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RESEARCH ARTICLE

Clinical and Neurophysiologic Phenotypes in Neonates With *BRAT1* Encephalopathy

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Abstract

Background and Objectives

BRAT1 encephalopathy is an ultra-rare autosomal recessive neonatal encephalopathy. We delineate the neonatal electroclinical phenotype at presentation and provide insights for early diagnosis.

Methods

Through a multinational collaborative, we studied a cohort of neonates with encephalopathy associated with biallelic pathogenic variants in *BRAT1* for whom detailed clinical, neurophysiologic, and neuroimaging information was available from the onset of symptoms. Neuropathologic changes were also analyzed.

Results

We included 19 neonates. Most neonates were born at term (16/19) from nonconsanguineous parents. 15/19 (79%) were admitted soon after birth to a neonatal intensive care unit, exhibiting multifocal myoclonus, both spontaneous and exacerbated by stimulation. 7/19 (37%) had arthrogryposis at birth, and all except 1 progressively developed hypertonia in the first week of life. Multifocal myoclonus, which was present in all but 1 infant, was the most prominent manifestation and did not show any EEG correlate in 16/19 (84%). Video-EEG at onset was unremarkable in 14/19 (74%) infants, and 6 (33%) had initially been misdiagnosed with hyperekplexia. Multifocal seizures were observed at a median age of 14 days (range: 1–29). During the first months of life, all infants developed progressive encephalopathy, acquired microcephaly, prolonged bouts of apnea, and bradycardia, leading to cardiac arrest and death at a median age of 3.5 months (range: 20 days to 30 months). Only 7 infants (37%) received a definite diagnosis before death, at a median age of 34 days (range: 25–126),

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Glossary

GOF = gain of function; **GLRA1** = glycine receptor gene; **ICU** = intensive care unit; **NADH** = nicotinamide adenine dinucleotide; **NeuN** = neuronal nuclear protein; **NGS** = next-generation sequencing; **SDH** = succinate dehydrogenase; **SNV** = single-nucleotide variant; **vEEG** = video-EEG monitoring.

and almost two-thirds (12/19, 63%) were diagnosed 8 days to 12 years postmortem (median: 6.5 years). Neuropathology examination, performed in 3 patients, revealed severely delayed myelination and diffuse astrogliosis, sparing the upper cortical layers.

Discussion

BRAT1 encephalopathy is a neonatal-onset, rapidly progressive neurologic disorder. Neonates are often misdiagnosed as having hyperekplexia, and many die undiagnosed. The key phenotypic features are multifocal myoclonus, an organized EEG, progressive, persistent, and diffuse hypertonia, and an evolution into refractory multifocal seizures, prolonged bouts of apnea, bradycardia, and early death. Early recognition of *BRAT1* encephalopathy allows for prompt workup, appropriate management, and genetic counseling.

BRAT1 encodes the breast cancer 1–associated ataxia telangiectasia mutated activation–1 protein[1] that plays a role in DNA repair, cell growth, apoptosis, and cell signaling.[2] *BRAT1* mRNA is ubiquitously expressed.[3] In the brain, high levels of BRAT1 protein are detected in the cortex,[2] suggesting its involvement in neuronal function and development.[4] Biallelic loss of function of *BRAT1* has recently been associated with a severe neonatal encephalopathy, defined as lethal neonatal rigidity and multifocal seizure syndrome (Online Mendelian Inheritance in Man 614498).[5] Children with a later onset and milder phenotype have also been reported.[6-10] This study focuses on the neonatal presentation of *BRAT1* encephalopathy. Few single-case reports, small series, and a comprehensive review of the literature have been published so far, describing intractable seizures, hypertonia, microcephaly, severe developmental delay, and early death.[11-19] Yet, most neonates were diagnosed only later in life or after death, and the reported electroclinical data were often limited to a late stage.[5,13-15,20] We aimed to define the neonatal electroclinical phenotype of *BRAT1* encephalopathy to improve early recognition and allow early diagnosis in the neonatal intensive care unit (ICU), orienting workup and management and providing families with appropriate counseling.

Methods

Through a collaborative including European, North American, and Saudi Arabia centers, we conducted a large-scale survey of 60 level 3 and 4 neonatal ICUs, pediatric ICUs, and pediatric neurology units, searching for patients with pathogenic biallelic variants in *BRAT1* and neonatal onset of symptoms for whom detailed clinical information and video-EEG (vEEG) since onset were available for review. Based on the electroclinical features of our first newborns diagnosed with *BRAT1* variants (patients 1–3, Table 1), a questionnaire was developed and sent to all referring physicians. Clinical, vEEG, MRI and genetic data were collected retrospectively. Actual vEEG recordings were reviewed by experienced epileptologists with expertise in neonatal EEG (M.R.C., R.D., T.G., R.G., P.S., and F.R.) together with the referring physician, either a child neurologist or a neonatologist.

BRAT1 variants were identified using next-generation sequencing (NGS) tests and classified as likely pathogenic or pathogenic using American College of Medical Genetics criteria.[21] Postmortem brain histopathologic examinations were performed using hematoxylin-eosin, Luxol fast blue periodic acid Schiff stainings, and antibodies detecting glial fibrillary acidic protein, neuronal nuclear protein (NeuN), and cluster of differentiation 163. Skeletal muscle biopsy was evaluated using nicotinamide adenine dinucleotide (NADH), succinate dehydrogenase (SDH), and cytochrome C oxidase/SDH (COX/SDH) stainings.

Standard Protocol Approvals, Registrations, and Patient Consents

The study was approved by the Ethical Committee of Saint-Luc University Hospital, and a waiver for informed consent was granted. Written informed consent, including authorization for the reproduction of video images, was obtained from family members.

Data Availability

Deidentified participants' data supporting the findings of this study are available for an indefinite period of time from the corresponding author. Data can be accessed by professionals for research purposes by contacting the corresponding author directly.

Results

Nineteen patients were included in the study (13 males). Two patients were previously published (patients 1 and 2).[22] Clinical, neurophysiologic, and neuroimaging features and their evolution are summarized in Table 1. All patients were born of nonconsanguineous parents. Most were at term, except for patients 6, 12, and 17 who were preterm. Seven patients had intrauterine growth restriction. Mother of patient 8 had reduced fetal movements during the last weeks of pregnancy, and the mothers of patients 9 and 10 had polyhydramnios and oligohydramnios, respectively.

