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Review article

Dravet syndrome: A quick transition guide for the adult neurologist

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ABSTRACT

Introduction: Dravet syndrome (DS) is still seen as a "pediatric disease", where patients receive excellent care in pediatric centers, but care is less than optimal in adult health care systems (HCS). This creates a barrier when young adults need to leave the family-centered pediatric system and enter the adult, patient-centered HCS. Here we create a guide to help with the transition from pediatric to adult for patients with DS.
Methods: Experts in Dravet syndrome flagged the main barriers in caring for adults with DS and created a 2-page transition summary guide based on their expertise and a literature review.
Results: The 2-page guide addresses: DS diagnosis in children and adults; clinical manifestations, including the differences in seizures types and frequencies between children and adults with DS; the natural history of intellectual disability, behavior, gait, motor disorders and dysautonomia; a review of optimal treatments (including medications not commonly used in adult epilepsy settings such as stiripentol and fenfluramine), as well as emergency seizure management; avoidance of triggers, preventive measures, and vaccine administration in adults with DS.
Conclusion: Several young adults with DS are still followed by their child neurologist. This 2-page transition guide should help facilitate the transition of patients with DS to the adult HCS and should be given to families as well as adult health care providers that may not be familiar with DS.

1. Introduction

Dravet syndrome (DS) - previously known as Severe Myoclonic Epilepsy of Infancy or SMEI - was first described by Dr. Charlotte Dravet in 1978 (Dravet, 1978). Although the onset of DS is in infancy and pediatric specialists are very familiar with its diagnosis and treatment, DS is a chronic, refractory, life-long disorder that persists into adulthood and is present throughout the lifespan. Transition to adult healthcare is a focus of attention for all forms of medical care from primary to tertiary care. Young people with DS have specific treatment needs, accompanying medical and behavioral comorbidities, and must rely on adult family members or other guardians for communication and implementation of treatment recommendations. Few adult practitioners, however, are familiar with the unique needs of patients with DS, and there is a paucity of adult neurologists able or willing to care for these complex patients (Borlot et al., 2014). Further, with the increased

Abbreviations: DS, Dravet syndrome; ID, intellectual disability; SE, status epilepticus; SUDEP, sudden unexpected death in epilepsy; VNS, vagus nerve stimulator.

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availability and use of genetic testing, more patients are being recognized in adulthood (Ali Zulfiqar et al., 2020; Andrade et al., 2017; Selvarajah et al., 2021; Wu et al., 2015)

In a focus group study with caregivers of patients with DS, two themes emerged: 1) concern about the lack of information regarding long-term outcomes and 2) barriers in identifying adult neurologists knowledgeable and interested in caring for patients with DS and related comorbidities after transition from the pediatric system (Boyce et al., 2020). Consequently, transitioning care for young adults with DS to adult practitioners in an adult healthcare setting meets with challenges and barriers. This may lead to poorer care, place young adults at risk of seizures and other medical complications, and increase an already considerable burden of care carried by family members.

Appropriate transition programs could help close this gap by preparing patients and families in the pediatric system to have a smooth and coordinated transfer of care to adult neurologists knowledgeable in the management of DS and other similar rare and severe disorders. In fact, the Child Neurology Society and American Academy of Neurology have included transition programs as a quality measurement (Patel et al., 2018). Individuals with medically complex conditions such as DS

GUIDE TO TRANSITION PATIENTS WITH DRAVET SYNDROME TO ADULT CARE

Dravet syndrome (DS) is a rare infantile-onset severe developmental and epileptic encephalopathy. It is characterized by drug-resistant epilepsy, developmental delay, and a high risk of early mortality. More than 90% of patients with DS have a pathogenic variant in the *SCN1A* gene. DS is associated with an increased premature mortality of 17% by 20 years of age, mainly by sudden unexpected death in epilepsy (SUDEP) and status epilepticus (SE), but aspiration pneumonia and drowning also occur. Seizure detection devices and caregivers sharing the bedroom may reduce the risk of SUDEP, although there is no definitive evidence to support this.

