THIS WEBSITE DOES NOT PROVIDE MEDICAL ADVICE: *The content of this document is for informational purposes only. It is not intended to be a substitute for professional medical advice, diagnosis, or treatment, and should not be used as a medical standard of care.*

A NOTE TO HEALTH CARE PROVIDERS: *Snyder-Robinson Syndrome (SRS) is an ultra-rare disorder. At the time of this writing, we are aware of fewer than one hundred cases worldwide. Consequently, the existing medical literature provides a limited description of the disorder. We hope the information on this page will enable providers to consider some helpful work-ups and evaluations that might not otherwise have been apparent, based on a review of SRS patient records in our Natural History Study. Considerations for these suggested work-ups are not exhaustive, and we welcome feedback from providers.*

If your SRS patient is currently enrolled in our Natural History Study, please discuss submitting ongoing medical data to the Natural History Study. This will help to expand the information for other physicians, researchers, and other SRS patients– even routine care may help indicate a trend.

If your SRS patient is NOT currently enrolled in the Natural History Study, please encourage them to help others by sharing their medical data. Their request to participate may be made by ***clicking here****.*

Thank you for your care of our SRS family members and your contributions to the SRS community!

Health Care Providers:
The purpose of this document is to aid physicians and other health care providers in the day-to-day management of the complex medical issues which arise in patients who have Snyder-Robinson Syndrome (SRS). We are also asking the medical community to help gather more data. This data will contribute to an expansion of the SRS phenotype, which has considerable variability.
Snyder-Robinson Syndrome has been reported in the literature and noted by clinical experts to exhibit various clinical findings, which can be referenced in the updated GeneReviews: Schwartz CE, Peron A, Kutler MJ. Snyder-Robinson Syndrome. 2013 Jun 27 [Updated 2020 Feb 13]. In: Adam MP, Ardinger HH,

Pagon RA, et al., editors. GeneReviews® [Internet]. Seattle (WA): University of Washington, Seattle; 1993-2020. Available from: www.ncbi.nlm.nih.gov/books/NBK144284/

Below, you will find a list of observational findings which have been reported in the SRS population. These observations are designed for consideration purposes and are listed with a 'systems' approach. Some of these findings have unclear clinical significance but have been reported by families and/or reported by clinicians. Many of these findings are discussed in the above mentioned GeneReviews article. Additional considerations are mentioned here to aid clinicians in their evaluation and treatment of the SRS patient, giving attention to further details which may be less commonly observed. In rare disorders, it is often helpful for families and health care providers to be aware of what has been reported even anecdotally to provide some guidance for care and potentially some reassurance.

General Systems Review:

Constitutional – Monitor weight, length, height and head circumference. SRS patients have an asthenic body habitus (thin, slender build) and many have a history of failure to thrive requiring intervention. Some patients have macrocephaly. Currently there is not a growth chart specific to the SRS patient. Developmental assessment should include motor, adaptive, cognitive, and speech/language milestones. Evaluation for early intervention/special education is recommended.

Sleep – There have been reports of abnormal sleep patterns in patients with SRS. These reports are varying and non-specific in nature; the significance is not known at this time, and it is mentioned here for informational purposes. It is recommended to document any sleep abnormalities in the medical record for trending purposes to help determine the nature of this symptom.

Pain – Parents of SRS patients have reported concerns for their child having 'pain'; to date, the etiology is unclear. Often these pain episodes are intermittent but significant enough to warrant medical evaluations. These events have been worked up by the primary care physician without a specific cause identified. It would be helpful for these patients to seek medical attention when pain episodes occur. Caretakers should document/journal the nature of complaints, the quality of the pain, time/duration of the pain, and what alleviates or aggravates the pain. The clinician should use a systematic approach for evaluation.

Sweating – Hypo- or hyperhidrosis, when present, appears to be an incidental complaint which is currently being followed for its significance. It is mentioned here because hyperhidrosis, when present, can be varied in nature. Screening studies should be considered to rule out other medical conditions such as hypoglycemia, thyroid disease and other hormonal imbalances. Recommendations are to clinically evaluate, document and track when present.

