Duration of Alzheimer's Disease

The duration of Alzheimer's disease in adults with Down syndrome is not clear. In those without Down syndrome, the course of Alzheimer's disease is thought to be approximately ten to twelve years. Particularly in people with Down syndrome who have a higher degree of functioning before the onset of Alzheimer's disease, an overall course of ten or so years might be expected. However, our experience suggests that the duration is shorter for many, particularly in those who have a lower level of functioning prior to the onset of Alzheimer's disease. In a sense, the further the person has to fall cognitively, the longer it generally takes. We have seen people live one year from the time of diagnosis to the time of death. On average, though, the time from the development of symptoms to death is usually in the five- to six-year range but has been much longer for some. Note that these time frames are referring to the time that symptoms are noted. It is known that the brain changes in Alzheimer's disease begin a number of years before the individual develops symptoms.

Again, the development of seizures (particularly if they are difficult to control) seems to accelerate the decline in some people. Losing the ability to walk and the complications seen when this skill is lost also seem to increase the rate of decline. The onset of swallowing dysfunction, when associated with recurrent aspiration pneumonias, is the symptom that most commonly contributes to death.

Future Considerations

At present, a great deal of research is addressing the issue of Alzheimer's disease, both for people with and without Down syndrome. People with Down syndrome receive particular attention when it comes to Alzheimer's disease because studies have found that all people with Down syndrome develop the neuropathologic changes that are seen in Alzheimer's disease by the age of sixty. Eventually, the findings in people with Down syndrome may be important keys in unlocking the mysteries of Alzheimer's disease for all people.

Chapter 27

Regression

When Jade, age thirty, came to see us for her first evaluation, she initially appeared to have autism. She made little or no eye contact with our staff and made many repetitive motions. She did not speak during the assessment and reportedly had no verbal skills. However, we soon learned that for many years, she had been a typically developing person with Down syndrome. As a child and teenager, she had had good verbal and self-care skills and only mild intellectual disabilities, and she had attended school and participated in a variety of activities.

Jade's mother reported that her daughter had suddenly regressed after being treated with an antibiotic for a cold at age seventeen. She had undergone extensive testing over the past thirteen years, including blood tests, imaging, and a sleep study. She had been diagnosed variously with depression, anxiety, late-onset autism, early Alzheimer's disease, and psychosis. She had been treated with different psychotropic medications and supplements. Although Jade's cognitive skills had not declined further, she had made little to no improvement.

Evan was twenty-three years old when he was evaluated. He had been given prednisone to treat a rash that had not responded to prescription lotions and oral antihistamines, and shortly thereafter, he began showing symptoms of depression. He had been a very social person, and his interactions with others rapidly decreased. His sleep was altered, and then his appetite diminished. Within a few weeks, he was not eating. His verbal skills deteriorated, and he could no longer take care of his own hygiene, clean his room, and go to work; all areas he was quite skilled and independent in previously. He was started on an antidepressant, but his symptoms worsened. He required hospitalization because he became dehydrated. There it was noted that Evan seemed "rigid," "not moving," and even "frozen," and he was diagnosed with catatonia. Treatment options were discussed, and Evan and his family selected electroconvulsive therapy (ECT). After the first treatment, he had remarkable

improvement and after several treatments, he was back to his baseline. He was again taking care of his own needs, working, and enjoying life.

For decades, health professionals with a special interest in people with Down syndrome have noted cases in which teens or young adults with Down syndrome experienced a puzzling decline in abilities. These individuals, usually in their twenties or younger, suddenly lost speech, cognitive, and daily living skills and often had behavioral or psychological changes. This "regression" has been given several names, the underlying diagnosis has varied, and response to treatment has been mixed.

As is evident from reading the two case summaries above, much has been learned about these changes in individuals with Down syndrome. Jade was first evaluated many years ago before regression in young people with Down syndrome was a regular topic of conversation at meetings among Down syndrome specialists. Evan was evaluated and treated more recently, when there was a better appreciation for the condition. However, there is still much that is unknown and there are differences in the understanding of the cause and treatment, and even different names for this cognitive decline. Is "regression" a specific condition from a specific cause or is it a large category that can have many causes from a variety of mental and physical health conditions? A variety of physical and mental health conditions can cause people with Down syndrome to have further cognitive impairment. Is regression a specific diagnosis or a description of symptoms that can be attributed to many of those causes? Answers to those questions are all part of the ongoing work to further understand these changes.