CLINICAL MANIFESTATIONS:

- Seizures in children: Previously normal children have their first seizure before age 19 months. Fever or hyperthermia are triggers initially. With time, afebrile seizures ensue. Other triggers include: emotional stress or excitement, visual patterns and flashing lights. Seizure types include: hemiclonic, generalized tonic-clonic, myoclonic, absence, focal impaired awareness, and sometimes tonic seizures. Prolonged seizures, clusters, convulsive or non-convulsive SE can be frequent.
- Seizures in adults: As patients age, they have fewer seizures and episodes of SE, and less fever sensitivity. Some seizure types may disappear, and many adults with DS tend to have seizures associated with (or sometimes only during) sleep. Most adult patients, however, still require polytherapy and still have severe epilepsy with episodes of convulsive or non-convulsive SE.
- Intellectual disability (ID) and autism: The large majority of adults with DS have moderate to severe ID. Periods of regression or loss of acquired skills can be seen following a prolonged seizure or episode of SE. Autism can be seen in some patients with DS.
- Behavior: Children can have attention deficit disorder, agitation, irritability, and aggressiveness. Adults tend to be calmer, but autistic traits and ID can worsen adaptive behavior and social relations.
- Gait, motor and skeletal: Teenagers and adults tend to develop crouch, dystonic, wide-based, ataxic, and/or parkinsonian gait. Parkinsonian features such as bradykinesia, asymmetric cogwheel rigidity, cerebellar speech and antecollis are also common in older patients. Gait, bradykinesia and speech symptoms may respond to levodopa. Skeletal abnormalities such as kyphosis and kyphoscoliosis are seen in children and adults with DS.

AVOIDANCE OF SEIZURE TRIGGERS AND PREVENTATIVE MEASURES:

- Avoid overexertion, hot or unsupervised baths and outdoor activities when the ambient temperature is too high
- Consider using cooling vests (not proven)
- Use prophylactic antipyretics with illness and vaccines
- Use prophylactic benzodiazepines with febrile illness

VACCINES: There are no studies about giving vaccinations to adults with DS. Given the risk-benefit, the authors' opinion is that the following vaccines should be given with careful monitoring in adults with DS (who can be given prophylactic antipyretics to avoid post-vaccination, fever-induced seizures): COVID-19, influenza, meningococcal, pneumococcal and HPV vaccines. In addition, Tdap (tetanus, diphtheria and pertussis) vaccine should be given once as adult if not received as adolescent. After that, Td (tetanus and diphtheria) vaccine boosters should be given every 10 years).

OTHER CONSIDERATIONS:

- Catamenial epilepsy: Women with DS and catamenial epilepsy may be tried on hormone therapy or acetazolamide.
- Fertility & contraception: There is no evidence that women with DS are less fertile. Therefore, depending on the degree of ID, it is important to educate families and sometimes patients about interactions between hormonal contraception and antiepileptic drugs, as well teratogenicity.
- Risk of abuse: As for any person with ID, patients with DS are at increased risk of abuse. These issues should be discussed with parents and caregivers.
- Guardianship and power of attorney: Before transitioning to adult care, these should be established.

Fig. 1. Two-pager transition guide for Dravet syndrome.

TREATMENT:

Maintenance medications: (As of June 2021)

- First line: valproate and clobazam
- Second line: stiripentol and topiramate
- Next options: clonazepam, levetiracetam, zonisamide, ethosuximide (for absence)
- Recently approved medications: cannabidiol, fenfluramine

- Other therapies: Classical ketogenic, modified ketogenic diet or low-glycemic diets, neurostimulation

Special considerations:

- As patients age and their brain matures, drugs that failed to control seizures in the past may be tried again. Agitation due to clobazam is more common in children and may not happen in the same patient as an adult.
- Stiripentol:
  - If used in polytherapy with fenfluramine, valproate, or clobazam, these other ASMs may need to be reduced
  - Pediatric dose of 50mg/kg/d is higher than typical adult dose of 10-30 mg/kg/d
  - Hyperammonemia and associated encephalopathy in patients taking valproate and stiripentol may be managed with carnitine
- Fenfluramine:
  - May need to reduce dose if used with stiripentol
  - Maximum dose: 0.4mg/kg/d or total daily dose of 17mg (divided twice daily)
  - Prescriber enrollment and surveillance echocardiograms as part of a REMS program required
- Cannabidiol:
  - Increased levels of aminotransferase, especially in combination with valproate, may require reduction of valproate dose
  - Increased N-desmethylclobazam levels may require reduction of clobazam dose.

