DLG4 SHINE FOUNDATION

MEDICAL CARE CONSIDERATIONS *for*

DLG4-related Synaptopathy

November 2024 (v3)

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Patients with DLG4-related Synaptopathy (DLG4-RS) should be seen for regular wellness checkups and screenings. Inform staff that extra time may be needed for visits to accommodate sensory or motor issues. ***Currently, DLG4-related Synaptopathy is considered a permanent disability for most patients. There is no current treatment for this disorder.***

MEDICAL RECORDS

DLG4 families in the US have free access to a Medical Records Solution called Citizen. They can sign up at no charge and have all records collected and kept in one place via https://www.citizen.health/partners/shine-syndrome. Those already enrolled in Citizen can share the entire medical record in one step. Alternatively, parents and caregivers should keep a binder of health records. The binder should include genetic testing results, summaries of all doctor visits (including specialist referrals), summaries of hospital admissions, laboratory studies, EEG, x-ray reports, and other imaging results. Many recommendations specific to schooling and access to services are US-specific but can be adapted within different educational and medical systems abroad. For questions email our organization at contact@dlg4shine.org.

MEDICAL DISCLAIMER

All information, content, and material provided in this document is for informational purposes only and is not intended to serve as a substitute for the consultation, diagnosis, and/or medical treatment of a qualified physician or healthcare provider. Always seek the advice of your physician or other qualified health provider with any questions you may have regarding a medical condition.

Areas of Assessment	Assessment Details	Baseline	Yearly	Every 6 Months	Every Visit	As Clinically Indicated
Genetics/ Testing Results	Counsel family on genetic test results and refer to genetic counselor if appropriate; family to keep a copy of genetic results.	✓				
General	Update current medications and allergies, including use and frequency of rescue medication for seizures or behavioral problems.				✓	
	Weight - Height - Head circumference - Tanner Stage.				✓	
	Laboratory evaluations, including antiseizure medication monitoring as indicated for the medications (medication levels, blood counts, electrolytes, hepatic function, thyroid function, etc.).					✓
Neurology	Screen for seizures and spells suspicious for seizures. Record description and frequency of seizures. Assess older children, adolescents, & adults for signs/symptoms of migraine headaches. Assess for hypotonia, ataxia, dystonia, sterotypies, and pain tolerance.			✓		
EEG	Baseline routine EEG. Consider 24-hour EEG to evaluate for DEE-SWAS (ESES) or subclinical seizure activity, particularly in persons with developmental regression or abnormal routine EEG.	✓				✓
Brain MRI	Can be considered in those with abnormal neurologic exam and/or seizures.	✓				
Development	Documentation of baseline acquisition of milestones and careful assessment for losses of milestones. To include motor, adaptive, cognitive, behavioral, and speech-language evaluations.	✓	✓			✓
GI	Vomiting: can be episodic or occur in association w/seizures, fatigue, &/or motion sickness. Chronic constipation should also be addressed.	✓				✓

Areas of Assessment	Assessment Details	Baseline	Yearly	Every 6 Months	Every Visit	As Clinically Indicated
Education/ Therapies	Referral to Early Intervention if younger than 3 years of age.	✓				
	Documentation of therapies (type and frequency).			✓		
	Review of communication needs and applicability of Augmentative Communication Device.		✓			
	Review Individualized Educational Plan (IEP).		✓			
	Ask about need for letters of medical necessity for equipment and need for school medication forms.		✓			
Other Behavioral	For persons aged >12 months: screening for behavioral concerns such as aggression, impulsivity, and self-injury, as well as for anxiety and depression.		✓			
	Screen for antecedent triggers or risk factors for problem behaviors.				✓	
	Inquire about sensory processing difficulties.		✓			
	Review medications taking for behaviors.				✓	
Autism, ADHD	Formal autism evaluation in those with findings suggestive of ASD. Refer for ABA therapy if appropriate.	✓	✓			
	Screen for ADHD.	✓	✓			
Sleep	Assess for signs of sleep disturbances. Assess sleep initiation, maintaining sleep, nocturnal seizures, naps, excessive daytime sleepiness, and frequency of nocturnal interventions by caregivers.	✓		✓		
	Assess for concurrent medications that could be contributing to sleep disruption polysomnogram & consider a referral to sleep specialist.	✓		✓		
	Review safety of bed and bedroom.	✓	✓			