As you will note below, the condition has been given several names. For the purpose of the chapter, we will call it "regression syndrome" or "adult regression syndrome."

What Research Has Found

Reports of regression in young people with Down syndrome go at least as far back as the 1940s, when a researcher (Rollin, 1946) described the development of catatonic psychoses in twenty-eight of seventy-three individuals with Down syndrome living in a residential facility. Many years later, another researcher (Prasher, 2002) observed regression over one to two years followed by a plateau in functioning in young adults with Down syndrome and reported on them in his letter titled *Young Adults with a Disintegrative Syndrome (YADS).*

Recently, there have been more clinical case reports of regression in adolescents and adults with Down syndrome who have shown unexpected and severe regression in cognitive and adaptive functioning, motor function, communication skills, and behavior. This regression is reported to occur following a period of stable functional skill acquisition in young adolescents or adults as described by their families.

In 2015, one group of researchers (Worley et al.) described a new onset of autistic-like regression they labeled "Down Syndrome Disintegrative Disorder." That same year, other researchers (Ghaziuddin, Nassiri, & Miles) described four individuals with Down syndrome and regression along with motor disturbances such as slowing or increased motor activity who were diagnosed with catatonia.

One researcher (Akahoshi, 2012) described a mean age of onset of 21.2 years of age. Another researcher (Mircher, 2017) found an average age of onset of 18 years in girls and 21 years in boys among the thirty individuals he identified. However, the youngest individual was eleven and the oldest was thirty when symptoms were noted.

What Regression Is Not

Both autism and Alzheimer's disease are relatively common in adults with Down syndrome and can cause behaviors and loss of skills similar to those seen in regression syndrome. However, there are also important differences that have led to the current conclusion that regression syndrome is not caused by either autism or Alzheimer's disease. Most importantly, autism and Alzheimer's disease each have a characteristic age of onset and timeline that are distinguishable from the regression syndrome. To determine whether one of these conditions is contributing to a decline in skills in a person with Down syndrome, careful history-taking and diagnostic assessment for autism and Alzheimer's disease are needed to determine the age of onset, preexisting level of function, and pattern of change over time. Ruling out other contributing conditions or illnesses via medical assessment is also necessary.

One group of researchers (Worley et al., 2015) did describe individuals with regression syndrome as having autism or an autistic-like condition. However, these individuals are "too old" to be diagnosed with childhood autism. This is true even though childhood autism has a later onset in children with Down syndrome than usual. (ICD-10 criteria specify onset by age three.) Even late-onset autism or childhood disintegrative disorder, as referred to by Worley and his colleagues, begins earlier in life than the regression syndrome. Those criteria include onset by ten years of age for late-onset autism, and by age seven years for childhood disintegrative disorder in those without Down syndrome.

On the other end of the age spectrum is Alzheimer's disease. Among adults with Down syndrome, the average age of onset has been reported as 54.7 years (Tyrrell et al., 2001) and 54.2 years (Lai & Williams, 1989). Symptoms of Alzheimer's disease are unlikely to occur in individuals with Down syndrome younger than 35 to 40 years (Moran et al., 2013). The onset of adult regression syndrome in the teens and early twenties is much earlier than the age of onset for Alzheimer's disease. In addition, Alzheimer's disease is marked by *progressive* impairment in cognitive, adaptive, and motor function. In contrast, regression syndrome often can plateau (sometimes for many years) after a rapid onset of symptoms. Also, Alzheimer's disease is often accompanied by seizures in people with Down syndrome (Zigman & Lott, 2007; Head, Powell, Gold, & Schmitt, 2014). These characteristics are significantly different from the symptoms of regression syndrome.

Due to these differences and the very young age that some individuals develop symptoms of regression syndrome, there is at least some agreement that Alzheimer's disease should be excluded as the cause of regression syndrome. For example, Akahoshi et al. (2012) concluded that regression syndrome has features and a clinical course that is different from those seen in typical Alzheimer's disease in people with Down syndrome.

What Is Known about Regression Syndrome?