Table 1 Electroclinical Presentation, Imaging, Treatment, and Evolution of 19 Neonates With *BRAT1* Encephalopathy

Pt: Sex	GA at birth	AS	BW (g)	HC (cm)	Race and ethnicity	Clinical findings in the neonatal period	Video-EEG evolution[a]	ASM	Imaging	Evolution	Death
1:M	37 wk	8/8/9	2,165	31.9 (P30)	White	MF myoclonus, hypertonia	8,17 d: nl BG, non-E myoclonus 23, 30 d: nl BG, MF spikes, clonic, myoclonic, E-only sz 60 d: MF status epilepticus	LEV, VPA–partial effect; PB, MDZ, CZP, PHT, FEN, LOR, ZNS, B6, P5p–no effect	29 d: nl	no milestones reached, acquired microcephaly	2 mo: central apnea, transition to comfort care
2:F	40 wk 1 d	7/8	2,515	32 (P4)	White, Native American, Latino	MF myoclonus, hypertonia, recurrent apneas	1 d: nl BG, non-E myoclonus 20, 60 d: nl BG, MF spikes, MF clonic, myoclonic and E-only sz, ictal apneas	PB, LEV, MDZ, CZP, CLB, FOS, KD, LOR, morphine, TPM, P5p, B6, B9–no effect	2 d: nl 28 d: microcephaly, low parenchymal volume	no milestones reached, acquired microcephaly, no eye contact	2.5 mo: central apnea, transition to comfort care
3:M	40 wk 1 d	9/10	4,000	34 (P43)	Latino	MF myoclonus, hypertonia, recurrent apneas	9 d: nl BG, F spikes, non-E myoclonus 30 d: nl BG, myoclonic sz	PB, LEV, CZP, morphine–no effect	11 d: nl 15 d: nl	no milestones reached, acquired microcephaly	3 mo: central apnea, transition to comfort care
4:M	39 wk 3 d	8/9	3,115	33.7 (P43)	NA	MF myoclonus, arthrogryposis, recurrent apneas	4 d: nl BG, non-E myoclonus, E-only sz 54 d: discontinuous BG	CZP, CBZ, CLB,–partial effect; PB, LEV, MDZ, PHT, KD, B6, B9, P5p–no effect	4 d: nl	no milestones reached, acquired microcephaly	12 mo: central apneas
5:F	39 wk	NA	SGA	<P3	White	MF myoclonus, hypertonia, recurrent apneas, microcephaly	9 d: discontinuous BG, MF spikes, non-E myoclonus 14 d: E-only sz 23, 63 d: MF clonic, myoclonic sz, status epilepticus	LEV, MDZ, CZP, CBZ, PPF–partial effect; PB, VPA–no effect	18 d: microcephaly 60 d: cerebral, cerebellar atrophy	no milestones reached, head growth arrest	2.5 mo: central apnea, sepsis
6:F	34 wk	6/8	1,460	32 (P81)	White	38 wk corrected age: nl exam 40 wk corrected age: MF myoclonus, hypertonia, recurrent apneas	37 d: nl BG, non-E myoclonus, MF clonic sz 50 d: discontinuous BG 60 d: burst-suppression	PB, LEV, MDZ, PHT, CBZ, B6, B9–partial effect	45 wk corrected age: brain atrophy	no milestones reached, acquired microcephaly	4.5 mo: central apnea, sepsis
7:M	38 wk 5 d	4/5/5	2,050	33 (P33)	Arab—Maghrebis	MF myoclonus, hypertonia, respiratory distress	1 d: discontinuous BG, MF spikes, non-E myoclonus 4 d: MF clonic, E-only sz	PB, LEV, MDZ, PHT, B6–no effect	4 d: microcephaly	no milestones reached, acquired microcephaly	20 d: central apnea, transition to comfort care
8:M	37 wk	7/9	2,400	32 (P30)	White—Italian	Hypertonia, poor suction, no eye contact 23 d: MF myoclonus	3 d: nl BG, F spikes 13 d: discontinuous BG, MF spikes, E-only sz 23 d: non-E myoclonus 18, 40 d: MF clonic, myoclonic, behavioral arrest sz 60 d: E-only sz	PB, CZP, LEV, MDZ, B6, B9 P5p–no effect	4 d: nl 50 d: cerebral atrophy	no milestones reached, acquired microcephaly, no eye contact	4 mo: central apnea, transition to comfort care
9:F	37 wk 5 d	4/6/7	2,400	29.4 (<P3)	White—Romanian	MF myoclonus, hypertonia, recurrent apneas, microcephaly	3 d: burst-suppression, non-E myoclonus, MF clonic sz, ictal apneas 6 d, 11 mo: low amplitude discontinuous BG, F sharp waves	CLB, PHT, TH–partial effect; PB, LEV, MDZ, TPM, B6–no effect	7 d: pachygyria 6 mo: cerebral and cerebellar atrophy, basal ganglia hyperintensity	no milestones reached, head growth arrest, no eye contact, no feeding ability	19 mo: central apnea
10:M	38 wk	NA	NA	33.5 (P60)	White—Italian	MF myoclonus, hypertonia	3 d: nl BG, non-E myoclonus 30 d: slow BG, MF spikes, MF clonic sz, ictal apneas	PB—partial effect; other ASMs—no effect	3 d: nl 12 d: microcephaly, delayed myelination, cerebellar atrophy	no milestones reached, acquired microcephaly	30 mo: central apnea

Continued

Table 1 Electroclinical Presentation, Imaging, Treatment, and Evolution of 19 Neonates With *BRAT1* Encephalopathy *(continued)*