Medications to avoid: Sodium channel inhibitor antiepileptic drugs such as carbamazepine, oxcarbazepine, phenytoin[1] and lamotrigine.

Emergency Seizure Protocol (ESP): Each patient should have a written ESP (-or seizure action plan), and copies should be given to parents and caregivers. This written plan should state what drugs to use, when, interval of repetition, and when to call 911 (or the emergency number in the relevant country). The child neurologist may help with a protocol that has been successfully used in the past.

- At home or in the community: Diastat (rectal diazepam) is commonly used in children, but not in adults. Most adults use sub-lingual lorazepam (1-2 mg per dose, at home most adults can safely receive up to 6mg in a 24-hour period) or intranasal/buccal midazolam (0.2mg/kg or 10 mg in adolescents and adults). Some adult neurologists can instruct caregivers to repeat the dose once or twice before calling an ambulance. Directions for VNS emergency use (through swiping magnet) should also be in the seizure emergency protocol. If the home rescue medication has been used and seizures are persisting, the protocol should instruct caregivers to call an ambulance.
- In the ambulance or Emergency Room: Once the patient is in the ambulance/emergency room, the treatment of status epilepticus is similar to the treatment of any other patient with epilepsy, with a few caveats: First line drugs are IV benzodiazepines[2] followed by non-bezodiazepine antiseizure medications such as valproate, levetiracetam[3] or fosphenytoin[1]. Even if seizures have ended with a benzodiazepine, a loading dose of a non-benzodiazepine is recommended to prevent further seizures. If the above treatment fails, the next steps should be done in the intensive care unit: midazolam drip, and/or propofol, etc., similar to SE caused by other diseases.

[1] Fosphenytoin can be successful in aborting clusters of seizures or status epilepticus in patients with DS, despite the fact that phenytoin is contraindicated in the long-term treatment of seizures in DS.

[2] Consider the amount of benzodiazepines received before arrival at hospital

[3] If patient is already on maintenance therapy with valproate or levetiracetam, consider another non-benzodiazepine.

Fig. 1. (*continued*).

require multidisciplinary care. However, multidisciplinary transition programs are expensive and require a significant time commitment from both pediatric and adult programs (Andrade et al., 2017; Brown et al., 2016). This results in many families of young-adults with DS having to leave a family-centered, specialized care program in which they are comfortable, to enter a more siloed (i.e. one specialty at a time), patient-oriented adult system that is poorly adapted for patients and families that, in addition to severe epilepsy, are also managing intellectual disability (ID) and behavioral comorbidities, including autism, as well as sleep, orthopedic, motor, and autonomic symptoms among others.

To address these concerns, a group of DS experts, who form the Dravet Syndrome Foundation Medical Advisory Board, collaborated on this review to produce a quick guide to the most critical aspects of DS for the adult neurologist and other adult providers who assume the role of care for young adults transitioning to their services. Topics covered include (a) the diagnosis and features of DS at initial presentation, (b) seizures in adults, (c) the goals of therapy and seizure management

strategies, (d) current knowledge on indicated medications and other therapies for daily use in controlling seizures, (e) contraindicated medications, (f) managing seizure emergencies, (g) co-morbid conditions and multidisciplinary care needs, and (h) other considerations that may be more general in a disability population (e.g. legal guardianship, risk of abuse). A convenient 2-page "Dravet Syndrome Transition Guide," was also created (Fig. 1). The Dravet Syndrome Transition Guide is a 2-page medical summary that can assist the adult neurologist to better care for patients with DS. It can be printed and given to the family as well as mailed to the adult neurologist at the time of referral. It could also support care in the adult emergency room, where knowledge about DS is often very poor.

2. Methods

A PubMed literature review on DS at all ages was carried out until June 2021. For this review, adults are defined as individuals 18 years or older. The search terms on PubMed included(("dravet"[Title/Abstract]) NOT (mouse)) OR (("severe myoclonic epilepsy in infancy"[Title/Abstract]) NOT (mouse)). For some of the issues where there was no relevant literature (such as vaccines for adults with DS), the authors drew on their extensive experience with DS patients. All authors are expert in DS, working in centers with large numbers of DS patients. DA is an adult neurologist, ATB, KGK, SK, LL, IM, MSP, IES, JS and EW are child neurologists

3. Results

The literature review uncovered 1132 manuscripts on PubMed and Medline. Initial screening excluded 317 irrelevant and non-English manuscripts. Another 439 manuscripts were excluded because they focused on animal models, genetic mechanisms, or they were reviews/commentaries. After filtering the remaining 376 eligible articles, only 32 focused exclusively in adults, while 216 focused exclusively in children (1:7 adult to children ration) and 128 combined adults and children.