Although researchers and clinicians now usually agree that regression syndrome is not due to autism or Alzheimer's disease, there is still much that is unknown or unclear. For example, in some cases, regression in adults with Down syndrome is due to depression, sleep apnea, or another treatable condition—should those individuals be considered to have the syndrome until they have recovered normal function? Should only those who are more challenging to treat and who never fully recover be considered to have the syndrome? Do the individuals with severe regression in some way form a unique group, or do the behaviors and other changes in regression syndrome occur along a continuum similar to the way symptoms of autism occur along a spectrum (Devenney & Matthews, 2011)?

There is some disagreement as to the answer to those questions. For this chapter, however, we include anyone with Down syndrome who is regressing for a variety of reasons (except for those with Alzheimer's disease or autism) and has a certain pattern of symptoms (see "Clinical Features" below). We will explore the differential diagnosis—how other diagnoses are ruled out—and give special attention to those for whom the diagnosis is less clear or who are more severely affected and provide a greater treatment challenge. Many conditions that cause similar symptoms that should be considered during differential diagnosis often don't include the breadth of symptoms described (although they can). Therefore, those with regression but without the breadth of symptoms are excluded from the diagnosis of regression syndrome. Instead, they could be described as having some regression as part of their primary diagnosed condition (for example, depression accompanied by regression).

Further study is obviously needed to improve our understanding of diagnosis and treatment of individuals with Down syndrome who experience a decline in skills. What is clear, however, is that the brain/cognitive function of people with Down syndrome can be "fragile" and susceptible to further impairment for a variety of reasons. It is also clear that regression syndrome includes symptoms that could be caused by a number of conditions.

Features of Regression Syndrome

There is not agreement, yet, on the name of the condition, nor is there agreement on the definition and clinical features—the signs/symptoms that an outside observer or health care provider would be able to note. However, the Down Syndrome Medical Interest Group-USA (DSMIG-USA) working group is developing a working definition to provide a framework for case finding and further study.

The discussions by this group have led to this operational definition:

Core features:

- Cognitive and executive dysfunction (executive dysfunction refers to difficulties with the brain function that helps us manage time, pay attention, switch focus, plan and organize, and perform other higher thought processes)
- social withdrawal
- loss of acquired skills
- loss of functional use of language

- duration of more than three months (see comment below)

Exclusions:

- not autism (although people with Down syndrome and autism can also develop regression)
- not Alzheimer's disease

Variable features:

- maladaptive behavior (new onset or change in behavior)
- psychiatric symptoms (including depression, compulsive behaviors, and others)
- failure to acquire new skills
- inattention-disorganization (new onset or change in behavior)
- motor changes (slowing or increased movements)
- vegetative symptoms (appetite/weight loss, incontinence, sleep pattern disturbance)

Demographics:

- typically, between ages fifteen and thirty years
- equally common in males and females

Based on the consensus of experienced clinicians, these core features are very common in regression syndrome: cognitive-executive dysfunction, social withdrawal, loss of acquired skills, and loss of functional use of language. Some or all the other variable features are often present as well. Initially, a duration of more than three months was considered necessary for the diagnosis, but more recently it has been recognized that early treatment can make a significant difference in some individuals. Therefore, the DSMIG group recommended against waiting three months to make the diagnosis and start treatment, as that delay may have a negative effect on recovery, even though the symptoms commonly last more than three months.

People at all cognitive levels may be affected, including many without prior mental health concerns (Akahoshi et al., 2012). These individuals are commonly in their teens or twenties (although older and younger individuals have been described), and their decline occurs mostly in association with other neuropsychiatric symptoms/conditions (e.g., depression, psychosis, obsessive-compulsive disorder, or catatonia) and rarely in isolation from other psychiatric symptoms (Prasher, 2002). The onset of symptoms is typically fairly acute (sudden), but changes often occur over an extended period of weeks to months.

The core findings of regression/loss of skills may not be apparent initially or may be less significant than other symptoms, particularly behavioral or psychological, and, therefore, not immediately recognized. For example, diagnosis and treatment of depression may or may not lead to improvement of mood disturbance, whereas symptoms of skill loss may only become apparent over time.