Pt: Sex	GA at birth	AS	BW (g)	HC (cm)	Race and ethnicity	Clinical findings in the neonatal period	Video-EEG evolution[a]	ASM	Imaging	Evolution	Death
11:M	41 wk	4/6/8	2,720	<P3	White—Belgian, Italian	MF myoclonus, arthrogryposis, microcephaly	4 d: nl BG, non-E myoclonus, F spikes 3 mo: nl BG, non-E myoclonus	MDZ, CZP, VPA, FEN–partial effect; PB, LEV, B6–no effect	10 d: nl 60 d: nl	no milestones reached, head growth arrest	3.5 mo: central apnea, transition to comfort care
12:M	31 wk 5 d	8/9/10	1,665	29.5 (P53)	White	Hypertonia, recurrent apneas 11 d: MF myoclonus	4 d: nl BG 24 d: nl BG, rare sharp waves, non-E myoclonus, clonic, myoclonic sz, ictal apneas 46, 62 d: nl BG, MF spikes	PB, CZP, VPA, DZP, OXC, B6–no effect	26 d: pachygyria	no milestones reached, acquired microcephaly, no eye contact	3.7 mo: ictal apnea and central apnea
13:F	37 wk 6 d	8/9/10	2,740	32 (P20)	White	MF myoclonus, arthrogryposis, recurrent apneas	3 d: discontinuous BG, F sharp waves, non-E myoclonus 20 d: discontinuous BG, F spikes, MF clonic, myoclonic sz 82 d: slow BG, MF sharp waves	PB, CZP, KD, CLH, VGB, ACTH, B6, B9–no effect	10 d: fronto-temporal pachygyria	no milestones reached, acquired microcephaly, no eye contact	3.8 mo: central apnea
14:M	38 wk 3 d	8/9/9	2,680	32.5 (P24)	White	MF myoclonus, arthrogryposis, recurrent apneas	9 d: nl BG, myoclonic sz 13 d: nl BG, clonic sz 26 d: discontinuous BG, MF sharp waves	PB, LEV, MDZ, PHT, CBZ, CLB, VPA, FOS, CLH, TPM, ZNS, VGB, CBD, LTG, B6, B9, P5p–no effect	17 d: pachygyria	no milestones reached, acquired microcephaly, no eye contact	4.3 mo: central apnea
15:M	41 wk 1 d	9/10	4,242	36 (P85)	White—Italian	Hypotonia, recurrent apneas	16 d: nl BG, MF spikes, F clonic sz 96 d: slow BG, behavioral arrest sz, ictal apneas	MDZ–effective; PB, PHT, FOS–partial effect; CLB, B6–no effect	17 d: nl 84 d: nl	no milestones reached, acquired microcephaly	4.5 mo: central apnea
16:M	39 wk 2 d	6/6	2,280	32 (P8)	White—Italian	MF myoclonus, arthrogryposis	1 d: burst-suppression, myoclonic sz 8 d: asynchronous burst-suppression, clonic sz	MDZ, FOS–partial effect; PB, LOR, KET, P5p, B6–no effect	7 d: frontal pachygyria	no milestones reached, acquired microcephaly	40 d: central apnea
17:M	31 wk 5 d	3/5/9	1,490	28.5 (P21)	White—Belgian	MF myoclonus, recurrent apneas	2 d: nl BG, non-E myoclonus, non-E apneas 10 d: nl BG, MF spikes 15 d: nl BG, clonic, myoclonic sz, ictal apneas 30 d: nl BG, E-only sz	LEV–partial effect; PB, MDZ, FEN, B6–no effect	32 d: microcephaly	no milestones reached, acquired microcephaly	35 d: central apnea, transition to comfort care
18:M	38 wk 4 d	10/10	2,280	NA	White	MF myoclonus, arthrogryposis, recurrent apneas	2 d: nl BG, non-E myoclonus, E-only sz, 15 d: continuous, slow BG	PB–partial effect	10 d: brain atrophy	no milestones reached	17 d: central apnea, transition to comfort care
19:F	39 wk	10/10	2,600	33.5 (P44)	White	MF myoclonus, arthrogryposis	4 d: nl BG, non-E myoclonus, clonic sz 40 d: continuous, slow BG, MF spikes, myoclonic sz	PB, LEV, CBZ, morphine, TPM, B6, B9, P5p–no effect	20 d: microcephaly	no milestones reached, acquired microcephaly	45 d: central apnea

Abbreviations: ACTH = Adrenocorticotropic hormone; AS = Apgar score; ASM = antiseizure medication; B6 = pyridoxine; B9 = folic acid; BG = background; BW = birth weight; CBD = cannabidiol; CBZ = carbamazepine; CLB = clobazam; CLH = chloral hydrate; CZP = clonazepam; DZP = diazepam; EEG = electroencephalography; E-only = electrographic-only; F = focal; FEN = fentanyl; FOS = fosphenytoin; GA = gestational age; HC = head circumference; KET = ketamine; KD = ketogenic diet; LEV = levetiracetam; LOR = lorazepam; MDZ = midazolam; MF = multifocal; nl = normal; non-E = non-epileptic; OXC = oxcarbazepine; P = percentile; PB = phenobarbital; PHT = phenytoin; P5p = pyridoxal-5-phosphate; PPF = Propofol; Pt = patient; SGA = small for gestational age; sz = seizure; TH = thiopental; TPM = topiramate; VGB = vigabatrin; VPA = valproic acid; ZNS = zonisamide.
[a] Electroclinical features are mentioned according to the age of appearance.

Clinical Presentation

Fifteen (79%) neonates were admitted to the neonatal ICU soon after birth for multifocal myoclonus, which occurred spontaneously and was exacerbated by tactile stimuli. Two neonates (patients 8 and 12) were admitted for prolonged episodes of apnea and diffuse hypertonia and developed multifocal myoclonus at 23 and 11 days of life, respectively. One neonate (patient 6) born at 34 weeks gestation initially showed an age-appropriate neurologic examination and was discharged home at 38 weeks corrected age. He was readmitted 2 weeks later at 37 days of life for multifocal myoclonus and apneic episodes. Only 1 infant in our cohort (patient 15) had not manifested multifocal myoclonus previously and was admitted for episodes of apnea and focal clonic seizures at 16 days of life. Twelve (63%) neonates experienced early bouts of unexplained apnea. Seven (37%) neonates had arthrogryposis. Two (patients 5 and 9) had congenital microcephaly.

All patients underwent comprehensive metabolic workup, including serum and CSF amino acids, CSF organic acids, and urine organic acids, which were uninformative. All neonates showed a rapid progression of symptoms, with head growth arrest and acquired microcephaly for those with normal head circumference at birth. By the end of the first week of life, most (18/19) exhibited persistent and diffuse hypertonia; by the end of the first month, all experienced prolonged episodes of central apnea and bradycardia requiring respiratory support. All required enteral nutrition and failed to reach developmental milestones. All patients died at a median age of 3.5 months (range: 20 days to 30 months).

vEEG Analysis

EEG recordings were obtained by digital acquisition using the international 10/20 system modified for neonates, including ECG, respiratory, and EMG traces in most patients. All infants underwent prolonged and repeated vEEG monitoring sessions from the first days of life. The median age during the first vEEG was 4 days (range: 1–37). The first vEEG demonstrated an age-appropriate background in 14/19 (74%) patients, including the 3 preterm infants, an excessively discontinuous background in 3/19 (patients 5, 7, and 13) patients, and a burst-suppression pattern in 2/19 (patients 9 and 16) patients. Nine (47%) patients had no interictal abnormalities at the onset. Ten (53%) patients showed focal (frontal and temporal-occipital) or multifocal epileptiform abnormalities.