3.1. Diagnosis and features at initial presentation and early course

3.1.1. Etiology

Eighty to 90 % of patients with DS have a pathogenic variant in the *SCN1A* gene which codes for the alpha-1 subunit of the neuronal, voltage-gated sodium channel $Na_{V1.1}$ (Claes et al., 2001). *SCN1A* variants, however, can also be seen in other conditions such as a milder syndrome, genetic epilepsy with febrile seizure plus or GEFS+ (Zhang et al., 2017), or a much more severe form of early infantile developmental and epileptic encephalopathy (Sadleir et al., 2017). Therefore, in the setting of a pathogenic *SCN1A* variant, it is important to ensure that the clinical phenotype is consistent with DS. Variants associated with DS are almost always de novo although rare instances of germline mosaicism or somatic mosaicism in a parent are occasionally reported (Claes et al., 2001; Nabbout et al., 2003; Nakayama et al., 2018; Sharkia et al., 2016).

Other genes have also been associated with a DS-like phenotype, especially in the first years of disease. These include: *PCDH19, GABRA1, GABRG2, SCN1B, SCN2A, SCN8A, SCN9A, STXBP1, HCN1, KCN2A* and *CHD2* (Connolly, 2016; Jonghe, 2011; Marini et al., 2011; Steel et al., 2017), although there are often phenotypic features that aid in distinguishing these diseases.

Ultimately, although pathogenic variants in *SCN1A* are identified in the large majority of patients with DS, the diagnosis of Dravet syndrome remains clinical, and a *SCN1A* variant is neither necessary nor sufficient for the diagnosis.

3.1.2. Initial presentation

The first seizure in DS usually occurs between 1–19 months of life in a previously healthy and typically developing infant. In one-third of patients, the first seizures are prolonged and triggered by fever. Generalized tonic-clonic or hemiclonic seizures are often seen initially. Other seizure types appear over time, including myoclonic, focal impaired awareness and atypical absence seizures. Non-convulsive status epilepticus, also called obtundation status by Charlotte Dravet, is frequent. Seizures can be triggered by fever, flashing lights, visual patterns, bathing, eating and physical exertion. Recurrent prolonged seizures or status epilepticus is common (Dravet, 2011; Epilepsy, 1989; Wirrell et al., 2017).

3.2. Seizures in adults

In adolescence, seizure frequency may decrease, but adults rarely become seizure-free. The most common seizures in adults include: focal, focal to bilateral or generalized tonic-clonic, tonic seizures, myoclonic, and atypical absence seizures. Myoclonic and absence seizures may disappear in adults while other types of seizures remain. Finally, convulsive seizures (generalized tonic-clonic, tonic or focal to bilateral tonic-clonic) tend to occur mainly during sleep, including during daytime naps. Adults may have less susceptibility to seizures triggered by fever or elevated ambient temperature and other triggers that caused seizures in childhood. They are also less likely to have episodes of status epilepticus, but some risk is always present (Akiyama et al., 2010; Dravet, 2011; Fasano et al., 2014; Genton et al., 2011; Jansen et al., 2006; Rilstone et al., 2012; Takayama et al., 2014). If the early history is not available, recognition of the clinical features of DS in an adult is much more challenging as some features may no longer be present (Aljaafari et al., 2017). Here, the most important resource is to access hospital records from the patient's initial presentations. Genetic confirmation may assist if the diagnosis of DS was not made in childhood. In 2017, a North American Consensus Panel optimized the diagnosis and management of DS (Wirrell et al., 2017).

3.3. Goals of seizure therapy and seizure management strategies

For most patients with epilepsy, the goal of seizure therapy is no seizures, no side-effects, as soon as possible (Glauser et al., 2006). Unfortunately for young people with DS, this goal is almost never achievable. Consequently, the therapeutic focus is on managing seizures and associated risks rather than a perfect seizure-free and side-effect-free outcome. In the North American Consensus report (Wirrell et al., 2017), the most important goal of therapy was to reduce the frequency of convulsive and prolonged seizures, limit side-effects from polytherapy, minimize functional impairments, and maximize quality of life.