Assessment of Regression

Darius, a twenty-three-year-old man with Down syndrome, was brought to a Down syndrome clinic because he had experienced

increasing cognitive impairment over several months (from his baseline of a stable, mild intellectual disability). According to his family, he had the following worrisome symptoms: social withdrawal and reduced verbal communication; periods of motor slowing alternating with times of increased motor activity and emotional agitation; difficulties with self-care tasks he had previously mastered; periods of increased sleep for weeks followed by weeks of difficulty sleeping; and inability to perform at his job. Darius was taking levothyroxine, which had been prescribed eight months ago when he was diagnosed with hypothyroidism. His thyroid blood testing had been normal five months prior, but now his lab results revealed a very low TSH and high free T4, which indicated that his dose of levothyroxine needed to be reduced. Neither adjusting the dose of his levothyroxine nor subsequently discontinuing it resulted in a return to normal of those lab values.

With further assessment, it became clear that Darius's thyroid was fluctuating from a hyperthyroid (overactive) state to a hypothyroid (underactive) state and back. Ultimately, his thyroid function was stabilized with radioactive ablation and levothyroxine treatment, and his regressive symptoms improved over several months. In Darius's case, fluctuating thyroid function likely contributed to psychological, motor, and cognitive symptoms.

The assessment of a person with Down syndrome who is regressing can require an extensive search for underlying health problems. A number of possible causes must be ruled out as the cause. However, there are conditions that are more common in people with Down syndrome and commonly result in some degree of regression: sleep apnea, celiac disease, depression, adjustment to life changes, and other conditions listed below in the section on differential diagnosis. Some people with Down syndrome with these conditions develop the full range of symptoms described above and thus meet the definition as proposed by DSMIG-USA, and some have milder symptoms or only some of the symptoms. A thorough assessment, initially focusing on the conditions that are more common in individuals with Down syndrome can help direct the diagnosis and treatment in either case.

It is important to remember that the complete picture of regression syndrome is often not evident on the first visit. Patients or families often focus on the symptoms that are particularly problematic and may not recognize or report other symptoms. Over time, medications prescribed for psychiatric symptoms may lead to improvement of some or all these changes, making other symptoms (e.g., psychomotor slowing) more evident. Sometimes all symptoms may intensify over time until they stabilize. Repeated assessment for new symptoms and improvements will often make the clinical picture clearer.

If you are seeking an assessment for a teen or adult with Down syndrome who is experiencing regression, you may have trouble finding a physician with experience evaluating and treating the condition. You are most likely to find health care providers with the expertise at a Down syndrome clinic. To help delineate cause and guide treatment, you may want to share

these recommendations on what to assess for:

- Duration, age onset, duration of symptoms (weeks-months-years): Has the person experienced prior episodes of regression? What is his developmental, behavioral, and psychiatric history?
- Specific adaptive skill loss, based on previously established skills:
  - cognitive-executive skills
  - social skills
  - speech/language skills
  - ability to learn new skills
  - loss of control of bodily functions (e.g., incontinence)
- Psychiatric symptoms:
  - mood, irritability
  - inattention, distractibility, disorganization
  - obsessive-compulsive behavior, perseveration
  - agitation, aggression
  - apathy, mutism, abulia (reduced initiative)
  - stereotypy, mannerisms (e.g., seemingly odd or purposeless repetitive actions)
- Maladaptive behaviors: self-injury, scratching, poking, skin-picking
- Motor symptoms:
  - catatonia-muscular rigidity, immobility, or either slowing or increased movements
  - tics
- Vegetative symptoms: sleep disturbance, loss of appetite and/or weight
- Additional history to obtain:
  - level of function prior to onset
  - snoring, pauses in breathing, daytime drowsiness
  - history of surgery and/or general anesthesia and relationship in time to the onset of symptoms
  - personal or family stressors
  - trauma, victimization
  - life changes (school, family changes, deaths)
  - recent infections
  - menstrual changes, dysmenorrhea
  - puberty
  - vision or hearing changes
  - change in gait, weakness
  - headaches

- Medication review: changes, additions, or subtractions and timing of these changes relative to onset of regression
- Examinations:
  - Observation-Mental Status-Physical-Neurologic examination
  - DSM-5 or DM-ID 2 criteria checklists
  - DSMIG-USA operational criteria checklist
- Neuropsychology assessment (by neuropsychologist or family/care providers completing checklists):
  - adaptive skills
  - cognitive function (executive skills) decline
  - maladaptive behavior
  - psychiatric symptoms
  - motor-movement (catatonia)

Differential Diagnoses

Miranda, age thirty-three, was brought to a Down syndrome clinic due to concerns about her reduced ability to manage her activities of daily living. Due to changes over the last six months, her family and her support staff were very worried that she was developing Alzheimer's disease. Miranda was not participating in activities, was speaking less, and had withdrawn from contact with others. She was not sleeping well and had taken to sleeping on the couch in the family room, even though outside lighting made it brighter than her bedroom. In addition, her appetite had decreased, and family and support staff reported that she seemed "nervous."