Among the 15 infants presenting with multifocal myoclonus, 13 (87%) had no EEG correlate for the myoclonus, which was nonepileptic (Video 1 and Video 2, links.lww.com/WNL/C568, links.lww.com/WNL/C569). Myoclonus was spontaneous and subcontinuous in all infants and was exacerbated by tactile stimuli (Video 3, links.lww.com/WNL/C570). None manifested stimuli-induced myoclonus only. The coexistence of a normal EEG background and nonepileptic myoclonus led to a misdiagnosis of hyperekplexia in one-third of the infants. By the end of the neonatal period, most infants (16/19, 84%) had progressed toward subcontinuous nonepileptic myoclonus while awake and sleeping, which persisted until death, and represented an extreme source of discomfort for patients, parents, and healthcare professionals.

The median age at seizure onset was 14 days (range: 1–29). Seizures eventually occurred in most patients (18/19) and consisted of clonic (15/19, 79%), multifocal myoclonic (11/19, 58%), electrographic-only (8/19, 42%), ictal apnea (6/19, 32%), and behavioral arrest (2/19, 11%). The seizure burden varied from 1 in 48 hours to 5 per hour.

The worsening of symptoms was paralleled by deterioration of EEG background in 12/19 (63%) patients with a discontinuous low-voltage tracing and the emergence of multifocal spikes or a burst-suppression pattern. The frequency and intensity of nonepileptic myoclonus, independently from the seizures themselves, led to escalating doses of medications, including high-dose benzodiazepines, which could have at least partly contributed to the discontinuity of the EEG background and burst-suppression pattern. In 7/19 (37%) patients, background EEG activity remained well-organized (eFigure 1, links.lww.com/WNL/C566).

Treatment

All patients were unsuccessfully treated with multiple antiseizure medications (ASMs), including drugs for nonepileptic myoclonus. Phenobarbital was the most commonly used ASM, with all patients receiving multiple loading doses. Nine patients were trialed with clonazepam, with no effect. Thirteen received levetiracetam, with transient improvement in 3. Thirteen received midazolam, with transient reduction of seizure frequency in 7. However, in 6 infants, high-dose midazolam continuous infusion allowed to mitigate the discomfort. Five received valproic acid, with transient reduction of seizure frequency in 2; the medication was discontinued in 1 patient (patient 12) because of an isolated increase in gamma-glutamyl transferase. Fifteen were trialed with various vitamins, including pyridoxine, pyridoxal phosphate, and folic acid, without improvement. Ketogenic diet was ineffective in the 3 infants in whom it was trialed. Morphine and synthetic opioids proved to be ineffective in reducing the discomfort associated with multifocal myoclonus and hypertonia.

MRI Findings

All infants had brain MRI, performed at a median age of 10 days (range: 2–77), showing a normal brain structure in 8 (42%). The MRI demonstrated pachygyria in 5 infants (eFigure 2, links.lww.com/WNL/C567), microcephaly in 4, and brain atrophy in 2. A follow-up MRI was performed in 6 patients with previously normal imaging, revealing cerebral and cerebellar atrophy in 3 (patients 2, 8, 10) and no changes in the remaining 3 patients (patients 3, 11, 15).

Genetic Investigations

Seven (37%) infants received a genetic diagnosis before death, at a median age of 34 days (range: 25–126), leaving the majority (12/19) diagnosed postmortem on stored DNA samples, after a median lapse of 6.5 years (range: 8 days to 12 years). Five neonates were initially diagnosed with hyperekplexia, thus

genetic testing was at first targeted on hyperekplexia genes. Table 2 describes each patient's distinct genotype. *BRAT1* variants were identified by targeted panels in 9 (47%) patients, whole-exome sequencing in 7 (37%), and whole-genome sequencing in 1. In 2 infants (patients 1 and 17), clinical recognition of the phenotype allowed for targeted molecular diagnosis by single-gene filtered NGS. Sixteen different variants were identified (Figure 1): 1 missense, 1 splice site, 3 nonsense, 9 frameshifts, and 2 deletions. Eight patients carried homozygous variants, and 11 were compound heterozygous carriers. The only missense variant occurred in combination with a frameshift variant. Five SNVs have been previously reported in published patients.[19] 11 variants are unpublished: 3 nonsense SNVs–p.(Glu105*), p.(Tyr733*), and p.(Glu522*); 5 frameshifts SNVs–p.(Cys401*), p.(Trp191Cysfs*28), p.(Leu77Thrfs*114), p.(Val23Alafs*5), and p.(Ser798Argfs*82); 1 splice site indel–c.431-10_431-7del-insTGGGTAGGG, (IVS4-10_IVS4-7del delCCCT-insTGGGTAGGG), 2 copy number variants–one 11.5 kb deletion involving exons 1–3, and 1 whole gene deletion. Two SNVs were recurrent among unrelated patients: p.(Val214Glyfs*189) in 10 probands, 3 of whom were siblings, and p.(Tyr733*) in 2 unrelated homozygous patients.

Family History

Patients 12, 13, and 14 and patients 18 and 19 were siblings (Figure 2). After diagnosis, the parents of patient 2 underwent 3 in vitro fertilization procedures with preimplantation genetic testing, which demonstrated that 8 of 8 embryos and the fetus of a subsequent spontaneous pregnancy were affected by biallelic variants. Because the maternal aunt was a heterozygous carrier, the parents elected to use an oocyte donor for their next pregnancy, which yielded a healthy daughter (Figure 2). Patient 7 had 3 healthy siblings, and patient 8 had 2. Patient 4 had 2 paternal uncles who died of unknown causes at ages 1 and 7 years, respectively. The mother of patient 16 had a history of multiple miscarriages.

