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

AVOIDANCE OF SEIZURE TRIGGERS AND PREVENTATIVE MEASURES

- Avoid overexertion, hot or unsupervised baths, and outdoor activities when 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.

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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.

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-desmethyclobazam levels may require reduction of clobazam dose.
GUIDE TO TRANSITION PATIENTS WITH DRAVET SYNDROME TO ADULT CARE
This guide was adapted from Andrade et al, Epilepsy Research (2021)

TREATMENT (CONTINUED)

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-benzodiazepine 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.

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