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FULL-LENGTH ORIGINAL RESEARCH

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A survey of the European Reference Network EpiCARE on clinical practice for selected rare epilepsies

Tobias Baumgartner[1] | **Mar Carreño**[2,3] | **Rodrigo Rocamora**[4] | **Francesca Bisulli**[5] | **Antonella Boni**[5] | **Milan Brázdil**[6] | **Ondrej Horak**[7] | **Dana Craiu**[8] | **Cristina Pereira**[9] | **Renzo Guerrini**[10] | **Victoria San Antonio-Arce**[2,11] | **Andreas Schulze-Bonhage**[11] | **Sameer M. Zuberi**[12] | **Tove Hallböök**[13] | **Reetta Kalviainen**[14] | **Lieven Lagae**[15] | **Sylvie Nguyen**[16] | **Sofia Quintas**[17] | **Ana Franco**[17] | **J. Helen Cross**[18] | **Matthew Walker**[19] | **Alexis Arzimanoglou**[2,20] | **Sylvain Rheims**[21] | **Tiziana Granata**[22] | **Laura Canafoglia**[23] | **Cecilie Johannessen Landmark**[24] | **Arjune Sen**[25] | **Rohini Rattihalli**[26] | **Rima Nabbout**[27] | **Elena Tartara**[28] | **Manuela Santos**[29] | **Rui Rangel**[29] | **Pavel Krsek**[30] | **Petr Marusic**[30] | **Nicola Specchio**[31] | **Kees P. J. Braun**[32] | **Patricia Smeyers**[33] | **Vicente Villanueva**[33] | **Katarzyna Kotulska**[34] | **Rainer Surges**[1]

[1]Department of Epileptology, University Hospital Bonn, Bonn, Germany

[2]Epilepsy Unit, Child Neurology Department, Hospital San Juan de Dios, Barcelona, Spain

[3]Hospital Clinic de Barcelona, Barcelona, Spain

[4]Epilepsy Centre, Faculty of Health and Life Sciences, Hospital del Mar-IMIM, Universitat Pompeu Fabra, Barcelona, Spain

[5]IRCCS Istituto delle Scienze Neurologiche di Bologna, Bologna, Italy

[6]Brno Epilepsy Center, Department of Neurology, St. Anne´s University Hospital, Medical Faculty of Masaryk University, Brno, Czech Republic

[7]Brno Epilepsy Center, Department of Child Neurology, Brno University Hospital, Medical Faculty of Masaryk University, Brno, Czech Republic

[8]Alexandru Obregia Clinical Hospital, Bucharest, Romania

[9]Centro Hospitalar e Universitario de Coimbra, Coimbra, Portugal

[10]Children's Hospital A. Meyer-University of Florence, Florence, Italy

[11]Epilepsy Center, Faculty of Medicine, University Medical Center, Freiburg, Germany

[12]Queen Elizabeth University Hospitals Campus, Glasgow, UK

[13]Department of Pediatrics, Institute of Clinical Sciences, Sahlgrenska Academy, University of Gothenburg and Queen Silvia Children's Hospital, Sahlgrenska University Hospital, Gothenburg, Sweden

[14]Pohjois-Savon Sairaanhoitopiiri, Kuopio University Hospital, (KUH), Kuopio, Finland

[15]University Hospital Gasthuisberg KU, Leuven, Belgium

[16]CHRU LILLE Epilepsy Unit, Lille, France

[17]Centro Hospitalar Universitário Lisboa Norte - Hospital de Santa Maria, Lisboa, Portugal

[18]Great Ormond Street Hospital for Children, NHS Trust, London, UK

[19]University College London Hospitals NHS Foundation Trust, London, UK

[20]Department of Paediatric Clinical Epileptology, Sleep Disorders and Functional Neurology, University Hospitals of Lyon (HCL), Lyon, France

See Appendix A for additional members of the Study Group

[21]Department of Functional Neurology and Epileptology, Hospices Civils de Lyon, University of Lyon, Lyon, France

[22]Department of Pediatric, Neuroscience Fondazione, IRCCS Istituto Neurologico Carlo Besta, Milan, Italy

[23]Epilepsy Unit, Fondazione IRCCS Istituto Neurologico Carlo Besta, Milan, Italy

[24]Department of Pharmacology, Oslo University Hospital, The National Center for Epilepsy, Oslo Metropolitan University, Oslo, Norway

[25]Oxford Epilepsy Research Group, NIHR Oxford Biomedical Research Centre, Nuffield Department of Clinical Neurosciences, John Radcliffe Hospital, Oxford, UK

[26]Department of Paediatric Neurology, Children's Hospital, John Radcliffe Hospital, Oxford, UK

[27]Department of Pediatric Neurology, APHP, Imagine Institute, Reference Centre for Rare Epilepsies, Paris Descartes University, Paris, France

[28]IRCCS Mondino Foundation, Pavia, Italy

[29]Centro Hospitalar Universitário do Porto, Porto, Portugal

[30]Departement of Neurology, Charles University, Second Faculty of Medicine and Motol University Hospital, Prague, Czech Republic

[31]Rare and Complex Epilepsy Unit, Department of Neuroscience, Bambino Gesu' Children's Hospital, IRCCS, Rome, Italy