3.4. Recommended medications and strategies for controlling seizures and their consequences

Only three medications have been tested specifically for DS in randomized trials: stiripentol, cannibidiol, and fenfluramine. These are often not used as first line therapy options as approval was only very recent. In the next year or two, in can be expected that cannabidiol and fenfluramine will be utilized earlier in the therapeutic armamentarium; however, their place in the treatment algorithm is not yet clear. Traditionally, valproate and clobazam have been considered the first line drugs for DS, but typically do not provide adequate seizure control (Wirrell et al., 2017). If needed, stiripentol can be added, but doses of clobazam (and possibly valproate) may need to be reduced. Careful monitoring of blood levels is required when making dosage changes in a patient on stiripentol. Topiramate and diet therapies (ketogenic diet, modified Atkins diet, low-glycemic index diets), were considered second line treatments for DS. Pediatric patients on a therapeutic diet face additional challenges when transitioning to adult care, as there are only a handful of adult epilepsy programs with dietary therapy clinics. Adherence to the diet may be problematic in an intellectually impaired adult who has some degree of functional autonomy. Clonazepam,

levetiracetam, zonisamide, ethosuximide (for absence seizures only) and neuromodulation were considered third line therapy choices.

3.4.1. Drug combinations with recently approved medications for DS–special considerations

i When combining stiripentol and valproate, the valproate dose might need to be reduced. When combining stiripentol with clobazam, the clobazam dose may need to be cut by 25 % or more (Chiron, 2018; Inoue et al., 2015). The recommended pediatric dose of stiripentol is 50 mg/kg/d. Adults usually do not tolerate such high doses, and stay in the 10−30 mg/kg/d range (Ali Zulfiqar et al., 2020; Chiron, 2018). Adults receiving stiripentol and valproate may have hyperammonemia, despite decreases in valproate. Hyperammonemia may be associated with encephalopathic features, drowsiness, agitation, insomnia, lack of appetite. Carnitine may help control ammonia levels while maintaining the benefits of stiripentol (Ali Zulfiqar et al., 2020).

ii Cannabidiol may lead to an increase in levels of aminotransferase especially in patients who are also taking valproate (Devinsky et al., 2017). N-desmethylclobazam levels may also increase with CBD, and clobazam dose may need to be reduced (Devinsky et al., 2016). In fact, approximately half of patients taking clobazam and/or valproate needed adjustment of these medications (Laux et al., 2019)

iii Fenfluramine dose also needs to be lowered in patients on stiripentol (Nabbout et al., 2020) with maximum fenfluramine dose 0.4 mg/kg/d or total daily dose of 17 mg divided twice daily.

3.4.2. Retrial of unsuccessful medications used in childhood

Patients with DS have typically had trials of many different medications by the time they are ready to transition to the adult setting. It is important to realize that as patients age and their brains mature, drugs that failed to control their seizures in the past may have a positive effect when tried again in adulthood. Some of the side effects observed in children may not be present in adults (for instance, children that could not tolerate clobazam due to agitation, when grown-up, may be able to successfully take clobazam and have better seizure control without agitation). Consequently, the adult practitioner should keep an open mind regarding retrying medications that were previously of little therapeutic value, as long as there were no serious side effects.

3.4.3. Other seizure management strategies and considerations

i Seizure triggers: Some adults remain susceptible to hyperthermia-induced seizures. Susceptible patients should avoid overexertion, hot baths (and unsupervised baths in general), and outdoor activities when the ambient temperature is too high. Cooling vests for hot days and prophylactic antipyretics with illness and vaccines have been suggested but are yet to be scientifically proven as efficacious. Some child neurologists also recommend prophylactic benzodiazepines with febrile illnesses. Some adults with Dravet syndrome also remain susceptible to seizures triggered by visual patterns and flashing lights. As in childhood, these triggers should be avoided if possible. The use of sunglasses (if tolerated by the patient), is a common practice; however, there is no specific literature about this intervention.

ii Vaccines: There are no studies about giving vaccinations to adults with DS. However, child neurologists recommend that their patients with DS receive vaccines as per the regular vaccination calendar but also receive antipyretics to avoid fever-induced seizures after vaccines. In some centers, infants with DS are routinely admitted for observation following vaccination. In light of the risks associated with vaccine-preventable illnesses, the authors' opinion is that the following vaccines should be given with careful monitoring in adults with DS (who can be given prophylactic antipyretics): COVID-19, influenza, meningococcal, pneumococcal and HPV vaccines. In addition, Tdap (tetanus, diphtheria and pertussis) vaccine should be given once as adult if not received as adolescent. After that, Td (tetanus and diphtheria) vaccine boosters should be given every 10 years.