Neuropathologic Findings

Autopsy was performed in 3 infants (patients 2, 7, and 12). In patient 2, it revealed an early closure of the anterior fontanelle, posterior slanting of the forehead, and microcephaly (2/3 of expected volume), with a normally convoluted brain. Microscopic analysis demonstrated marked neuronal loss and severe astrogliosis with relative preservation of the upper layer of the cortex, delayed myelination, and loss of myelinated axons with no evidence of microgliosis (Figure 3, A–E). Similarly, severe neuronal loss and astrogliosis were noticed in the CA1-2 regions of the hippocampus (Figure 3, F–H). In patient 7, autopsy revealed microcephaly, micrognathia, and cranial hyperostosis with partial closure of the bregmatic and coronal sutures. Microscopic evaluation of the brain revealed neuronal loss, indistinct gray/white matter junction, delayed myelination with reactive astrogliosis in frontal and parietal cortex, focal loss of Purkinje neurons in the cerebellum, and nuclear pyknosis and neuronal loss with astrogliosis in the hippocampus. In patient 12, neuropathology demonstrated normal gyration and cortical thickness, not confirming the finding of pachygyria on neuroimaging. An indistinct gray/white matter junction was also noted. Microscopic examination showed a cortical organization into 6 layers and normal neuronal density. Skeletal muscle biopsies in patients 2 and 17 showed neurogenic changes. However, normal NADH, SDH, and COX/SDH staining patterns allowed to rule out mitochondrial dysfunction.

Discussion

Early diagnosis of rare diseases is challenging, particularly in neonates with seizures. Neonates are often diagnosed with "neonatal seizures" as a single disease, regardless of the etiology. In the past few years, the delineation of etiology-specific phenotypes has allowed for prompt recognition and targeted treatment for some genetic epilepsies.[22-26] Accordingly, the new classification of seizures in neonates encourages the use of vEEG to differentiate seizures from nonepileptic events and to pay attention to seizure semiology as a relevant element of etiology.[27]

Our data, based on accurate and deep phenotyping of neonates with *BRAT1* encephalopathy, provide a recognizable phenotype of this ultra-rare disorder. Sixteen (84%) of the 19 neonates with *BRAT1* encephalopathy presented with spontaneous multifocal nonepileptic myoclonus, often exacerbated by stimulation and associated with progressive and persistent hypertonia. Background EEG was continuous in 74% (14/19) at onset, and despite the occurrence of seizures, the background pattern remained fairly organized in more than a third of infants (7/19, 37%). EEG features in patients with *BRAT1* encephalopathy have been previously described as ranging from slow background to burst-suppression.[11-13,16,18,28-30] However, in most reported patients, EEG was performed later in the disease course, after seizure onset.[5,11,14,15,17,18,20]

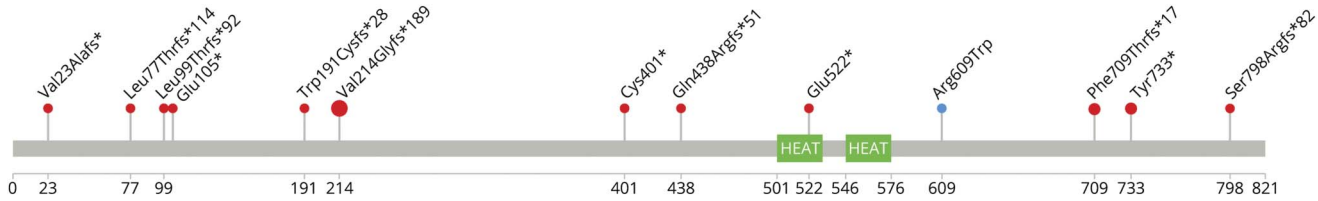
The coexistence of multifocal myoclonus and normal EEG background led to the misdiagnosis of hyperekplexia in one-third of our cohort. Hyperekplexia is an ultra-rare genetic condition either autosomal dominant with high penetrance or autosomal recessive. Three genes are mainly involved: *GLRA1*, *GLRB*, and *SLC6A5*, disrupting inhibitory glycine neurotransmission and resulting in exaggerated startle response with lack of habituation. This disorder has a prevalence of <1/1,000,000, with approximately 100 cases reported in the literature.[31,32] Neonates with hyperekplexia exhibit, in the very first days of life, exaggerated startle responses to tactile or acoustic stimuli and short episodes of diffuse stiffening associated with apnea. Both manifestations are nonepileptic and EEG is normal at onset and throughout the disease.[33] The episodes of stiffening respond to the Vigevano maneuver, consisting in forced flexion of head and legs toward the trunk.[34] Neonates with *SLC6A5* variants may present with episodes of severe life-threatening apnea, while infants with *GLRB* variants may have a more severe phenotype with diffuse hypertonia at birth.[31] However, hypertonia disappears during sleep and improves over time, toward the end of the first year of life. This condition is usually improved by oral clonazepam.[33,35]

Table 2 Genetic Findings in Neonates With *BRAT1* Encephalopathy

Patient ID	Zygosity	Variant description (NM_152,743)	Type	Origin	Variant classification (ACMG)	Reported	Minor allele frequency (GnomAD)	Testing method
1	Compound heterozygous	c.638dup, p.(Val214Glyfs*189)	Frameshift	Mother	Pathogenic	[5-8,11,16,28]rs730880324	0.000246 V2	Single gene filtered NGS
		c.1825C>T, p.(Arg609Trp)	Missense	Father	Likely pathogenic	[10]rs886039312	0.000006569 V3	
2	Compound heterozygous	c.1203_1204del, p.(Cys401*)	Frameshift	Mother	Pathogenic	rs773772842	0.000014 V2	WES
		c.431-10_431-7delinsTGGGTAGGG, (IVS4-10_IVS4-7del delCCCT-insTGGGTAGGG)	Splice site	Father	Pathogenic	novel	NA	
3	Homozygous	c.1313_1314del, p.(Gln438Argfs*51)	Frameshift	Not tested	Pathogenic	[15]rs749240175	0.000066 V2	NGS panel
4	Homozygous	11.5 kb deletion of exons 1-3	Deletion	Both parents	Pathogenic	novel	NA	WGS
5	Compound heterozygous	c.638dup, p.(Val214Glyfs*189)	Frameshift	Not tested	Pathogenic	rs730880324	0.000246 V2	NGS panel
		c.313G>T, p.(Glu105*)	Nonsense	Not tested	Pathogenic	novel	NA	
6	Homozygous	c.2199C>A, p.(Tyr733*)	Nonsense	Both parents	Pathogenic	novel	0.000006570 V3	NGS panel
7	Homozygous	c.573del, p.(Trp191Cysfs*28)	Frameshift	Not tested	Pathogenic	novel	NA	NGS panel
8	Compound heterozygous	c.294dup, p.(Leu99Thrfs*92)	Frameshift	Mother	Pathogenic	[10,19,50]rs776913277	0.000239 V2	NGS panel
		c.638dup, p.(Val214Glyfs*189)	Frameshift	Father	Pathogenic	rs730880324	0.000246 V2	
9	Homozygous	c.638dup, p.(Val214Glyfs*189)	Frameshift	Both parents	Pathogenic	rs730880324	0.000246 V2	WES
10	Homozygous	c.2199C>A, p.(Tyr733*)	Nonsense	Both parents	Pathogenic	novel	0.000006570 V3	WES
11	Homozygous	c.638dup, p.(Val214Glyfs*189)	Frameshift	Both parents	Pathogenic	rs730880324	0.000246 V2	WES
12 13 14	Compound heterozygous	c.228insA, p.(Leu77Thrfs*114)	Frameshift	Mother	Pathogenic	novel	NA	WES
		c.638dup, p.(Val214Glyfs*189)	Frameshift	Father	Pathogenic	rs730880324	0.000246 V2	
15	Homozygous	c.638dup, p.(Val214Glyfs*189)	Frameshift	Both parents	Pathogenic	rs730880324	0.000246 V2	NGS panel
16	Compound heterozygous	c.1564G>T, p.(Glu522*)	Nonsense	Father	Pathogenic	novel	NA	NGS panel
		Whole gene deletion	Deletion	Mother	Pathogenic	NA	NA	
17	Compound heterozygous	c.638dup, p.(Val214Glyfs*189)	Frameshift	Mother	Pathogenic	rs730880324	0.000246 V2	Single gene filtered NGS
		c.2125_2128del, p.(Phe709Thrfs*17)	Frameshift	Father	Pathogenic	[20]rs763527391	0.00002 V2	
18 19	Compound heterozygous	c.65_66insAGCC, p.(Val23Alafs*5)	Frameshift	Not tested	Pathogenic	novel	NA	NGS panel
		c.2392_2393insAAGA, p.(Ser798Argfs*82)	Frameshift	Not tested	Pathogenic	novel	NA	