[32]Department of Child Neurology, University Medical Center Utrecht, Utrecht, The Netherlands

[33]Refractory Epilepsy Unit of Hospital Universitario y Politécnico La Fe, Valencia, Spain

[34]The Children's Memorial Health Institute, Warsaw, Poland

Correspondence
Rainer Surges, Department of Epileptology, University of Bonn Medical Center, Venusberg-Campus 1, 53127 Bonn, Germany.
Email: rainer.surges@ukbonn.de

Abstract

Objective: Clinical care of rare and complex epilepsies is challenging, because evidence-based treatment guidelines are scarce, the experience of many physicians is limited, and interdisciplinary treatment of comorbidities is required. The pathomechanisms of rare epilepsies are, however, increasingly understood, which potentially fosters novel targeted therapies. The objectives of our survey were to obtain an overview of the clinical practice in European tertiary epilepsy centers treating patients with 5 arbitrarily selected rare epilepsies and to get an estimate of potentially available patients for future studies.

Methods: Members of the *European Reference Network for rare and complex epilepsies* (*EpiCARE)* were invited to participate in a web-based survey on clinical practice of patients with Dravet syndrome, tuberous sclerosis complex (TSC), autoimmune encephalitis, and progressive myoclonic epilepsies including Unverricht Lundborg and Unverricht-like diseases. A consensus-based questionnaire was generated for each disease.

Results: Twenty-six of 30 invited epilepsy centers participated. Cohorts were present in most responding centers for TSC (87%), Dravet syndrome (85%), and autoimmune encephalitis (71%). Patients with TSC and Dravet syndrome represented the largest cohorts in these centers. The antiseizure drug treatments were rather consistent across the centers especially with regard to Dravet syndrome, infantile spasms in TSC, and Unverricht Lundborg / Unverricht-like disease. Available, widely used targeted therapies included everolimus in TSC and immunosuppressive therapies in autoimmune encephalitis. Screening for comorbidities was routinely done, but specific treatment protocols were lacking in most centers.

Significance: The survey summarizes the current clinical practice for selected rare epilepsies in tertiary European epilepsy centers and demonstrates consistency as well as heterogeneity in the treatment, underscoring the need for controlled trials and recommendations. The survey also provides estimates for potential participants of clinical trials recruited via EpiCARE, emphasizing the great potential of

Reference Networks for future studies to evaluate new targeted therapies and to identify novel biomarkers.

KEYWORDS

autoimmune encephalitis, Dravet syndrome, orphan disease, progressive myoclonic epilepsy, targeted therapies, tuberous sclerosis complex

1 | INTRODUCTION

Epilepsy is one of the most common neurological diseases. Its causes are manifold, and a significant proportion of the patients suffer from rare and complex epilepsies. In Europe, a disease is classified as rare if less than 1 in 2000 individuals suffer from it.[1] Accordingly, the general knowledge and expertise of rare diseases is limited, and evidence-based guidelines and treatment recommendations are still lacking for most rare epilepsies. Seizure freedom is difficult to achieve with "standard" antiseizure drugs (ASD) in many cases and concomitant symptoms including intellectual disability, behavioral, and other psychiatric symptoms and the affection of other organs complicate management and require an interdisciplinary approach. Given the aforementioned challenges, only a minority of patients with rare and complex epilepsies receive best therapy possible. There is hope that in light of uncovered pathomechanisms, targeted therapies will be developed in the future.[2]

Therapies which take into account identified pathomechanisms or target abnormally altered pathways are already applied in selected diseases. For example, tuberous sclerosis complex (TSC) is treated with everolimus to block overactivity of the mammalian target of rapamycin-TOR) pathway.[3] In people with mutations of genes coding for voltage-gated sodium channels (SCN1A, SCN2A, SCN8A), sodium channel blockers are commonly avoided in those with loss of function mutations, but are used in people with gain of function mutations.[4–6] In Glucose Transporter Type 1 (GLUT1) deficiency syndrome, ketogenic diet provides a specific therapy,[7,8] and in mitochondriopathies, the application of valproic acid is commonly avoided because of potential lethal liver failure.[9]

The major goal of this survey was to obtain information on experience and clinical practice with rare and complex epilepsies in tertiary, comprehensive epilepsy centers across Europe. Furthermore, the survey should promote the discussion on future recommendations and guidelines for diagnostics and therapies, and should help to get an overview of available patient cohorts to facilitate the planning of future studies.

Our survey focuses on five arbitrarily selected epilepsy syndromes (Box 1) reflecting the broad spectrum of pathophysiological mechanisms of rare epilepsies: channelopathies (Dravet syndrome), immune-mediated epilepsies (autoimmune encephalitis), mTORopathies (TSC), and progressive (metabolic, degenerative) myoclonus epilepsies (Unverricht-Lundborg disease, Unverricht-like disease). Furthermore, the selected diseases illustrate a wide range of varying degrees of severity, prevalence, treatment options and age of onset.