3.5. Contraindicated medications for daily maintenance therapy

Sodium channel inhibitor drugs, such as phenytoin, carbamazepine, oxcarbazepine, and lamotrigine are contraindicated as daily seizure therapies. These drugs can increase seizures, myoclonus and are associated with worse cognitive outcomes (Ceulemans, 2011; Guerrini et al., 1998; Lange et al., 2018). One report however, describes 3 DS patients who had more seizures at every attempt of discontinuing lamotrigine (Dalic et al., 2015).

3.6. Managing seizure emergencies

3.6.1. Seizure action plans and rescue medications

Seizure clusters and status epilepticus are very common in DS. Every patient with DS needs an updated and yearly re-evaluated seizure action plan: a seizure emergency protocol that includes management of clusters of seizures as well as prolonged seizures. During the transition period, it is critical that a clear plan is set in place about which provider -pediatric or adult – should be contacted in the event of a seizure emergency. We strongly recommend direct communication between the two providers and with the parents to ensure everyone is familiar with the seizure action plan and agrees to it. The adult provider to whom the patient is transitioning care must be fully aware of the current seizure action plan including when parents and caregivers have been instructed to give rescue medication at home or in the community, when to call an ambulance or take the patient to the emergency room, and whether there is a preferred hospital familiar with the patient's needs. Often, the rescue medication to be used at home or in the community is a form of benzodiazepine. Pediatric patients often use a gel formulation of diazepam that is introduced rectally (Diastat) (Wirrell et al., 2017). However, most adults use sub-lingual lorazepam (1−2 mg per dose, at home most adults can safely receive up to 6 mg in a 24 -h period) (Alldredge et al., 2001) or intranasal/buccal midazolam (0.2 mg/kg or 10 mg in adolescents and adults) (McKee and Abou-Khalil, 2015). For people with DS, two doses are often needed before the seizures stop. After two doses have failed to stop seizures, the protocol should instruct caregivers to call an ambulance. Directions for vagus nerve stimulator (VNS) emergency use (through swiping magnet) should also be in the seizure action plan's emergency protocol of those patients with DS who have a VNS.

3.6.2. Emergency room treatment of seizure emergencies

Once the patient is in the ambulance/emergency room, the treatment of status epilepticus (SE) is similar to the treatment of SE in any other patient with epilepsy (with a few caveats, see below): First line drugs are IV benzodiazepines followed by non-benzodiazepine antiseizure medications like fosphenytoin, valproate or levetiracetam. Even if seizures have ended with a benzodiazepine, a loading dose of a non-benzodiazepine is recommended to prevent further seizures (Brophy et al., 2012). If the above treatment fails, the next steps should be done in the intensive care unit, as for any other cause of SE.

Caveats: 1) One should keep in mind the amount of benzodiazepine already given before the patient arrived at the hospital. 2) If a patient is already on valproate maintenance therapy, other non-benzodiazepines should be favored first. 3) Despite the fact that phenytoin is contraindicated in the long-term treatment of seizures in Dravet syndrome, many experts in Dravet syndrome may still recommend the use of fosphenytoin for emergency termination of seizures in a hospital setting. However, some patients may have more seizures following administration of fosphenytoin or this drug may not be effective in SE (Knupp and Wirrell, 2018). In the North American Treatment Consensus study, a panel of 13 expert clinicians were unable to reach a consensus on the use

of phenytoin or fosphenytoin for the treatment of SE in DS, with 7 physicians rating these agents as preferred choices, 4 rating as non-preferred, and the remainder unsure or neutral (Wirrell et al., 2017).