Neurology

Seizures – Seizures differ in type and intensity and are often present by early childhood. EEGs should be appropriately followed per neurologist's recommendations. Severity, frequency and success of treatment vary. Medical management of the seizures has been successful; however, in some patients the seizures are refractory and require multiple anticonvulsant medications. The following medications have been utilized with some success: clobazam, levetiracetam, valproic acid, and rufinamide. In addition, there are a few patients in which carbamazepine and phenobarbital have been utilized. Epilepsy should be managed by a neurologist experienced in seizure management, and medical management should be tailored to the specific need of the patient. For instance, some anti-epileptic drugs are known to decrease bone density. These agents should be avoided if possible due to potential worsening of underlying osteoporosis and increasing the risk of spontaneous fractures. Many antiepileptic drugs have side effects, and it is recommended that families partner with their treating physician to balance the risks of epilepsy, its treatment, and SRS. It is important to obtain baseline laboratory studies prior to the initiation of any anti-epileptic regimen to follow hepatic and renal function as some SRS patients are at risk for related complications.

Hypotonia – Patient's with SRS have been documented to have hypotonia secondary to poor muscular development. Loss of muscle mass occurs even in males who are ambulatory, suggesting that the loss is

probably the result of an underlying defect, versus merely lack of use. Early intervention with occupational and physical therapy is recommended to help maintain mobility.
Brain – Patients with SRS have been found to have varied brain abnormalities. MRI studies should be followed for atypical features including calcifications, white matter changes, thin corpus callosum and minimal ventricular enlargement.
Progression – It does not appear that there is any progressive neurologic decline or loss of previously acquired skills; however, there are a few patients who have had loss of previously acquired skills. It is recommended that SRS patients be followed closely to further delineate the stable or progressive nature of their neurologic exam.

Ophthalmology
Brain dysfunction must be evaluated to rule out cortical visual impairment in SRS patients who may have visual problems which are not specifically attributed to the physiology of the ocular structures, refraction or abnormal eye movement.
Cortical Vision Impairment (CVI) – At this time, a few patients have been reported to have CVI. It is unclear if this is a statistically significant SRS characteristic, but it is mentioned here for the purposes of discussion in order to encourage providers to seek further ophthalmologic evaluation when medically indicated. Pediatric neurology as well as pediatric ophthalmology exams should be considered to evaluate any acquired visual impairment.
Some common presenting symptoms of CVI include: inability to follow, focus or track, which may be intermittent in nature, photophobia, inconsistent visual responses with an avoidant social gaze or a gaze which appears to be blunted. These patients may or may not have poor visual acuity. The behaviors are varied and there are inconsistencies in visual responses to similar stimuli. They typically have fatigue from visual tasks and may have difficulty seeing objects in a busy background.
Myopia – It appears that myopia may be an ophthalmologic finding in SRS patients. It would be recommended that SRS patients are screened yearly for this concern.
Of note, other findings/complaints which have been recorded include: crowded drusen, pale optic nerve, torpedo shaped retinal lesion, pigmented retina, eye pain and photophobia; however, significance to SRS patients is unclear at this time.

ENT
Abnormal palate morphology – cleft/narrow/high arched palate and/or bifid uvula has been reported. Clinical evaluation including feeding assessment should be done when indicated.

Hearing
Hearing impairment – Some SRS patients have sensorineural and/or conductive hearing impairment significant enough to require hearing aids. A few SRS patients have hearing loss, which has been reported to be progressive. These are being followed. Yearly audiology evaluation should be performed. Despite the appearance of a generally normal evaluation, it would be beneficial to have the audiologist compare the waveforms to the previous exam to determine if there are subtle changes. It would also be valuable to track this over time to determine if hearing loss is progressive in the SRS patient.