Key Points

- Most tertiary epilepsy centers across Europe have cohorts of a relevant size for Dravet syndrome, tuberous sclerosis complex (TSC), and autoimmune encephalitis that can be recruited for future studies
- Despite the lack of guidelines, the antiseizure drug therapy is rather consistent between expert centers for Dravet syndrome, infantile spasms in TSC, and Unverricht Lundborg
- Available targeted therapies are commonly in use in expert epilepsy centers across Europe
- Specific treatment protocols for comorbidities in epilepsy patients are lacking in most epilepsy centers

2 | METHODS

2.1 | Survey

The *European Reference Network for rare and complex epilepsies* (*EpiCARE)* is a European effort to facilitate patients' access to specialized centers and to foster research and clinical trials with the ultimate goal to improve clinical care of people with rare and complex epilepsies (https://epi-care.eu/). The *EpiCARE* network is composed of more specialized working packages on diagnostic and therapeutic issues. The members of the working group 7 "Targeted medical therapies" proposed and initiated this survey on 5 arbitrarily selected rare and complex epilepsies (Dravet syndrome

BOX 1 Short summary of the selected epilepsy syndromes

Epilepsy syndrome	Simplified description
Dravet syndrome	Dravet syndrome is a developmental and epileptic encephalopathy caused by pathogenic variants in the voltage-dependent sodium channel SCN1A in at least 80% of cases. First seizures (tonic-clonic or hemi-clonic seizures) normally occur in the first year of life. Fever or physical activities often trigger the seizures. Early development is normal, followed by a cognitive impairment. Later atypical absence seizures, focal seizures, and myoclonic seizures occur. Seizures are pharmacoresistant. Valproate, clobazam, bromide, and stiripentol are usually used in Dravet syndrome. The administration of sodium channel blockers may worsen seizures and should be avoided.[10]
Tuberous sclerosis complex (TSC)	TSC is a neurocutaneous disorder mostly due to mutations in TSC 1 or TSC 2 genes. Both genes encode for proteins which indirectly inhibit the mTOR pathway. Patients suffer from benign tumors in the brain and other organs. The brain is involved in nearly all cases and epileptic seizures usually occur in childhood. 80% of the patients develop a pharmacoresistant epilepsy. Everolimus is a mTOR inhibitor, which is used as a targeted therapy for TSC patients. Everolimus was initially used to treat benign tumors (SEGA, AML) in patients with TSC but it has additionally shown to reduce seizure frequency.[3]
Autoimmune encephalitides	Autoimmune encephalitides are a group of diseases characterized by subacute onset of cognitive decline, behavioral changes, and seizures. CSF pleocytosis, MRI features suggestive for encephalitis, or EEG abnormalities are often found.[11] Antibodies against cell-surface (LGI1, CASPR2, NMDA-R, $GABA_A$, $GABA_B$) or intracellular proteins (GAD65, Hu, Ma2) help to classify the individual immunological subgroup of an AE and allow a better estimation of the prognosis and the course in some cases. An early immunotherapy has been shown to improve the functional outcome.[12]
Unverricht-Lundborg disease (ULD)	ULD is a progressive myoclonus epilepsy. The most common mutation in ULD affects the cystatin B gene (CSTB). Patients are suffering from action- and stimulus-sensitive myoclonus, tonic-clonic seizures, and ataxia. Typical onset of the disease is between 6 and 16 years. Cognitive decline is usually only mild. Even if there is no causal therapy for the disease, some antiseizure drugs (ASD) such as zonisamide, topiramate, piracetam, or perampanel demonstrated good control of myoclonus.[13–15]
Unverricht-like disease	Heterogenous group of progressive myoclonus epilepsies which are associated with homozygous or compound heterozygous mutations of the SCARB2, KCNC1 or NEU1 genes. • Mutations of the SCARB2 gene cause a progressive myoclonus epilepsy associated with renal dysfunction. Additional neurological features can be present.[16] • KCNC1 mutations can lead to a progressive myoclonus epilepsy with ataxia and mild cognitive decline.[17] • Sialidosis type I and II are lysosomal storage diseases due to a mutation in the NEU1 gene presenting with a variable phenotype consisting of progressive myoclonus epilepsy associated with a characteristic macular change—"cherry-red spot." Sialidosis type II is the more severe infantile type with dysmorphic features, hepatomegaly, and inner ear hearing loss.[18]

(Appendix S1), TSC, Unverricht Lundburg, Unverricht-like disease and autoimmune encephalitis). The aim of the questionnaire was to collate patient characteristics, common comorbidities and usual diagnostic and treatment regimes. The individual items of the questionnaire were discussed by the members of *EpiCARE* and a consensus was reached for each questionnaire with 24-53 items depending on the disease. The final versions were implemented on a web-based platform for surveys ((https://www.soscisurvey.de/). Thirty tertiary epilepsy centers were invited by e-mail to fill-out the web-based questionnaires. The online survey was opened for two weeks on three occasions between December 2018 and November 2019. Incorrectly filled out questionnaires were rejected and in case of multiple responses from one institution the most complete questionnaire was evaluated. The participating centers are listed in Appendix S2.

2.2 | Data analysis

To conduct the survey and collect the data, an online tool (https://www.soscisurvey.de/, Version: 3.2.03-i) was used. The results of the survey were processed and analyzed with Excel (version 16.16.17). We performed descriptive statistics including percentages and frequencies.