A Japanese study involving 99 patients, showed that in the emergency room, the best results for ongoing seizures in patients with DS are usually obtained with intravenous barbiturates (75–100 % efficacy in terminating ongoing SE) (Tanabe et al., 2008). However, 3 cases of anoxic-ischemic lesions were later reported in children that received barbiturates for the acute treatment of status epilepticus. It was postulated that high doses barbiturates may reduce local cerebral blood flow, although the confounds of concurrent SE make the interpretation difficult. Interestingly, 2 of these 3 patients were on stiripentol, which through inhibition of CYP450, could lead to increased levels of barbiturate (Chipaux et al., 2010).

3.7. Co-morbid conditions and multidisciplinary care needs

Villas, Meskis, and Goodliffe provide an overview of the multimorbidity typical of patients with DS (Villas et al., 2017). Based on a survey of caregivers of 256 patients between 9 months and 32 years, they found that after seizures, speech/communications and cognitive impairment were the caregivers' top concerns. Furthermore, caregivers also mention sleep, cardiac arrhythmias, and gait (in older patients).

3.7.1. Intellectual disability, autism and behavior

Although at the onset of DS children tend to display typical developmental patterns, cognitive development usually slows and may plateau between the ages of 2–6 years. Most adults with DS have moderate to severe ID and cannot live independently. One study found that a higher proportion of older adults have moderate or severe ID compared to adolescents (80 % and 70.5 %, respectively) (Darra et al., 2019). Another study showed that patients exposed to sodium channel blocking antiseizure drugs in the first 5 years of life had a worse cognitive outcome compared to those not exposed to this class of drugs (Lange et al., 2018). A small study showed that 61 % of adults with DS have autism spectrum disorder (ASD) (Berkvens et al., 2015). Hyperactivity, a common finding in children, is no longer a problem in adults, who tend to have attention-deficit disorder. Other problems include anxiety, perseveration, rule breaking, aggressiveness, and, in some patients, obsessive compulsive disorder (Darra et al., 2019). Hoarding behavior is not uncommon in adults with DS (Fasano et al., 2014). Behavioral problems are associated with a lower health-related quality of life (Sinoo et al., 2019).

3.7.2. Gait and motor disorders

There are no longitudinal studies on gait in patients with DS. However, several cross-sectional studies showed there is an evolution in the pattern of gait abnormalities with age (Fasano et al., 2014; Rilstone et al., 2012; Rodda et al., 2012; Wyers et al., 2019). Children 6 years old and younger may have a normal gait, joint hypermobility and/or ataxia. By early adolescence, a crouch gait often becomes apparent consisting of a flexed gait with passive knee extension deficit. Adults with DS tend to have a parkinsonian gait (small steps, turn en bloc, little arm swing, festination, postural instability) which can be responsive to levo-dopa (Fasano et al., 2014). Ataxia, dystonic gait, and tiptoeing may co-exist with parkinsonian features (Aljaafari et al., 2017; Fasano et al., 2014; Gitiaux et al., 2016; Rilstone et al., 2012; Rodda et al., 2012). Other motor abnormalities include antecollis in teenagers and adults, camptocormia in middle aged adults (Fasano et al., 2014), and dysarthria (Turner et al., 2017). Orthopedic interventions including Ankle Foot Orthotics, or AFOs, are not uncommon, although surgical interventions are rare. A proportion of adults with DS experience such significant deterioration in gait that they become largely dependent on a wheelchair or similar mobility device.

3.7.3. Sleep

Sleep is one of the most common and distressing morbidities reported by parents. In a parent survey (Villas et al., 2017), 97 % of parents reported sleep as a concern. Sleep is often disrupted because of seizures but also spontaneously. In another parent survey, 40/76 (53 %) of parents reported nocturnal seizures; however, many also reported nocturnal awakenings without apparent seizures as well as nocturnal restless. Ninety-two percent of parents monitored their children's sleep, often by sleeping in the same room (Van Nuland et al., 2021) or through the use of medical devices and monitors (Villas et al., 2017).

3.7.4. Autonomic

A large variety of dysautonomic symptoms have been reported in people with DS and include unusual breathing patterns, abnormalities in cardiac rhythm, temperature regulation, diaphoresis, and gastrointestinal function (primarily constipation or gastric dysmotility) (Berg et al., 2021; Villas et al., 2017).