Dental
Abnormal dental morphology – Various presentations of dental issues have been documented in SRS patients. These include overcrowded teeth, caries, blackened teeth, enamel hypoplasia and abnormal or peg-shaped teeth. Dental exams by a pediatric dentist are recommended every 6 months at eruption of the first tooth or 12 months of age.

Pulmonology
Reactive Airways Disease – Patients with SRS may have a history of asthma or episodic asthma, but also may present with respiratory distress of unclear etiology, which requires a bronchodilator and/or

supplemental oxygen. An interesting clinical presentation in some SRS patients is that they may have an abundance of respiratory/mucous secretions, which are quite thick in nature. This finding does not have statistical significance at this time but needs to be followed closely due to the dramatic viscosity in presentation. A few patients have significant respiratory compromise and/or apnea, which require additional support with CPAP/BiPAP. Some patients require a tracheostomy. Treatment regimens are varied and include oral steroids, nebulized treatments with bronchodilators, hypertonic saline, acetylcysteine, and/or inhaled corticosteroids. Some patients also receive airway clearance via suctioning, chest physiotherapy and/or supplemental oxygen when clinically indicated. Any SRS patient who has multiple episodes of reactive airways requiring bronchodilator or oral steroid therapy should be evaluated by a pulmonologist. In addition, those patients with recurrent respiratory infections should be assessed by pulmonology as well as immunology. (See immunology comments below).

Cardiology

Abnormal heart morphology – A few SRS patients have been reported to have various congenital structural heart abnormalities. It is unclear as to the statistical significance in comparison to the general population, but echocardiogram should be considered in SRS patients when medically indicated.

Gastroenterology

Failure to Thrive – Many SRS patients have a diagnosis of failure to thrive for various reasons. Any patient who is not meeting appropriate growth parameters should be evaluated and tracked. Currently, there is not a growth chart developed specifically for SRS patients. This should be taken into consideration when tracking growth on standard growth charts.

Feeding issues – Many SRS patients have feeding issues requiring intervention.

Constipation – Chronic constipation is a finding in most SRS patients. This does not appear to be related to immobility; patients who are both ambulatory as well as non-ambulatory suffer with chronic constipation. Most of these patients are managed with polyethylene glycol (Miralax).

Findings of unknown/unclear statistical significance include: Diarrhea, gastrointestinal inflammation, gastroesophageal reflux disease, vomiting and elevated hepatic transaminases.

- Diarrhea – Some SRS patients have intermittent diarrhea, which may contain blood or mucous.
- Gastrointestinal inflammation such as Crohn's, colitis and gastritis – Varied presentations of gastrointestinal inflammation are noted in some SRS individuals. (Statistical significance is unknown at this time).
- Gastroesophageal Reflux Disease/Vomiting – GERD is another gastrointestinal presentation of unclear statistical significance at this time. Clinical evaluation and treatment would be warranted.
- Elevated hepatic transaminases (intermittent in nature) – This finding has been noted in a few SRS patients, some of which are severe. It is mentioned here because of its intermittent nature and the need to follow liver studies closely over time.

Despite the unclear statistical significance of the varied gastrointestinal presentations in SRS patients, a baseline formal evaluation by a gastrointestinal physician is recommended. It is also suggested to consider following liver function studies at routine intervals and during illnesses as medically indicated.

Urology

Urine with whitish powder or sediment – There have been some reports of SRS patients who have an unknown whitish powder or sediment in their urine, which has been noted as a prominent debris/layering in the bladder on ultrasound reports. (See nephrology comments below). At this time, the etiology of this powder is unclear. Samples have been reported as calcium phosphate (apatite) also known as carbonate apatite. Due to the dramatic presentation of this sediment in a few patients, it is mentioned here for informational purposes. Routine microscopic urine analysis is recommended during well visits and should be considered at sick visits. A urology referral is recommended to work up this sediment when medically indicated.