3 | RESULTS

3.1 | Respondents

Twenty-six (87%) of the 30 expert centers who agreed to participate completed at least one of the five questionnaires. Nine institutions completed all questionnaires, nine completed

four questionnaires, four completed three questionnaires, one completed two questionnaires, and three completed one questionnaire. The responses of the centers were different depending on the disease. The questionnaire on clinical practice of Dravet syndrome was completed by 26 centers, of TSC by 23 centers, for autoimmune encephalitis by 21 centers and for Unverricht-like disease and Unverricht-Lundborg by 16 and 12 centers, respectively.

3.2 | Characteristics of patient groups

The age range of patients treated at the different tertiary epilepsy centers of the EpiCARE network varied considerably. Patients with Dravet syndrome (85%; 22 out of 26) and TSC (70%; 16 out of 23) were predominantly children and adolescents, whereas patients with autoimmune encephalitis were predominantly adults (57%; 12 out of 21) in most responding centers, followed by centers which treat both age groups equally (24%; 5 out of 21). In Unverricht-like diseases both age groups were equally represented in most responding institutions and in Unverricht-Lundborg the same proportion of the centers reported to have mostly adult (42%; 5 out of 12) or to have mostly pediatric patients (42%; 5 out of 12) in charge. These data naturally do not allow conclusions on the epidemiology of a given disease, but rather reflect the emphasis of the responding centers of the EpiCARE Network with respect to the age range (adults or pediatric populations) and particular scientific or clinical expertise.

The number of new patients seen per year varied between the different diseases (Figure 1). All centers expect to see at least one new patient per year with Dravet syndrome, autoimmune encephalitis and TSC. With respect to Unverricht Lundborg and Unverricht-like diseases, the centers expect to diagnose fewer patients.

At most centers cohorts of patients with TSC (20 out of 23; 87%), Dravet syndrome (22 out of 26; 85%), and autoimmune encephalitis (15 out of 21; 71%) are followed up. For Unverricht-Lundborg (6 out of 12; 50%) and Unverricht-likes disease (5 out of 16; 31%), fewer and smaller cohorts were reported. The largest cohorts were found for TSC: All centers reported more than 10 patients and 30% (6 out of 20) of the centers take care of more than 100 patients (Figure 2). In Dravet syndrome, 91% (20 out of 22) and in autoimmune encephalitis 73% (11 out of 15) of the cohorts included more than 10 patients. For Unverricht-like disease and Unverricht-Lundborg cohorts tended to be small. Cohorts at referring collaborating centers were reported by 26% (6 out of 23) of the responding reference centers for TSC, 17% (2 out of 12) for Unverricht-Lundborg, 25% (4 out of 16) for Unverricht-like diseases, and 38% (10 out of 26) Dravet syndrome. This information was not assessed for autoimmune encephalitis.

3.3 | Treatment practices

An important objective of this survey was to assess the medical treatment, namely the ASD therapy and specific disease-targeted treatments (eg, immunotherapy in autoimmune encephalitis and application of everolimus in TSC) (Table 1).

In Dravet syndrome there was good concordance among the different centers for the ASD regimen. The most frequently established first-line ASD was valproate (VPA). Clobazam (CLB), stiripentol (STP) and topiramate (TPM) were the most commonly reported drugs for second, third and fourth line, respectively.

In autoimmune encephalitis, levetiracetam (LEV) was the first-choice ASD, irrespective of the results of antibody testing (GAD65, NMDA-R and LGI1), the second-line treatments varied widely for care with autoimmune

