DSMIG-USA®
Down Syndrome Medical Interest Group

Regression in Persons with Down Syndrome: Current Consensus Update for Families

What is Regression?

Regression is a general term for the loss of previously acquired developmental skills in an individual. This can be in the areas of daily living, language, motor abilities/function, or social interaction. Regression can occur, over weeks to months, or more quickly and time course may help in determining the likely cause of the regression. *Regression can be caused by many things and is associated with a marked decline in previously established function.*

One of the causes of regression is a specific disorder that is referred to as Down syndrome regression disorder (DSRD), Down syndrome disintegrative disorder (DSDD) or unexplained regression in Down syndrome (URDS) and these terms are sometimes used interchangeably. In this document, we will use 'Down syndrome regression disorder' (DSRD)'.

What are Some of the Symptoms Associated with Down syndrome Regression Disorder?

- Social withdrawal from friends, family, and school/classmates
- Loss of language or diminished language
  - Decreased or loss of speaking, loss of certain word use, sentence structure changes, "baby talk", speaking in a whisper
- Loss of previously acquired developmental milestones or abilities
- Loss of independence in activities or need for significant assistance with activities (e.g., can no longer toilet or use the bathroom independently, feed self, dress self, or bathe self when previously able)
- Development of autism-like features that were not previously present (onset over weeks, not chronic)
  - Decreased eye contact, repeating things that other people say or repeating lines from movies/television, decreased showing of empathy or emotions towards others, anger or frustration with or without behavioral outbursts, stereotypy (repetitive hand or body movements), lack of interest in others
- Changes in motor activity (stiffness, slow movements, freezing, tics and/or extra movements that are not purposeful)
  - Repetitive purposeless (random) movements, resistance to passive movement (stiffness), and sudden loss of tone (cataplexy) can sometimes be seen as well
  - "Freezing" or slowness in moving. This can sometimes look like a slow and shuffling gait where the feet don't lift off from the floor
  - Catatonia is a term that describes stiffness or rigidity of the muscles when placed in certain positions (like moving a mannequin). Persons with catatonia can also move slow or not initiate movements well, maintain odd postures or may have repetitive or purposeless overactivity
- Change in eating patterns (e.g., not wanting or not having interest in eating, extreme

slowness with eating)
    - This may or not be associated with weight loss.
- Insomnia and difficulty sleeping
- Compulsive and/or obsessive behaviors (e.g., lining up toys, rigidity with routines not previously present, only talking about one specific show/activity/game)
- Facial grimacing (contorted face as if in pain or tasting something sour) or repetitive movements of the mouth that can mimic chewing behavior
- Bizarre thought content or experiences (psychosis)
    - This can include hallucinations (seeing or feeling things that are not there), delusions (belief in things that are not true), altered awareness, or distortions of memories/historical knowledge.
- Inappropriate mood and affect (crying for seemingly no reason, laughing uncontrollably to themselves even in an otherwise solemn situation)
- Aggressiveness towards self or others
- Increased self-talk or start of self-talk not previously present

Of note, persons with DSRD often have a sub-acute (less than 3 month) onset of these symptoms as opposed to more gradual decline. If you or a loved one has a constellation of any of these symptoms, we recommend expedited evaluation by an expert. The presence of "triggers" that precede the onset of symptoms can be present and can include negative life events, changes in the home/school environment, and medical illness or hospitalization disease.

Do I Need to Get Evaluated?

If your loved one is experiencing any of these symptoms, prompt evaluation is recommended. There may be medical or psychological issues that cause symptoms that mimic DSRD that could be reversible. Therefore, it is very important for a person with Down syndrome to get a medical evaluation early if they are showing symptoms of regression as described above. Although doctors don't know for certain, it is also presumed that early diagnosis and treatment may improve outcomes.

What are the Other Causes of Regression in Persons with Down Syndrome?

- Medical: Individuals with Down syndrome are at an increased risk for developing several medical conditions. This can include obstructive sleep apnea (OSA), hypothyroidism, cervical spine disorders and celiac disease, to name a few. While a direct association has not been made with these medical conditions and regression, it is very important that you work with your medical provider to rule out any possible medical diagnoses that may be a contributing factor to symptom presentation.