Areas of Assessment	Assessment Details	Baseline	Yearly	Every 6 Months	Every Visit	As Clinically Indicated
Vision	Ophthalmologic exam to assess for reduced vision, abnormal ocular movement, best corrected visual acuity, refractive errors, nystagmus, & strabismus that may require referral for subspecialty care and/or low vision services.		✓			
Nutrition	Screen for caloric and fluid intake. Assess growth parameters, BMI, and source of nutrition.			✓		
	Review vitamin D intake and supplementation. Obtain vitamin D level.		✓			
Orthopedics/ Rehabilitation	Estimate curvature of spine. Recheck every 6 months if scoliosis present; refer to Orthopedics if >20 degrees.	✓		✓		
	Include assessment of mobility, ADL, and need for adaptive devices.			✓		
	Assess need for PT (gross motor skills) and/or OT (fine motor skills).		✓			
Family/Social Supports	Assess for family stress (financial, social, fatigue).		✓			
	Review available community, insurance resources (aka DMV permit, respite care, age-based waiver programs, etc.).		✓			
	Assess need for home nursing referral		✓			
Transition to Adulthood	Review plans for transition to adulthood (i.e. guardianship, medical/financial power of attorney, shared decision agreements, etc).		✓ Starting at age 16			
	Referral to social work and local government agency for permanent disability application and benefits.	✓				
	Identify goal age of transition to adult providers (i.e .18 yo or 21 yo). Identify adult health care providers to transition care for all specialties involved.		✓ Starting at age 16			

GENETICS

Most cases are de novo, meaning new in the individual and not inherited from a parent. For suspicion of DLG4-RS or VUS (Variant of Uncertain Significance), genetic counseling is recommended. Follow up with a genetic provider per their recommendation or every 1-2 years.

NEUROLOGY

Seizures

The median seizure onset age is 6-7 years (Rodríguez-Palmero et al. 2021, Kassabian et al. 2023). Refer to a neurologist for seizures and spells suspicious for seizures. Seizures can be subtle and easily missed. Baseline EEG at DLG4-related synaptopathy diagnosis is recommended if not already obtained. A subgroup of individuals with DLG4-related synaptopathy has developmental epileptic encephalopathy (DEE), and around one-fourth of them have DEE-SWAS/ESES (Kassabian et. al 2023). The occurrence of DEE-SWAS (ESES) in DLG4-RS requires to be properly investigated with 12-24 hour video-EEG monitoring that captures sleep/awake periods. The most common seizure types were focal seizures and generalized tonic-clonic seizures. To read more about seizure types and what they look like and find links to videos of the seizure types, visit: https://www.epilepsydiagnosis.org/seizure/seizure-classification-groupoverview.html

Families with documented seizure(s) should be provided with a rescue medication and a plan for how to manage a seizure at home for each type of seizure, as well as be given guidance for when to use rescue medication and when to call a neurology provider vs. present to an emergency department.

Abnormal Movements

Hypotonia, coordination problems (ataxia), or other gait abnormalities are common. Physical and occupational therapy is recommended. Some medications (including some antiseizure medications) can worsen coordination.

DEVELOPMENT

Developmental Delay and Intellectual Disability

Developmental delay before age two years is one of the first signs of DLG4-RS, although it may not be appreciated until later in childhood. Developmental delay in more than one developmental domain is seen in most individuals. Others may have isolated motor or language delays, and some individuals are nonverbal. Intellectual disability in individuals with DLG4-RS ranges from mild to severe.

Regression

Regression in motor development and/or language has been reported in about 40% of individuals with DLG4-RS. Most individuals with language regression (with or without motor regression) have autism spectrum disorder (ASD), but not all individuals with ASD have language regression. Epilepsy can commonly be associated with developmental regression. Regression in verbal and/or motor domains was observed in all individuals who suffered from DEE-SWAS/ESES, but also in some who did not (Kassabian et. al 2023).

Therapies

Therapies to consider are speech therapy (ST), physical therapy (PT), occupational therapy (OT), augmentative and alternative communication (AAC), low-vision services, hippotherapy (horse), swim/pool therapy, music therapy, and applied behavior analysis (ABA) therapy. These can be accessed free or at low cost through referral to Early Intervention if under 3 years or public school special education if over 3 years.