Abbreviations: ACMG = American College of Medical Genetics; AR = autosomal recessive; NA = not applicable; NGS = next-generation sequencing; WES = whole-exome sequencing; WGS = whole-genome sequencing.

Figure 1 Schematic Representation of the BRAT1 Protein and the Location of 13 Single-Nucleotide Variants Found in Our Patients



Frameshift and nonsense variants are shown in red, while the missense variant is shown in blue.

As also observed in hyperekplexia, neonates with *BRAT1* encephalopathy present with hypertonia and nonepileptic myoclonus exacerbated by stimuli. However, differently from hyperekplexia, in *BRAT1* encephalopathy, myoclonus is spontaneous and subcontinuous, hypertonia persists through wakefulness and sleep, and the bouts of apneas and bradycardia are not related to paroxysmal stiffening but rather represent disease worsening, often leading to death. Moreover, in our study, clonazepam was never effective.

Genetic conditions that can mimic hyperekplexia also include the encephalopathy associated with *KCNQ2* gain-of-function (GOF) variants. These infants, however, present with diffuse hypotonia, often associated with a burst-suppression EEG pattern.[36] Most recently, a severe form of neonatal developmental and epileptic encephalopathy has been associated with *SCN1A* GOF variants, sharing features with *BRAT1* encephalopathy such as neonatal onset, congenital arthrogryposis, and apneas.[37] However, newborns with SCN1A GOF encephalopathy exhibit

Figure 2 Family Trees of Patient 2 and 3 Siblings; Patients 12, 13, 14 and 2 Siblings; Patients 18 and 19