At this exam, dense cataracts were diagnosed, although no cataracts had been visible at her eye exam about eighteen months earlier. In addition to the cataracts, Miranda was diagnosed with depression, possibly related to her emotional response to the rapid loss of vision. The evaluation did not reveal any other causes for Miranda's regression. Several months after cataract surgery and treatment with an antidepressant, Miranda returned to her previous level of function.

As mentioned above, people with Down syndrome are susceptible to a variety of medical conditions that can affect their brain function, leading to further cognitive, behavioral, motor, and communication impairment. For this reason, it is often important to rule out a number of conditions when exploring the diagnosis of regression syndrome in adolescents and adults with Down syndrome.

As noted earlier, some conditions such as depression and sleep apnea are more common in people with Down syndrome and should be assessed for as part of the initial evaluation.

It is actually common to find that the person has multiple disorders rather than just one. Additionally, people with Down syndrome often have limited verbal skills, resulting in difficulties reporting physical symptoms. As a consequence, a physical problem often develops secondary mental health or behavioral symptoms. For all these reasons, multiple medical and psychosocial causes must be considered when assessing an individual with Down syndrome with regression.

Some of the conditions to consider include the following:

1) Medical conditions
   a) medication side effects
   b) sleep apnea
   c) seizures
   d) vitamin B12 deficiency
   e) cervical myelopathy: spine injury (subluxation, spinal stenosis)
   f) chronic pain
   g) dental pain/problems
   h) sinus pain/problems
   i) menstrual pain/problems
   j) gastrointestinal diseases or conditions (e.g., celiac disease), severe constipation
2) Cardiovascular disease
   a) uncorrected congenital heart disease with pulmonary hypertension, congestive heart failure, or Eisenmenger's syndrome (a form of severe cyanotic heart disease)
   b) stroke: ischemic or hemorrhagic
3) Infectious disease
   a) urinary tract infection
   b) pneumonia
   c) sepsis
   d) viral/bacterial meningitis/encephalitis
   e) Lyme's disease
4) Toxic-metabolic
   a) Various electrolyte (e.g. sodium, potassium, calcium) abnormalities
   b) Ingestion of various toxic substances
5) Neuropsychiatric disorders
   a) catatonia (see section below)
   b) mood disorder (depression, anxiety)
   c) obsessive-compulsive disorder
   d) psychotic disorder
   e) complex tic disorder
   f) post-traumatic stress disorder
   g) Parkinsonism, dystonia
   h) adjustment to life events – transitions and relationships

i) loss of family, friends, pets
ii) school graduation, work setting changes, physical relocation
iii) response to hospitalization or medical condition

6) Visual impairment
   a) glaucoma
   b) retinal detachment
   c) cataracts
   d) keratoconus

7) Hearing impairment
   a) impaired hearing: for example, due to high frequency hearing loss or due to ear infections or fluid in the middle ear
   b) hyperacusis (overly sensitive hearing)
   c) tinnitus (ringing in the ears)
   d) vertigo (sensation of spinning)

8) Endocrine disorders
   a) hypo- or hyperthyroidism
   b) adrenal insufficiency
   c) diabetes mellitus
   d) puberty-associated
   e) menopause-associated

9) Autoimmune disorders (additional evidence required)
   a) Hashimoto's encephalopathy
   b) pediatric autoimmune neuropsychiatric disorders associated with streptococcal infections (PANDAS)
   c) central nervous system manifestation of celiac disease
   d) central nervous system manifestation of systemic lupus erythematosus (SLE)
   e) autoimmune encephalopathy
   f) limbic encephalitis

Recently researchers described a method to guide the assessment of a person with Down syndrome and regression (Jacobs, Schwartz, McDougle, & Skotko, 2016). This approach involves grouping possible causes into tiers and assessing for the more likely diagnoses first, gradually working down the tiers to more obscure possibilities. To decide how far to go down the tiers, practitioners rely on clinical assessment, the conditions diagnosed, and the response to treatment. In practice, most individuals with Down syndrome and regression do not need to be evaluated for all the causes of regression listed above. The further down a practitioner goes in the tiers, the less likely one of those conditions is present.