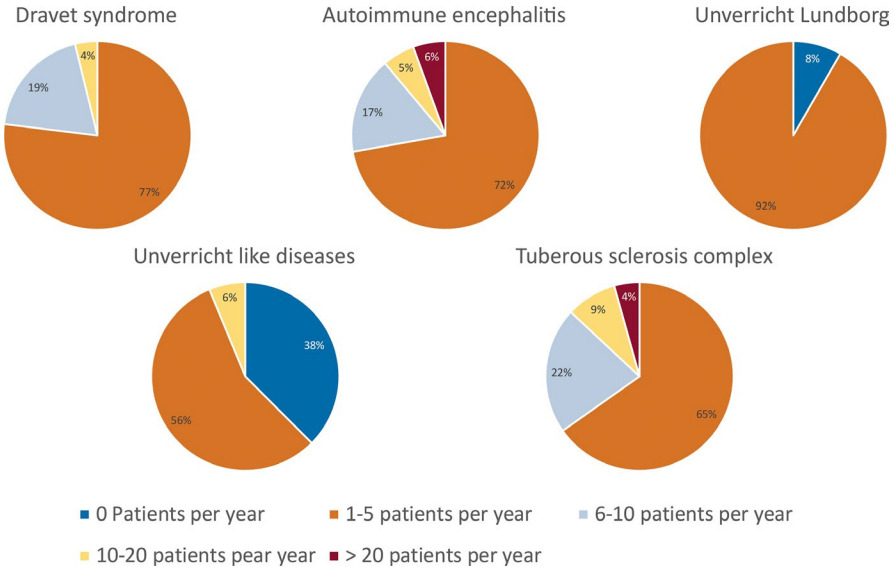

FIGURE 1 Patients expected to recruit per year for each disease

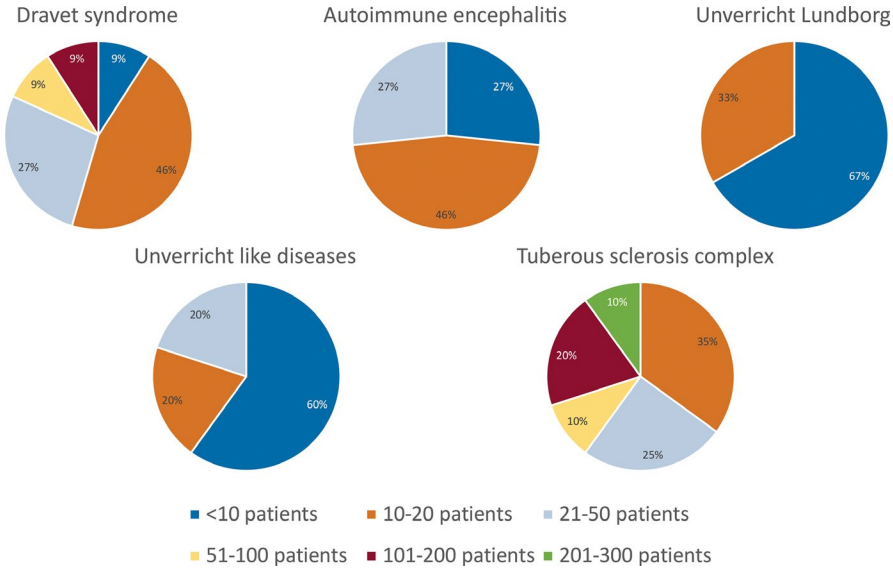

FIGURE 2 Reported size and quantity of patient cohorts in the centers for each disease

TABLE 1 Reported anti-epileptic drug therapy

Epilepsy syndrome/disease	First-line ASD therapy	Second-line ASD drug therapy	Third-line ASD therapy	First-line status epilepticus treatment	Second-line status epilepticus treatment	Third-line status epilepticus treatment
Dravet syndrome (26*)	VPA 92%	CLB 77%	STP 54%	MDZ 58% (benzodiazepine 100%)	VPA 31%, LEV 23%, PB 19%	LEV 27%
Unverricht Lundborg (12*)	VPA 67%	LEV 58%	CZP 25%, ZNS 25%, CLB 25%	MDZ 50%, (benzodiazepine 83%)	VPA 67%	LEV 50%
Unverricht-like disease (16*)	VPA 63%	LEV 43%	Benzodiazepine 44%	MDZ 25%, (benzodiazepine 56%)	VPA 31%, LEV 19%	LEV 31%
Autoimmune encephalitis (21*)	GAD: LEV 52% LGI1: LEV 33% NMDAR: LEV 43%	GAD: LTG 24% LGI1: none 19% NMDAR: VPA 14%, none 14%	GAD: VPA, LCM, CBZ 14% LGI1: LTG 19%, none 19% NMDAR: LCM 14%, none 14%	MDZ 35%, (benzodiazepine 71%)	LEV 41% , VPA 19%	PHT 25%
Tuberous sclerosis (23*)	Infantile spasms: VGB 96% Other seizures: VGB 30%	Infantile spasms: ACTH 48% Other seizures: CBZ 22%	Infantile spasms: VPA 26% Other seizures: LEV 26%	MDZ 52%, (benzodiazepine 100%)	PHT 30%, LEV 30%	PHT 26%

Abbreviations: ASD, anti-epileptic drug; CLB, Clobazam; CZP, Clonazepam; LCM, Lacosamide; LEV, Levetiracetam; LTG, Lamotrigin; MDZ, Midazaolam; PB, Phenobarbital; PHT, Phenytoin; STP, Stiripentol; VGB, Vigabatrin; VPA, Valproate; ZNS, Zonisamide.

*Responding centers.

encephalitis. Lamotrigine (LTG), lacosamide (LCM), carbamazepine (CBZ), and VPA were reported to be common drugs for second-line and third-line therapies. There was no difference in the immunosuppressive treatment between subgroups of patients with different antibodies (Table 2). Intravenous cortisone was the most frequently established first-line treatment in about half of the centers, followed by intravenous immunoglobulin therapy (IVIg) and plasma exchange for second- and third-line therapies. Combinations of different immunotherapies were not separately assessed in the questionnaire. Rituximab was reported to be the most common fourth-line therapy. Cyclophosphamide, azathioprine, methotrexate, and bortezomib were mentioned to be in use by some centers for third our fourth-line immunosuppressive treatment.

In Unverricht Lundborg and Unverricht-like diseases VPA and LEV were mainly the choice for first- and second-line therapies followed by benzodiazepines, TPM,

TABLE 2 Reported immunosuppressive treatment in autoimmune encephalitis

Antibodies against	First-line immunosuppressive treatment	Second-line immunosuppressive treatment	Third-line immunosuppressive treatment	Fourth-line immunosuppressive treatment
LGI1 (21*)	IV cortisone 52%	IVIG 48%	Plasmapheresis 29%	Rituximab 52%
NMDA-R (21*)	IV cortisone 57%	IVIG 48%	Plasmapheresis 29%	Rituximab 43%
GAD65 (21*)	IV cortisone 52%	IVIG 21%	Plasmapheresis and Immunoadsorption 29%	Rituximab 43%

Abbreviations: GAD65, glutamic acid decarboxylase 65; IVIG, Intravenous Immunoglobulin; LGI1, Leucine-rich, glioma-inactivated 1; NMDA-R, N-methyl-D-aspartate receptor.