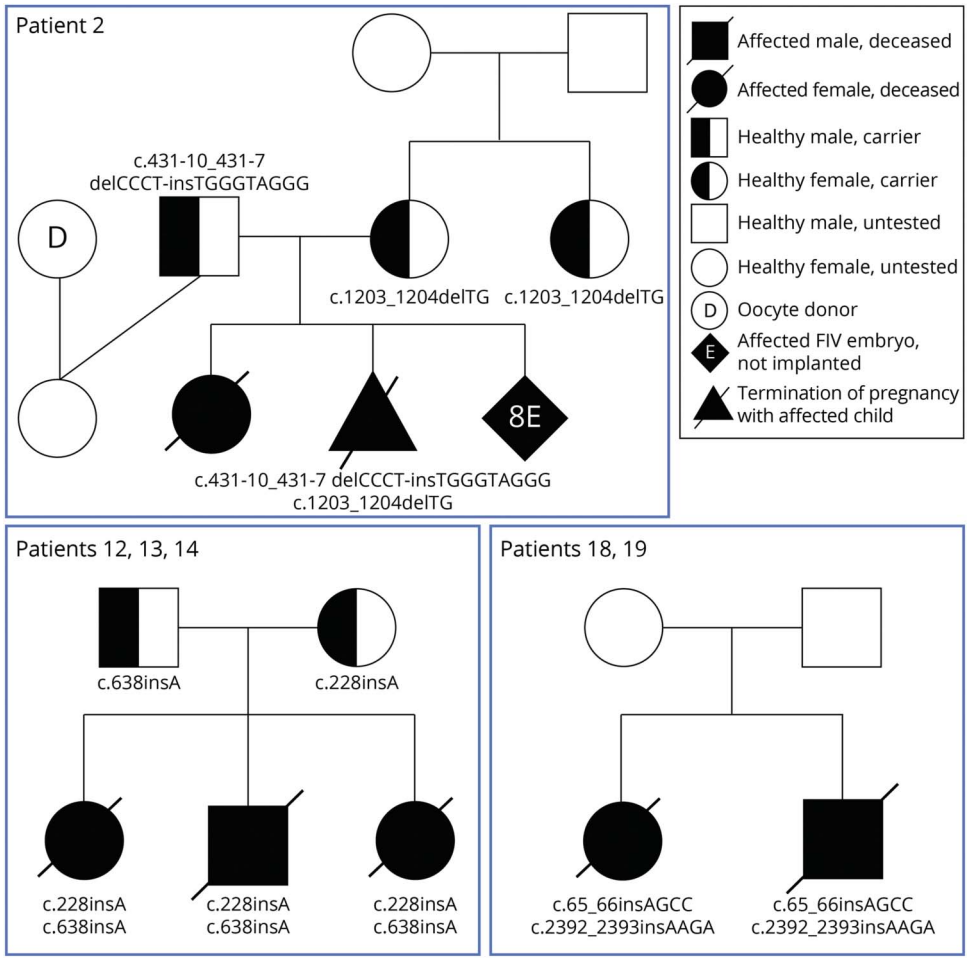
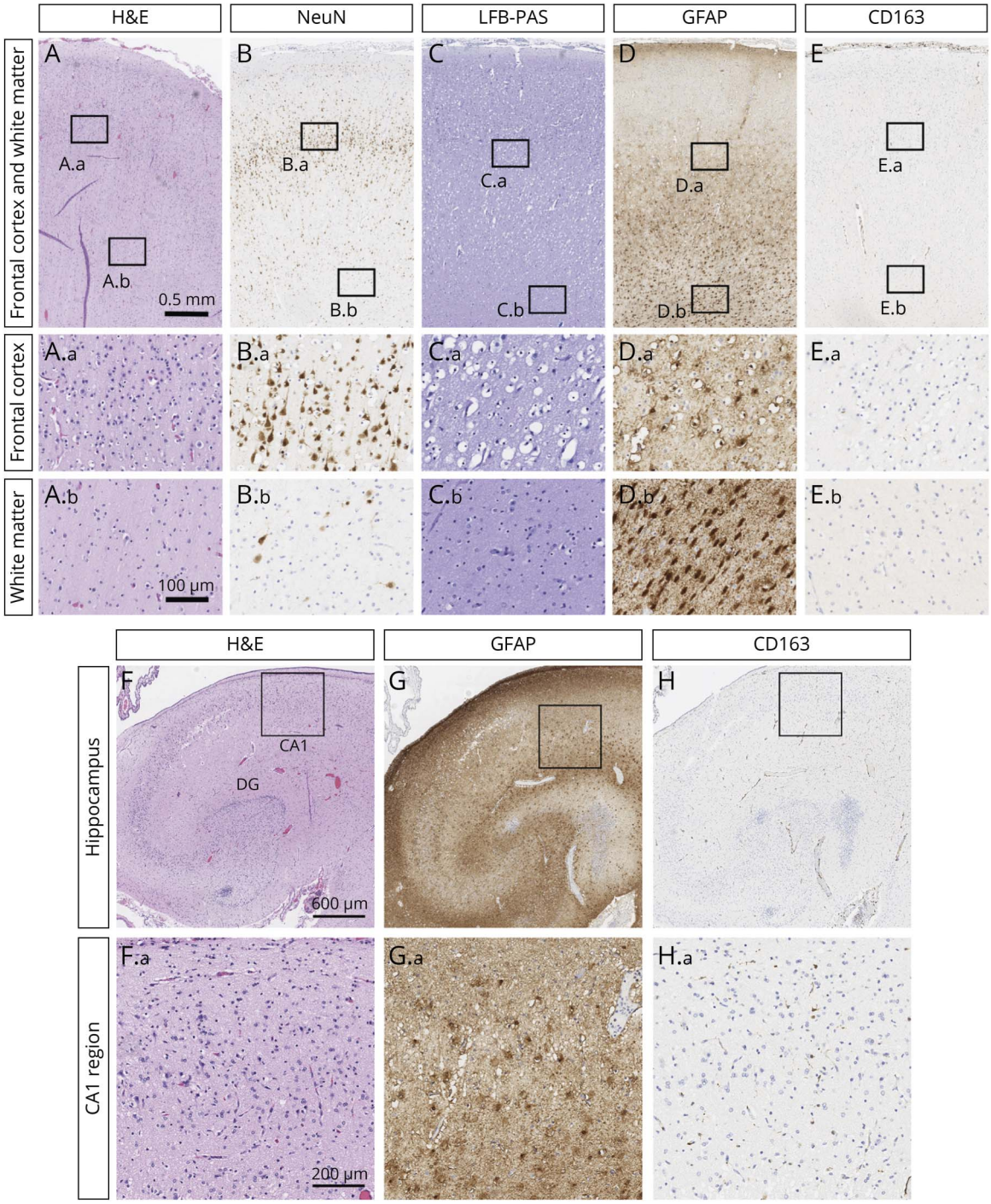


Figure 3 Neuropathologic Findings in Patient 2



Severe loss of neurons and astrogliosis in cerebral cortex, white matter (A, B, C, D, and E), and hippocampus (F, G, H). (A) Hematoxylin and eosin (H&E) sections show indistinct gray-white junction with reduced neuronal density in the frontal cortex (A.a). The subcortical white matter shows a modest increase in astrocytes and decrease in oligodendroglia (A.b). (B) Immunohistochemical stain for neuronal marker NeuN confirms a significant loss of neuron most severely affects the deeper layers of the frontal cortex (layers 5 and 6) (B.a). Scattered NeuN-positive neurons are present in the white matter near the gray-white junction (B.b). (C) LFB-PAS stain shows marked reduction in myelination in the white matter (C.b). In addition, this stain also highlights many cortical neurons with prominent vacuoles (C.a). (D) Immunohistochemical stain for GFAP shows severe astrogliopathy with profound and diffuse astrogliosis throughout the subcortical white matter. The astrogliosis seemed to be extending into the deeper layers (layers 5 and 6) of the cerebral cortex but sparing the more superficial layers (layers 1–3) (D.a). The morphological features of the astrocytes were characterized by abundant cytoplasm and prominent astrocytic processes (D.b). (E) Immunohistochemical stain for CD163 shows a distinct lack of microglia in frontal cortex (E.a) and white matter (E.b). (F) H&E sections show a marked reduction in neuronal density in the dentate gyrus (DG) and CA1 region of the hippocampus (F.a). (G) Immunohistochemical stain for GFAP shows severe astrogliosis in the dentate gyrus and CA1 region of the hippocampus (G.a). (H) Immunohistochemical stain for CD163 shows a very modest increase in microglia in the CA1 region of hippocampus (H.a). CD163 = Cluster of Differentiation 163; GFAP = glial fibrillary acidic protein, LFB-PAS = Luxol fast blue with periodic acid Schiff.

in the very first days of life multiple seizure types including tonic, apneic, and reflex seizures and develop a hyperkinetic movement disorder with choreoathetosis later in life.[37]

Our patients exhibited progressive clinical deterioration. While continuing to manifest nonepileptic myoclonus, almost half of them (9/16) subsequently developed epileptic myoclonus too and other seizure types including focal clonic, multifocal myoclonic, and, less frequently, electrographic-only, and apneic seizures. Both nonepileptic myoclonus and seizures were refractory to multiple treatments. In some infants (6/13) the escalation to continuous midazolam infusion markedly reduced myoclonus and discomfort, thereby facilitating the transition into comfort care, whereas morphine and synthetic opioids were ineffective. Clinical deterioration was paralleled by progressive MRI brain atrophy, suggesting that *BRAT1* encephalopathy is a neurodegenerative disorder.[11,12,18,20]