- Psychiatric/Psychologic: Persons with Down syndrome are known to have higher rates of depression, anxiety, catatonia, autism spectrum disorders, and attention-deficit disorder than neurotypical persons. The presence of these psychiatric conditions in an

individual with Down syndrome is complicated by the fact that intellectual disability is nearly always present as well, limiting an individual's ability to express what he/she is experiencing, thinking, or feeling. One hypothesis of regression is that it is triggered by or a result of psychiatric illness.

- There is no "blood test" for diagnosing psychiatric/psychologic disorders. A psychiatric or psychological professional may utilize screening tools, symptom checklists, interviews, and some formalized evaluation to determine what diagnosis fits.
- Catatonia has been recognized as a common feature associated with DSRD. Catatonia can be caused by either psychiatric and/or medical conditions. Symptoms can be easily overlooked. Catatonia is important to detect because there are specific treatments for catatonia. Benzodiazepines (especially Lorazepam/Ativan) are effective for the treatment of catatonia, but other psychiatric medications can also be helpful. A treatment called electroconvulsive therapy (ECT) is also effective in treating individuals with regression.
- Individuals with psychiatric/psychologic mediated regression may also respond to anti-depressants, anti-convulsant medications (seizure medications/mood stabilizers), anti-psychotic medications and/or electroconvulsive therapy (ECT).
  - Consultation with a specialist is recommended prior to starting these interventions. Every patient is unique and there is no single medication or intervention that is best, which may require trying multiple different medications before finding a positive response.
- Autism spectrum disorders are more common in young individuals with Down syndrome. For chronic or slowly developing regression, co-morbid autism may be a possible explanation especially when other causes are ruled out. Autism spectrum disorder itself (regardless of presence of Down syndrome) is also associated with a higher incidence of catatonia.

- Neurologic: Persons with Down syndrome are at risk for multiple neurologic diseases. Ruling out common entities like seizures (also called epilepsy), dementia (also called Alzheimer's disease), stroke, and mitochondrial disease is important. Given the higher prevalence of these disorders in Down syndrome, we generally recommend that all persons with Down syndrome experiencing regression be evaluated by a neurologist, preferably one familiar with assessing people with Down syndrome, or a physician familiar with Alzheimer's disease in Down Syndrome.
  - Some of the testing that neurologists may order include an EEG (which evaluates for seizures and/or epilepsy), MRI (done with and without contrast to evaluate for structural causes of regression and brain changes associated with inflammation and infection) and sometimes a spinal tap (also called a lumbar puncture) which helps evaluate for infection, changes in neurotransmitters and

inflammation. Doctors may also order a special type of MRI called an MRA which is used to look at the blood vessels, specifically in the brain and neck. Sometimes patients will receive a special type of CT scan called a CTA instead of an MRA depending on the need for sedation and the type of imaging available at the specific hospital.

- Some families have been told that their loved one with Down syndrome and regression has "early onset Alzheimer's disease". This is *very rare* in persons less than 40 years old and other causes should be ruled out prior to arriving at this diagnosis.
- If a person with Down syndrome is experiencing any sudden onset (<24 hours) symptoms of weakness, slurred speech, vision difficulties, problems swallowing, difficulty walking, or facial asymmetry, this could indicate a medical emergency and urgent evaluation is recommended.