*Responding centers.

TABLE 3 Reported availability and usage of drug monitoring

Epilepsy syndrome/disease	Is the treatment monitored by therapeutic drug monitoring?	Do you use serum concentrations to adjust doses and the total drug load?
Dravet syndrome (26*)	54% majority, 38% selected, 8% never	Yes 81%
Unverricht Lundborg (12*)	58% majority, 42% selected	Yes 75%
Unverricht like diseases (16*)	63% majority, 25% selected, (13% not answered)	Yes 75%, (13% not answered)
Tuberous sclerosis (23*)	61% majority, 39% selected	Not requested

*Responding centers.

zonisamide (ZNS), perampanel (PER), and piracetam as further alternatives.

Vigabatrin (VGB) was the most established drug for treating infantile spasms in TSC. In other seizure types (apart from infantile spasms), VGB (30%), LEV (22%), and VPA (17%) were the most common first-line ASDs. In 91% (21 out of 23) of the responding centers, mTOR inhibitors were available, but everolimus was mainly incorporated as a third- (65%), fourth- (35%), or fifth-line (35%) choice of treatment. In 87% (20 out of 23) of the centers, there is an epilepsy surgery program for TSC.

There was broad agreement on reported first-line treatment of status epilepticus in the context of the selected diseases between the expert centers. Benzodiazepines were predominantly used with midazolam being the most common drug. In second-line status therapy, VPA, LEV, and phenytoin (PHT) were mainly selected. In Unverricht-Lundborg, Dravet syndrome, and Unverricht-like diseases, sodium channel blockers were nearly completely avoided.

3.4 | Diagnostic tools

Laboratory-based therapeutic drug monitoring was available in most responding centers (25 out of 26; 96%). Measuring unbound drug concentrations of highly protein bound drugs as VPA and PHT was less well established (15 out of 26; 58%). Depending on the specific disease, 56%–63% of the centers reported to measure drug concentrations in the majority of cases. Another 25%–42% carried out drug monitoring in selected cases. Serum concentration measurements are used to adjust doses or the total drug load by 75%–81% of the centers. Laboratory detection of antibodies associated with autoimmune encephalitis was at least partly available in 81% (17 out of 21) of the centers. Commercial testing was performed in 33% (7 out of 21), and in-house (live or fixed-cell based) testing was performed in 43% (9 out of 21) of the centers (Table 3).

3.5 | Comorbidities

Cognitive impairment, mood, and sleep abnormalities were commonly screened for by the expert centers independently of the disease entity (Table 4). In TSC cardiac dysfunction, renal dysfunction, abnormalities of skin, lung and eyes were additionally reported to be screened on a regular basis. In autoimmune encephalitis the majority of the centers (81%) screen for associated tumors. Depending on the specific antibody, it was reported that 100% (NMDA-R), 71% (GAD65) and 88% (LGI1) of the patients are screened for tumors. Eighty-six percent of the centers reported to follow up with their patients after the acute disease phase. The follow-up visits were highly individualized.

Treatment protocols targeting the specific comorbidities exist only in a few centers for Dravet syndrome (31%; 8 out of 26), or autoimmune encephalitis (24%; 5 out of 21). By contrast, treatment protocols are regularly employed for TSC (74%; 17 out of 23). For Unverricht-Lundborg and Unverricht-like diseases, this information was not requested.

TABLE 4 Frequency for which comorbidities the patients are generally screened

Epilepsy syndrome/disease	Cognitive impairment (%)	Mood (%)	Sleep (%)	Appetite (%)	Cardiac dysfunction (%)	Others	None
Dravet syndrome (26*)	96	81	81	58	65	42% (gait, autism spectrum disorders, endocrine disorders)	
Unverricht Lundborg (12*)	100	100	75	58	50	-	
Unverricht like diseases (16*)	63	50	44	44	25	6%	13%
Tuberous sclerosis (23*)	100	87	78	61	87	74% (renal dysfunction, abnormalities of skin, lung, eyes)	

*Responding centers

4 | DISCUSSION

Our survey summarizes the current clinical practices for five selected rare and complex epilepsies and the size of patient cohorts in 26 responding tertiary centers of the EpiCARE network across Europe.

4.1 | General aspects of the survey

The overall participation in the survey was satisfactory, as 26 of the 30 invited centers completed at least one questionnaire. Highest response rates were for autoimmune encephalitis, Dravet syndrome, and TSC. In contrast, the response for Unverricht Lundborg and Unverricht-like diseases was less forthcoming, possibly reflecting the lower prevalence of these diseases.