Published *BRAT1* genotypes show a wide range of variant types including SNVs, indels, copy number variations (deletions and duplications), and splice site disruptions.[38] It has been suggested that the phenotype of *BRAT1*-related disorders depends on the type, localization, domain, and zygosity of the identified variants.[13,16,29,39] In our cohort, all but 1 neonate (patient 1) carried biallelic null variants (splice site, frameshift, nonsense, or deletion), suggesting that the early severe phenotype is associated with complete or near-complete *BRAT1* loss of function, in line with a previous report on phenotype-genotype correlation depending on the variant type.[39]

The frameshift variant p.(Val214Glyfs*189) was identified in 10/19 patients, including 3 homozygous and 7 compound heterozygous. This previously reported variant[5-8,11,16,28] interferes with *BRAT1* nuclear translocation and renders the protein unstable in humans.[5] We observed a discordant clinical presentation in patients 9, 11, and 15 who carried the same homozygous p.(Val214Glyfs*189) variant. Particularly, patient 15 presented with hypotonia and apneic episodes without multifocal myoclonus and eventually developed intractable focal clonic, behavioral arrest, and apneic seizures. Patient 11 had arthrogryposis but no seizures, while patient 9 exhibited the typical phenotype of hypertonia and multifocal myoclonus.

One neonate (patient 1) carried the same compound heterozygous missense variant p.(Arg609Trp) previously reported in a child with a late-onset milder phenotype, combined with a null variant in both.[10] This phenotypic variability even within the same family could be explained, at least partly, by different stages of a neurodegenerative process that starts prenatally.[28] Genetic modifiers may also contribute to phenotypic variability within a family. It is unclear why the phenotypic consequences of pathogenic variants in the *BRAT1* gene may present at different ages. We hypothesize that null variants result in a severe neonatal phenotype caused by complete lack of BRAT1 protein expression, while hypomorphic variants, resulting in a reduced level of protein activity, account for the incomplete penetrance observed in patients with identical genotype and discordant phenotype. Future studies should address transcriptomics in BRAT1 mRNA isolated from patients' fibroblasts and functional characterization of the BRAT1 protein.

BRAT1 is a ubiquitously expressed gene that encodes a protein interacting with the tumor suppressor Breast Cancer gene 1 and binding to ataxia-telangiectasia mutated 1 (ATM1) protein and DNA-dependent protein kinase catalytic subunit (DNA-PKcs). BRAT1 potentially protects the phosphorylated sites of DNA-PKcs and ATM1, playing a role in DNA damage response pathways. It also interacts with mechanistic/mammalian target of rapamycin and is implicated in p53-mediated apoptosis.[1,4,40] BRAT1 is highly expressed in the cortex, suggesting a relevant role in neuronal development.[2] Defective BRAT1 results in developmental arrest, increased apoptosis, progressive atrophy, and neuronal loss.[2,20] Neuropathologic findings in our patients included microcephaly, severe astrogliosis, myelination delay, and loss of myelinated axons, but normal gyration, suggesting that the genetic defect affects primarily brain growth rather than architecture.[11] Of interest, the process seems to spare, at least initially, the upper layers of the cortex, which could account for the relatively organized brain activity on EEG in some infants.[13] We observed a discrepancy between imaging and neuropathology in 1 patient, with pachygyria observed at MRI but normal gyration on neuropathologic examination.

BRAT1 encephalopathy was first described in 2012.[5] Sixteen infants of our cohort were born after 2012, and yet, 9 (9/16, 56%) of them did not receive a definite diagnosis before death. The average time for accurate diagnosis of a rare disease is approximately 4–5 years because rapid diagnostic genomic sequencing and specialist clinical expertise are not widely available.[41] For critically ill neonates, the traditional path is often too long, requiring extensive evaluations that may be invasive and/or costly.[42] Increasingly, exome and genome sequencing are being used to accelerate the diagnostic odyssey in a variety of clinical settings, including the neonatal ICU.[43,44] The diagnostic yield in the neonatal population varies from 21% to 60%,[42,43,45,46] but a phenotype-driven selection of critically ill neonates for rapid sequencing improves the rate of definite diagnosis.[42] For instance, in our most recent patients, the recognition of the distinct clinical features prompted fast genetic confirmation by single gene-filtered NGS.

While *BRAT1* encephalopathy is considered ultra-rare, with less than 30 patients reported,[19] it is most likely underdiagnosed. For instance, previous reports of severe, even lethal, cases of hyperekplexia may have included infants with *BRAT1* encephalopathy.[47]

A strength of our work is reporting the largest series of infants with *BRAT1* encephalopathy to date, with an emphasis on phenotype at presentation. Our findings derive from the effort to share the genotype and the "full narrative" of the clinical history, with good quality vEEGs recorded from the onset of symptoms, providing a significant contribution to early recognition and diagnosis.

Our study shares the limitations of retrospective studies, including the potential for ascertainment bias and the overall small number of cases despite our multicenter international collaborative. We included only patients with neonatal onset in whom detailed electroclinical information was available. Therefore, this study does not represent the whole spectrum of *BRAT1*-associated disorders, which also includes the late-onset milder phenotype.[19] Neuropathologic examination was performed only in 3 infants of different ages, which limits the generalization of results. In addition, postnatal exposure to environmental factors, including chronic hypoxia, may have contributed to neuronal apoptosis. The limited number of neuropathologic examinations in our cohort reflects the overall low rate of parental acceptance for autopsy in neonates admitted to the ICU.[48]

BRAT1 encephalopathy is an autosomal recessive disorder with onset in the neonatal period. The key phenotype characteristics are multifocal myoclonus, both nonepileptic and epileptic over a relatively organized EEG background, progressive, persistent, and diffuse hypertonia, and evolution into refractory multifocal seizures, prolonged bouts of apnea, bradycardia, and early death. Even if little can be done therapeutically so far, the importance of the diagnosis to infants and families should not be overlooked because it has a far-reaching clinical impact. Providing knowledge on disease trajectory and prognosis may facilitate the transition to comfort care. In the context of an autosomal recessive disorder with a high recurrence risk, genetic diagnosis offers families the opportunity to address future reproductive choices and consider preimplantation genetic testing for subsequent pregnancies. Translational studies in conditional mouse mutants may elucidate the role of *BRAT1* in CNS morphogenesis and inform about the type and timing of intervention. Novel gene therapy techniques such as CRISPR/Cas9 gene editing may potentially offer a cure for preimplantation human embryos.[49]

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Appendix *(continued)*

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Continued

Appendix *(continued)*

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