Nephrology
Nephrolithiasis has been reported in some SRS patients. A screening renal ultrasound should be considered and repeated periodically to document the presence or absence of kidney stones and/or structural abnormalities. Tubulopathy has been documented in at least 3 patients. Additionally, as stated above, debris in the bladder, as well as urinary sediment consisting of calcium phosphate/carbonate apatite has been reported.
Creatinine level as it relates to kidney disease – It is recommended to monitor the serum creatinine in SRS patients, as they typically have low muscle mass. It is not uncommon for SRS patients to have a low creatinine at baseline due to this decreased muscle mass. A creatinine result listed as normal by standard laboratory parameters may be falsely reassuring when in fact that level may actually be elevated relative to the low muscle mass. This could be an important indication of renal disease. When following creatinine levels, compare and trend changes from the patient's baseline.

Hematology
Anemia – Iron deficiency anemia has been noted in some SRS patients, but it may not be statistically significant when compared to the general population. Consider screening labs for anemia.
Thrombocytopenia – Episodes of neonatal thrombocytopenia have been documented. Currently there is not a recommendation to check platelets at birth as a screening lab. If a patient is born with a diagnosis of SRS which was determined antenatally (due to prior knowledge of SRS family history), consideration for following platelet trends at birth would be valuable. Some SRS patients have had intermittent thrombocytopenia of unclear significance. Consider the trending of routine complete blood counts as medically indicated.

Endocrinology
Osteoporosis – Nearly all SRS patients have early onset osteoporosis and fractures in the absence of trauma. It is recommended that the clinician obtain bone mineral density studies/DEXA scans early and follow for evidence of osteopenia or osteoporosis. Several individuals are on calcium supplementation and/or treated with bisphosphonates. If a patient is receiving bisphosphonates, it is recommended to follow serial bone mineral density studies/DEXA scans to evaluate efficacy. The overall effectiveness is being trended.
Hypoglycemia – Some patients have neonatal hypoglycemia, and it has been noted that hypoglycemia is an intermittent finding of unclear significance in the SRS population. Consideration should be given to follow chemistry panels routinely and/or during illness when medically appropriate.
Hyperglycemia – Hyperglycemia is another finding noted in the SRS population. This can be tracked in a patient when chemistry panels are obtained.

Immunology
There may be a possible immune component to SRS. Multiple types of infections are noted, which include frequent episodes of otitis media (requiring PE tubes), sinusitis, upper respiratory infections, pneumonia and urinary tract infections. Several patients have had recurrent, intermittent, and unexplained fevers. There has been documentation of abnormal immunoglobulins in a few patients and, in some cases, Ig therapy (IVIG or SCIG) is administered as treatment. Immunologic treatment on at least one patient includes immunosuppressants. The significance of this is being followed closely, and consideration for a comprehensive immune work up would be recommended in patients when medically indicated. Often, the work-up is negative except for abnormal immunoglobulins and an abnormal response to the pneumococcal vaccines. Nevertheless, due to the paucity of this syndrome, it would be advantageous to obtain a more detailed immune work up to aid in the discovery of what might be an immunologic component in the SRS patient, as findings have been quite varied (including one patient with memory B cell defect) and inconsistent.
At this time, some treating physicians of these patients have suggested immune dysregulation and/or an autoimmune component, which is being followed.

Orthopedic/Musculoskeletal
Along with osteoporosis, SRS patients have both scoliosis and kyphoscoliosis. Imaging studies should be obtained and followed yearly at the first sign of scoliosis. Abnormal pectus has also been noted. Ulnar deviation and some forms of abnormality of joint mobility (joint laxity/contractures/joint subluxation) have also been observed. Appropriate referrals for orthopedics, physical therapy, occupation therapy and physiatry are recommended when indicated.

Psychiatry/Developmental Pediatrics
When clinically appropriate, evaluation with psychiatry and/or developmental pediatrics should be considered. We are currently tracking reports of autism and/or sensory issues. It would be recommended to obtain psychiatry/developmental pediatric evaluations when clinically indicated.

Genetics
Counseling with a geneticist and/or genetic counselor is advised.

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