According to our survey, most centers follow up cohorts of patients with TSC, autoimmune encephalitis, and Dravet syndrome. Furthermore, all centers expect to see at least one patient, and there were at least five centers expecting to see more than six new patients per year with these disease entities. Consequently, across the EpiCARE network it should be possible to recruit sufficiently large numbers of patients for clinical trials. By contrast in Unverricht-like disease just five and in Unverricht-Lundborg, six of the centers reported to take care of patient cohorts. Considering the fact that the term Unverricht-like disease refers to three different diseases (mutations in SCARB2, KCNC1 or NEU1 gene), it may be very difficult to recruit larger cohorts. On the other hand, especially in these diseases with a very low prevalence, collaborative efforts and communication between the centers is indispensable in order to assemble reasonably large patient groups. Our results can help to plan future multi-center studies and to estimate the number of patients that may be included.

4.2 | Treatment practices across centers

Despite the lack of guidelines in most rare epilepsies, the choice of ASD therapy was quite consistent between the expert centers. It was also demonstrated that targeted medical therapies are in common use. In Dravet syndrome sodium channel blockers were avoided by all centers and STP, which has an approval for adjunctive therapy in Dravet syndrome,[19,20] was the most commonly third-line therapy. VGB was reported to be the drug of first choice to treat infantile spasms in 96% of patients with TSC, which is in line with the strong evidence demonstrating its superior efficacy for this indication.[21–24] Even if the routine use of STP and VGB is not very surprising in these conditions, the widespread use of these substances in clinical practice could be confirmed. Furthermore, everolimus, which might have an influence on the underlying pathomechanisms of epileptogenicity in TSC,[25] was incorporated to be used as third-line therapy in about 65% of the centers. In Unverricht Lundborg and Unverricht-like diseases sodium-channel blockers (such as CBZ and PHT) were avoided, as they can worsen myoclonus or myoclonic seizures. It remains to be seen whether fenfluramine[26] and cannabidiol,[27,28] which demonstrated their efficacy in recent studies for Dravet syndrome, will also be incorporated in the common treatment regimes.

Interestingly, there was also a great concordance in the choice of pharmacotherapy in some cases where suggested treatment regimens are based on expert opinions alone and no good evidence or pathophysiological consideration exists. For example, VPA was the most commonly established first-line treatment in Dravet syndrome and in Unverricht Lundborg in 92% and 67% of centers, respectively. A more variable picture was found for the ASD therapy in TSC (apart from infantile spasms) and in autoimmune encephalitis, where no high consistency was found between the centers. Interestingly, there is some evidence supporting greater efficacy of sodium channel blockers in seizure treatment in autoimmune encephalitis compared to other ASDs.[29,30] This might be relevant when assessing larger cohorts.

The reported immunosuppressive therapy in autoimmune encephalitis was quite consistent, independently of the specific antibody. Initial therapy was usually reported to be cortisone, IVIgs, or plasma-exchange followed by Rituximab in refractory cases by the majority of the centers. This approach is in line with major recommendations[31,32] and well-established treatment strategies for NMDA-R and LGI1 encephalitis.[12,30,33] It needs to be clarified whether this approach is appropriate in autoimmune encephalitis associated with GAD65 antibodies.

4.3 | Assessment of comorbidities

In addition to epileptic seizures, people with epilepsy are often affected by a wide spectrum of neurological, psychiatric and systemic comorbidities including depression, anxiety, dementia, migraine, heart disease, peptic ulcers, osteoporosis and arthritis. These comorbidities are up to eight times higher in patients with epilepsy than in the general population and about 50% of the patients with active epilepsies have at least one comorbidity.[34] The fact that the premature mortality in patients with epilepsy is increased, even if seizures are sufficiently controlled,[35] shows the need to detect comorbidities early and to treat them sufficiently. Especially in rare and complex epilepsies the prevalence of comorbidities is high due to several direct and indirect mechanisms. Regardless of the epilepsy syndrome, cognitive impairment, mood, and sleep disorders were the comorbidities most frequently screened for by the centers in our survey. However, in TSC, cardiac dysfunction and disease manifestations in other organ systems (eye, lung, kidney, skin) and in autoimmune encephalitis associated tumor diseases were naturally one of the most screened for comorbidities. However, in most cases no specific treatment regime for these comorbidities was reported. Prospective studies to determine optimal treatment regimens would also be of great benefit in improving the comprehensive care of the affected patients.

4.4 | Laboratory diagnostics

Therapeutic drug monitoring and laboratory detection of antibodies associated with autoimmune encephalitis were available in most centers, which demonstrates the high diagnostic standard in the epilepsy centers of the EpiCare network and the possibility to conduct pharmacological studies in these centers. Therapeutic drug monitoring was reported to be performed in the majority of cases and the serum concentrations measurements were used to adjust doses and the total drug load in most centers. This reflects the fact that especially patients with rare epilepsies are pharmacoresistant and frequently receive combination therapies with the frequent use of first-generation ASDs. In these cases, therapeutic drug monitoring is important due to lower therapeutic indexes, extensive pharmacokinetic variability and many drug interactions, also as they are frequently combined with second or third generation ASDs.[36]