In addition to assessing for the possible causes of regression listed above, it may also be worthwhile to perform an MRI or CT scan of the brain. This is because regression may be associated with changes visible on MRI/CT. One study (Akahoshi et al., 2012) reportedly found atrophy or hypoplasia in the basal ganglia of individuals with Down syndrome and regression, but there was no data on controls with Down syndrome who did not have regression, so it is not clear if this finding is unique to regression.

Here are a few other considerations when considering causes of regression:

Immune System Dysfunction. It is known that the immune system of people with Down syndrome functions differently than that of people without Down syndrome (Kumar, Rajadhyaksha, & Wortsman, 2001; Pellegrini et al., 2012). This includes a higher rate of autoimmune conditions—conditions in which the person's immune system attacks a part (or parts) of the person's own body. In regression, in theory, the immune system could be functioning against the person's brain (Worley et al., 2015). Ongoing study should help improve the understanding of the role the immune system may play in regression syndrome and how that understanding can improve treatment.

Sleep Disturbance. Sleep is another area that is more commonly a concern in people with Down syndrome, and sleep disturbance can contribute to mental health changes. Sleep disturbances are extremely common in adolescents and adults with Down syndrome who experience new or worsening mental health changes. In one study, researchers (Capone, Aidikoff, Taylor, & Rykiel, 2013) found that sleep apnea was more common in those with depression, and functional decline was found only in those with depression.

Depression. Severe depression can also be a cause of regression syndrome. In one study (Capone, Goyal, and Ayres et al., 2006), researchers suggested that stressors, such as a growing awareness of being different and bereavement, may exacerbate symptoms of depression in adolescents. Some of these depressed individuals appear to have regression in relation to a life event (or events). However, the nature of these events and their potential for triggering neuropsychiatric change is not at all clear and there are no data on life events in individuals without regression.

Although mood disturbances such as depression are often part of the regression syndrome and many individuals are treated with antidepressants, the causal relationship between depression and regression, sleep disturbance, and stressful life events is unclear presently.

Treatment for Regression

Treatments for many of the commonly diagnosed conditions that can lead to regression in people with Down syndrome are covered elsewhere in this book and in our book *The Guide to Good Health for Teens & Adults with Down Syndrome*. Consequently, these treatments will not be discussed in detail here, although we will briefly describe issues related to some of the major causes of regressive symptoms. It is important to note, however, that no one medication or combination of medications has been found to address the symptoms of all individuals with regression syndrome. This is consistent with the finding that there are a number of possible causes. Several researchers (Worley et al., 2015; Mircher, 2017) have described some medications that were beneficial for some individuals but found that no medication or combination of medications was consistently effective. Likewise, one group of researchers (Akahoshi et al., 2012) described diagnosing a variety of psychiatric diagnoses in people with regression, including anxiety, depression, and psychosis, with variable responses to treatment—from nonresponsive to fully responsive. A combination of medications may be necessary.

Despite, or perhaps due to the lack of universal, clear understanding of the cause of regression syndrome, health care providers often prescribe treatment that targets symptoms such as psychiatric, behavior, attention, motor, sleep, and other medical symptoms, with a focus on the symptoms that cause the most impairment and are most likely to respond to treatment. Treatment often involves an approach that includes medications; changes to the person's home, school, or work environment; and treatment of coexisting medical conditions. Depending on the person's symptoms, occupational, physical, speech, and behavioral therapy may all be helpful. Which treatment to prioritize will depend on the provider's experience, family preferences, and the patient's response to treatments. Support for the individual's caretaker is generally part of the treatment regimen and may include assistance with adapting to a new reality and the future.

A very important consideration during treatment is how to handle the withdrawal from activities or reluctance to leave home that often occurs in people with regression syndrome. Many of these individuals need a gradual, "safe" reentry into activities. To prevent abrupt reversal of improvement, it is essential that the person successfully participate in activities that are unlikely to provoke significant anxiety or fear. Strategies to help the person ease into activities may include the following:

- giving the person lots of reinforcement for small steps;
- initially not expecting him to do things as long or as well as he used to;
- giving the person input into the selected activity, the participants, etc.; and
- carefully observing the individual's response to a gradual increase in the amount and intensity of the activity (to avoid too rapid of an increase that could result in excessive stress).