- Neuro-Immunologic: In a subset of individuals with Down syndrome and regression, inflammation of the brain has been found. This is typically identified and confirmed through a spinal tap, EEG and brain MRI. Spinal taps (in spite of the name) require a needle to be inserted between spinal bones into a fluid filled space surrounding the spinal cord. The fluid which surrounds the brain and spinal cord is analyzed in a lab to tell doctors if there is evidence of infection which would require treatment or if there are immune cells that could be causing inflammation.
  - If inflammation is found there is some case-based evidence to suggest the use of immune-based therapy may be helpful in DSRD although consultation with a specialist in this area is strongly recommended. The causes of inflammation in the brain are variable and sometimes the term "autoimmune encephalitis" may be applied. Although that term may be used for descriptive purposes, it remains unclear if this process is actually an autoimmune encephalitis or not. Testing for specific antibodies as noted above can be helpful in cases where there is a suspicion for neuro-immunologic phenomenon.
  - Immunotherapies have been identified as being beneficial in both individuals with and without diagnostic abnormalities in two large studies however not all individuals should receive these treatments. Discussion of the risks and benefits of immunotherapy is strongly advised with your multidisciplinary care team.

- Immunologic/Endocrinologic: Persons with Down syndrome are at risk for a host of inflammatory and endocrine disorders like thyroid disease, celiac disease, rheumatologic conditions (including inflammatory skin conditions such as psoriasis), and diabetes. Although these are more linked to longstanding (chronic) symptoms of regression, ruling in/out these diseases is of value as they are treatable.

- Genetic: The majority of persons with Down syndrome have trisomy (three copies) of

chromosome 21. Despite this commonality other genetic variations are present in everyone. Thus, the possibility of having more than one gene variation in a single person is well-established and reported. Depending on symptoms and the presence of other medical issues, testing may include a targeted panel or more broad analysis, referred to as whole exome sequencing. Metabolic testing of blood or urine can sometimes detect genetic variation, but not every person with regression requires genetic or metabolic testing.

- Nutritional/Environmental: Some cases of regression can be caused by severe vitamin deficiencies, heavy metal or toxin exposure or infection. These are less frequently reported in persons with regression but can be evaluated as well, especially if there is a history of exposure or very restricted eating or diet.

Arriving at the most likely reason for regression in a person with Down syndrome is very important as the therapies that can be offered are different depending on the cause. We encourage discussion with other families about regression but please be aware that no case of regression is exactly like the next.

We as a medical community are still learning the best ways to test, diagnose, and treat persons with DSRD and an open dialogue between you and your doctor is the best way to optimize care.

What Tests Should Be Done?

As there are many potential causes of regression in persons with Down syndrome, we propose a broad work up which tests for various causes based on each individual's profile of symptoms. Recently published (2022) guidelines for physicians are available in the references section below.

We suggest that you encourage your physician to read through the articles referenced at the end of this document to familiarize themselves with the regression and some of the tests that are used. It is possible that your doctor may not be comfortable with obtaining each test and they ask you to see a "specialist" doctor (or consultant) for additional evaluation and testing.

Do I Need to Do All the Testing?

Testing is based on an individual's symptoms and then determining the most likely cause of regression. DSRD is a diagnosis of exclusion and for this reason, comprehensive testing is advised. Sometimes a combination of treatments will be considered and discussed. You do not need to have all testing performed before starting a treatment although some testing (like MRI or spinal tap) may help guide the most appropriate treatments to start with.

Is There a Treatment?

There is no one singular treatment for persons with DSRD. However, once a reason for regression is found, your doctor(s) can work together to provide the best treatment options.

We recommend seeking consultation from an expert in psychiatry, neurology, and/or a provider familiar with treating people with Down syndrome and regression before starting a therapy. Multidisciplinary care is strongly encouraged when available.

Your doctors may recommend treatment while still waiting to get tests done. Typically, this will not interfere with the accuracy of the testing when performed after starting a treatment.

For consideration of immune therapy (e.g., steroids or IVIg) you should be under the care of a neurologist or immunologist with prior experience in the use of immune therapy. When considering psychiatric medications or ECT, you should work with a psychiatrist or neurologist familiar with Down syndrome. Seeking the care of allied health professionals including psychologists, therapists, and social work can also be beneficial when available.

Are There Clinical Trials or Research Available for Regression in Down Syndrome?

Professionals working with the Down syndrome community are actively investigating the causes of and treatment for regression in persons with Down syndrome. All clinical trials (not just regression related) are listed at: https://clinicaltrials.gov/

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Selected Reading Materials: *(listed alphabetically)*

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