proband’s asymptomatic mother and have been found in a very small number of control individuals (NHBLI Exome Sequencing Project). Incomplete penetration, where-by some individuals carry an allele but do not display a disease trait, has been previously reported in various epilepsies including idiopathic focal epilepsies associated with GRIN2A variants [9]. Furthermore, polygenic heterogeneity for this complex spectrum of epilepsies and the contributing mechanisms of the underlying genotype are likely to emerge as further cases are analyzed using next generation sequencing [22].

In conclusion, the idiopathic focal epilepsies with CSWS, including ABPE, may affect development or lead to regression in any/all of motor, language, cognitive, and social communication functions. We detected potentially pathogenic variants in relevant epilepsy genes in a boy with ABPE, broadening our understanding of the molecular mechanisms contributing to such disorders. While such complex genomic variations may play a role in many neurodevelopmental disorders without epilepsy or predated epilepsy onset, this detailed longitudinal follow-up of a child with ABPE, characterized by deterioration, stabilization, and improvement in certain aspects of motor, cognitive, language, and social communication dysfunctions, correlated with the onset and course of the specific epilepsy syndrome. Thus, it seems that the epileptic discharges per se significantly contribute to such manifestations within this complex group of genetically determined epileptic disorders. Similar prospective longitudinal follow-up studies are important to understand new or specific disordered profiles (e.g., lexical semantic deficit in this case), hidden within this spectrum of epilepsies, and to enhance our understanding of the underlying developmental neuronal networks involved in their pathogenesis.

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**Disclosures**

This paper has been prepared in line with the journal guidelines. We confirm that we have read the Journal’s position on issues involved in ethical publication and affirm that this report is consistent with those guidelines.

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**Appendix A. Supplementary data**

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