This gradual resumption of normal activities without fear and anxiety is therapeutic in itself.

Catatonia and Regression

Catatonia is an especially worrisome condition that may occur in people with Down syndrome and regression. Catatonia is a condition that traditionally was associated with psychoses, but it is now recognized that it can occur with a variety of psychiatric or medical conditions such as depression (Daniels, 2009). It has also been proposed that it be a separate diagnosis not associated with any psychiatric or medical conditions (Shorter, 2012; Padhy, Parakh, & Sridhar, 2014). The condition has not been studied much in Down syndrome, but one group of researchers (Ghaziuddin et al., 2015) described catatonia in a small series of people with Down syndrome.

There are two primary treatments for catatonia: medications and electroconvulsive therapy (ECT). ECT involves sedating an individual with anesthesia and then inducing a seizure with a short electrical stimulation of the brain. The authors of the 2015 study (Ghaziuddin et al.) used high dose lorazepam combined with ECT to treat the four individuals with Down syndrome in their study and reported that they all recovered their baseline level of functioning. However, the patients in this study needed prolonged usage of ECT to successfully

recover from catatonia. The researchers speculated that this raises the possibility that differences in pathophysiological mechanisms may underlie catatonia in individuals with Down syndrome and other developmental disabilities versus those with typical development. The authors concluded that they suspect catatonia is a common cause of unexplained deterioration in adolescents and young adults with Down syndrome.

More recently, Judith Miles (2017), a coauthor on the paper with Neera Ghaziuddin, described successfully treating patients with Down syndrome and catatonia using medications without ECT. In addition to high dose lorazepam, she reported using *N*-methyl-D-aspartate receptor (NMDA) antagonists including dextromethorphan-quinidine (Nuedexta), memantine (Namenda), and amantadine. She reported best success with dextromethorphan-quinidine. In patients without Down syndrome, another researcher (Daniels, 2009) successfully used NMDA antagonists to treat individuals whose catatonia did not respond to lorazepam. These medications may be effective because a dysregulation of dopamine, *gamma*-Aminobutyric acid (GABA), and glutamate is proposed as being involved in catatonia. Lorazepam enhances GABA activity, and the NMDA antagonists reduce the effect of glutamate.

Despite Ghaziuddin's successful use of ECT in treating four patients with Down syndrome and catatonia, further investigation of the use ECT for this purpose is warranted. A recent meta-analysis of the use of ECT in people without Down syndrome who were diagnosed with catatonia found serious side effects in seven studies, including mental confusion, memory loss, headache, or adverse effects associated with anesthesia (Leroy et al., 2017). The study further concluded that the "literature consistently describes improvement in catatonic symptoms after ECT. However, the published studies fail to demonstrate efficacy and effectiveness." Additional study is needed to understand the role of ECT in people with Down syndrome and catatonia. However, in our experience and the experience other clinicians have reported to us, treatment with ECT does result in dramatic improvement in some individuals.

Prognosis

For people with Down syndrome, recovery from regression syndrome is highly dependent on both the cause and the certainty of the diagnosis. For those with more challenging regression, recovery of mental health changes and loss of skills may take many months or years. One group of researchers (Mircher et al., 2017) found that only 10 percent of the individuals they followed completely recovered from regression syndrome. They also reported that 10 percent actually worsened, 37 percent stabilized but did not recover (they did not keep regressing but did not regain their lost skills or their previous level of mental health), and 43 percent had partial recovery. As we learn more about the causes of regression in people with Down syndrome, the prognosis for recovery will hopefully improve.

Conclusion

Regression in adolescents and younger adults with Down syndrome has only recently begun to be studied in earnest. At present, we do not even have a universally agreed-upon name for the condition, although the name *regression syndrome* has been proposed by the Down Syndrome Medical Interest Group in the United States. People with Down syndrome can lose skills due to many disorders or combinations of disorders. Clearly, there are significant gaps in our knowledge of regression syndrome, and further study is needed to define and optimize treatment for affected individuals.

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