ORTHOPEDICS/REHABILITATION

Increased risk of scoliosis and joint laxity . Equipment and accommodations in school are frequently needed. Antiseizure medications may reduce absorption of vitamin D, which increases risk of fracture. Monitor vitamin D levels and supplement if level<30.

PSYCHOLOGICAL/BEHAVIORAL

Autism Spectrum Disorder

Referral to specialty care with a neurologist, developmental-behavioral pediatrician or psychologist should be considered by age 2 years for assessment for autism spectrum disorder. Early ABA referral even without diagnosis of autism or autism spectrum has been very helpful in many patients.

Anxiety and Executive Dysfunction

Anxiety, which can be triggered by different factors such as sound or separation, is reported in many individuals and may be present starting in childhood. Behavioral inconsistency is typical and may be affected by physical factors such as sleep, seizure frequency, medications, or environment. Assess for intolerance of excessive stimuli.

Psychiatric Evaluation

While behavioral symptoms should be discussed at every visit, it is helpful to have "formal" neurodevelopmental and behavioral assessments/screeners completed every 3 to 5 years either through the school or through a physician or neuropsychologist. Pychiatric evaluation may be necessary as there may be risk for other behavioral disturbances.

SLEEP

Sleep Problems

Sleep and the circadian rhythm are often disrupted. Medications, such as melatonin, are often tried to improve the initiation and maintenance of sleep. Consider a sleep study if there are concerns with sleep.

Sleep Safety

Patients may get out of bed at night, which could be unsafe if able to wander. Consider a tent-style bed or similar engineering controls to keep the child in bed and safe (covered by some insurance as Durable Medical Equipment DME).

PAIN

Pain assessment and sensitivity: Patients may have an atypical pain response with higher or lower pain thresholds. Pain expression may occur through behavioral changes or sleep problems rather than through crying or verbal expression. There is susceptibility for individuals with DLG4-RS to experience migraines.

SCREENING

Ophthalmology

Difficult vision assessment. Strabismus and cortical visual impairment can be present, as well as hyperopia, nystagmus, and cortical blindness. Myopia, amblyopia, and slow upgaze are also seen but less frequently.

Auditory

Increased sensitivity to auditory stimuli can be present. Noise-reduction headphones can be helpful.

EDUCATION/THERAPIES

Children with DLG4-RS age 0-3 years will qualify to receive therapies through the state-run Early Intervention program. During the preschool years (starting age 3 years), school-based therapies can be obtained through a preschool at the local public school district. Services for school-aged children (3 through 21 years of age) are provided free of charge through the public school system.

Most DLG4 patients have mild-moderate intellectual disability. Formal neurodevelopmental testing through a neuropsychologist or educational testing through the school should be performed by school age to develop an Individualized Educational Plan (IEP) or 504 plan that meets the child's educational needs.

Educators may not have experience with DLG4-RS. They should focus on communication, mobility, and socialization with attention to the persons specific needs. For those whose primary form of communication is not verbal, augmentative communication utilizing pictures or devices should be considered early.

SOCIAL CONCERNS

The family/caregivers may need respite care. Refer to social work and local government agency for permanent disability application and benefits, as well as age-based waiver programs for which the family may qualify. ***Currently DLG4-related synaptopathy is considered a permanent disability for most patients***.

In adolescent patients, the family may need assistance with the transition to adulthood and determining the level of support anticipated for adult years. Review options for level of independence, including guardianship, medical/financial power of attorney, and shared decision agreements. Guardianship will be needed for most. Review steps to obtain guardianship and a Special Needs Trust.

HOSPITALIZATION CONCERNS

For those with behavioral challenges, it is helpful to involve Child Life specialists and determine plans at the beginning of the hospitalization for intervention if behavior problems escalate.

ADULTHOOD

Given the lack of knowledge we have about adults with DLG4-RS, it is recommended to follow the above guidelines for adults and pediatric patients.

Thank you to contributors:

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Medical Disclaimer: The information in this document is for informational purposes only and is not intended to serve as a substitute for healthcare provider advice. The recommendations are subject to change as we learn more about the condition.

References:

Rodríguez-Palmero et al. (2021). DLG4-related synaptopathy: A new brain disorder. Genetics in Medicine (PMID:33597769).

Tümer et al. (2023) DLG4-related synaptopathy. GeneReviews® (https://www.ncbi.nlm.nih.gov/books/NBK592682/).

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