4.5 | Limitations of the survey

The survey has a number of limitations. The selection of epilepsy syndromes was arbitrary, even though the idea was to take different disease mechanisms into account to cover a broad spectrum of rare and complex epilepsies. Of course, it may also have played a role in the selection of the epilepsy syndromes that in some entities, for example Dravet syndrome or TSC, specific therapies exist or new drugs are expected to be approved. However, the focus was to get a general overview on the clinical practice in European tertiary epilepsy centers. Nevertheless, this survey is only a snapshot and it is not unlikely that the same survey would yield different results when performed in the near future. For instance, some new therapies such as fenfluramine or cannabidiol were not included in the survey because the survey was created at a time, when these drugs were not yet approved or generally available. This limitation also underlines the potential that new data can be collected quickly through EpiCARE and the change in therapies over time can be observed in future studies. Another weakness of the manuscript is that the results of the survey for treatment were combined for children and adults. This is due to the fact that members of EpiCARE represent a heterogeneous group of epilepsy centers with centers treating either pediatric or adult patients only, or centers treating both age groups, but perhaps focusing on one particular age group. Therefore, for each disease entity, the participants were asked if they treat mostly adults, mostly children or both age groups. This allows certain conclusions to be drawn about the selected therapies. Naturally the predominantly treated age group was also dependent on the syndrome (eg, Dravet syndrome vs. autoimmune encephalitis). The groups were too small to identify differences in the therapy. Likewise, specialized epilepsy centers are more likely to see patients with autoimmune encephalitis in the chronic phase, whereas departments of general neurology are more likely to treat patients in the acute phase. All healthcare providers of EpiCARE also cover acute neurology, as the presence of a department of neurology was a prerequisite to become member. However, healthcare providers with separate departments of neurology and epileptology are likely to be biased toward the chronic phase of autoimmune encephalitis. A further limitation of this survey relates to the therapy of TSC. In the questionnaire on TSC, the different therapies (ASD, everolimus, epilepsy surgery) were assessed separately and only for everolimus it was requested at which timepoint of the therapy it is used. Regrettably, it was not assessed how many ASD are used before epilepsy surgery was considered or if this decision deviates from the consensus definition of drug resistant epilepsy.[37] Probably it remains mostly an individual decision depending on the complexity of the specific case and the severity of the seizures. Specific treatment protocols for everolimus in TSC were not assessed.

5 | CONCLUSIONS

In summary, the survey shows that despite lack of evidence-based treatment recommendations there is a fairly

similar approach in the pharmacotherapy of some of the selected rare epilepsies. In diseases for which recommendations or studies with high evidence exist (Dravet syndrome, TSC), these are largely implemented in the tertiary epilepsy centers of the EpiCARE network. In instances where controlled trials are lacking, for example most forms of autoimmune encephalitis, the treatments vary to a greater extend and underscore the need for concerted efforts to perform controlled clinical trials. Importantly, the survey demonstrates that most of the centers already have cohorts for these specific disease groups and therefore, through collaboration between centers, larger cohorts could be recruited for future studies to evaluate new targeted therapies and to identify novel genetic, biochemical, electrophysiological or imaging biomarkers. The present survey also reveals that there is a great need for agreed recommendations on the screening and treatment of comorbidities in rare epilepsies—an aspect that is often neglected despite their high prevalence.

This paper highlights the excellent opportunities to initiate studies through a consortium like EpiCARE as well as to gather expert opinions. The current results also allow other physicians treating patients with rare epilepsies to compare and reflect their approach. Collaborations like EpiCARE will help to improve the care of patients with rare epilepsies, a group of patients which is always challenging for physicians.

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CONFLICTS OF INTEREST

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ORCID

Rodrigo Rocamora https://orcid.org/0000-0001-7345-4300
Francesca Bisulli https://orcid.org/0000-0002-1109-7296
Milan Brázdil https://orcid.org/0000-0001-7979-2343
Renzo Guerrini https://orcid.org/0000-0002-7272-7079
Victoria San Antonio-Arce https://orcid.org/0000-0002-2780-6560
Andreas Schulze-Bonhage https://orcid.org/0000-0003-2382-0506
Lieven Lagae https://orcid.org/0000-0002-7118-0139
Ana Franco https://orcid.org/0000-0002-4371-9272
J. Helen Cross https://orcid.org/0000-0001-7345-4829
Alexis Arzimanoglou https://orcid.org/0000-0002-7233-2771
Sylvain Rheims https://orcid.org/0000-0002-4663-8515
Tiziana Granata https://orcid.org/0000-0002-0170-6836
Laura Canafoglia https://orcid.org/0000-0002-5385-761X
Cecilie Johannessen Landmark https://orcid.org/0000-0002-0877-8912
Arjune Sen https://orcid.org/0000-0002-8948-4763
Elena Tartara https://orcid.org/0000-0003-1656-5420
Nicola Specchio https://orcid.org/0000-0002-8120-0287
Rainer Surges https://orcid.org/0000-0002-3177-8582

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SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section.

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APPENDIX A

ADDITIONAL MEMBERS OF THE STUDY GROUP

Paolo Tinuper[5], Laura Licchetta[5], Roberto Michelucci[5], Joseph Toulouse[20], Eleni Panagiotakaki[20], Karine Ostrowsky-Coste[20], Gaetan Lesca[20], Marco de Curtis[22], Martin Elisak[30], Dorota Domańska-Pakiea[34], Krzysztof Sadowski[34]