3.7.5. Mortality

Dravet syndrome is associated with premature mortality in all age groups. A recent review of DS in adults shows that the main causes of death are sudden unexpected death in epilepsy (SUDEP) and SE, but drowning and accidental death are also common (Selvarajah et al., 2021). As with younger patients, SUDEP is still the main cause of death in adults (Cooper et al., 2016; Genton et al., 2011; Myers et al., 2017; Sakauchi et al., 2011; Takayama et al., 2014). Seizure detection devices and parents or caregivers sharing the bedroom are strategies employed by many families in an attempt to reduce the risk of SUDEP and monitor for nocturnal seizures. However, there is no definitive literature on the effectiveness of these measures.

3.8. Other important considerations

3.8.1. For women with DS

There are no studies showing that women with DS are less fertile than other women with epilepsy. Therefore, depending on the degree of intellectual disability and independence of the patient, it is important to discuss issues such as sexual activity, contraception, and interactions between antiseizure medication and hormonal contraceptives. Teratogenicity and risk of a patient with DS having a child with DS are other important issues to consider. For women with DS and catamenial seizures, possible therapies include hormone therapy (including long-acting reversible contraceptives) or acetazolamide, which is recommended in general for women with catamenial seizures.

3.8.2. Guardianship and power of attorney (POA)

Young adults with DS will almost inevitably require life-long guardianship for financial and medical purposes. It is absolutely essential that guardianship and medical POA be prepared in the young person's jurisdiction of residence *before* a young person reaches the age of majority and be established by the appropriate legal authority on or immediately after the day a young person attains the age of majority. Without this legal procedure in place, parents or other guardians may not be able to direct the care of the young adult in an emergency and may not have the rights to make critical decisions.

3.8.3. Sexual abuse

Finally, patients with DS are at increased risk of sexual abuse (as are other patients with ID), an issue which should be discussed with parents and caregivers prior to puberty and ongoing throughout the lifespan, so that vigilant monitoring of individuals in at-risk settings is ensured.

4. Discussion

Although Dravet syndrome is an extremely rare disorder in the population (estimated only about 250 new cases per year in the US) (Wu

et al., 2015), it may represent about 2–3 % of children with refractory epilepsy who transition to adult care (Berg and Rychlik, 2015). The complex care needs and the seizure treatment considerations follow patients into adulthood. Many adult neurologists feel uncomfortable managing patients with associated comorbidities such as ID and autism as well as the multi-system impairments and disorders that are common in patients with DS (Borlot et al., 2014). Familiarity with some of the most important medications used for DS, particularly stiripentol, fenfluramine (Nabbout et al., 2017), and cannabidiol may be limited in the adult setting. Finally, patients with DS have different social, educational and financial needs, and often adult neurologists lack the multidisciplinary support to address these aspects (Andrade et al., 2017; Brown et al., 2016).

Topics including housing and work placement options, health insurance, respite care and power of attorney, should be addressed before a patient with DS leaves the pediatric system, as is being done in many pediatric centers. But if all of this is ready and no adult neurologist can be found to take over the care of this patient, he or she will have to remain with the child neurologist, which is not a good long-term solution. In fact, in the caregivers' focus group study, 71 % of adults with DS were still being followed by their pediatric neurologist (Boyce et al., 2020).

The relative paucity of literature on adults versus children with DS highlights this gap in knowledge and perhaps interest. For instance, a recent systematic review found that as of February 2021, there were 208 studies on children with DS but only 28 on adults with DS (Selvarajah et al., 2021). This lack of research substantiates the concerns of parents of adults with DS.

Limitations: given the scarcity of literature on adults with DS and transition for patients with DS, part of this work was based only on the DS experts' experience with patients with DS. This was mainly in the areas of use of fosphenytoin in emergency rooms, avoidance of seizure triggers and vaccinations.

5. Conclusion

There is limited literature on adults with DS and no specific guidelines to aid in the transition of youth with DS to the adult system. We have created the "Dravet Syndrome Transition Guide" which we hope will ease the transition process to the adult health care system. This 2-page document (Fig. 1) will also be available for download from the Dravet Syndrome Foundation website and can be carried by parents or caregivers as well as mailed to adult neurologists who will assume the care of these young adults. Future studies should look at the efficacy of this guide, as well as how to further educate adult neurologists on caring for adults with DS.

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