Down syndrome (DS), or trisomy 21, is a common disorder associated with several complex clinical phenotypes. DS is estimated to occur in approximately 1 per 650–1000 live births. A recent study from the United States of America showed a decrease in the prevalence owing to DS related elective terminations. The features of DS were identified 150 years ago by Sir John Langdon Down who published his findings in London Hospital Clinical Lectures and Reports in 1866. After 66 years, P. J. Waardenburg suggested that DS was caused by a chromosomal aberration due to nondisjunction. After almost a century later, an extra copy of chromosome 21 was identified as the etiology. In the 20th century, almost all individuals with DS were separated from their families and institutionalized. They were also denied medical support which culminated in increased mortality in children with DS. However, the advances in the medical and surgical treatment have led to improved life expectancies such as specialized surgical procedures of the congenital cardiac diseases, management of malignancies and endocrinopathies. There has also been a change in the social circumstances for individuals with DS, as most are being reared at home.

DS is diagnosed through karyotyping along with the phenotypic presentation. Maternally derived additional copy of an entire chromosome 21 due to non-disjunction is the most common cause of DS occurring in approximately 90–93% of the cases. Translocation is the other pathological mechanism which causes DS in ~2–4% of the cases. Mosaicism is found in ~1.3–5% of cases. In 95% of the children, the condition is sporadic.

The prenatal screening strategies have been developed ranging from amniocentesis to less invasive tests for different trimesters that incorporate various blood tests, nuchal translucency via ultrasonography.

Substantial research has been carried out in the past several decades to unravel the molecular genetics of DS. Although, some studies have suggested that duplication of an extended region on chromosome 21 (HSA21) is associated with DS features but it is yet to be established. It is also hypothesized that there is a critical region involved, the DS consensus region that is responsible for severe DS phenotype.
DS is the most common known genetic cause of intellectual and developmental disabilities. Although there is a global involvement encompassing motor, language, cognitive, self-care and personal-social dimensions, there is a disproportionate impairment in certain cognitive domains such as language and memory in comparison to other intellectual disabilities resulting in a characteristic neurocognitive phenotype. However, there is heterogeneity amongst individuals in the cognitive abilities and skills phenotype due to genetics, cellular, neural, behavioral and environmental factors. Research studies have shown that there is anomalous functional neural connectivity as compared to individuals with similar intellectual disabilities. Also, mitochondrial dysfunction has been studied in correlation with the pathogenesis of DS and there is evidence to show increased oxidative stress in DS cells. However, it is not known how oxidative stress causes clinical symptoms and there is a knowledge gap in the understanding of the molecular events leading to intellectual disability.

**Motor skills**

There is a need for proficient motor skills in individuals with DS to perform day to day tasks. Children with DS demonstrate challenges in terms of increased risk of motor delay and motor coordination capabilities which occur due to neuroanatomical and physiological changes because of muscle hypotonia, lax joints and slower reaction times causing alterations in postural control and muscle synergy. This delay in motor skills may also hinder the child from the essential sensory stimulation that is needed for other aspects of learning.

The gap in motor development emerges around 4 months of age and becomes more apparent as the age advances. Dissimilarities in the postural reactions have also been observed while comparing to neurotypical infants. This happens as expectations for more coordinated motor tasks increase especially for skills requiring high levels of muscle co-activation against gravity. The sequence of attaining motor milestones is similar but qualitatively different which probably results from the compensatory mechanism. There is a wide range in the acquisition of motor milestones such that walking can be attained between 15 and 74 months while for the neurotypical children it is earlier than 18 months. The percentage of children who were able to walk by 2 years of age has been reported between 25% to 44%, and by 3 years 78% to 82.

There is a paucity of literature on the fine motor development in DS. It is heterogeneous and like gross motor skills has a broad range of acquisition. The achievement of early fine motor skills and writing skills is around the same age range as the typical children. However, with the increasing complexity of tasks, the difference increases between the children with DS and their typical peers.

An interesting phenomenon in enhancing motor capabilities in individuals with DS is an improvement in tasks with practice as unfamiliarity of the motor tasks results in even worse motor coordination. The existing body of literature, although limited, suggests that neuromuscular training which is characterized by stimuli provided by physical activities aims to enhance a myriad of neuromuscular components including muscular strength, physical coordination, and functional movements may be employed to promote general and maximal muscular strength development in children and youth with DS. However, there is a small impact on functional mobility performance owing to limitations in executive functioning. Thus, rehabilitation contributes to the improvement of motor skills and ultimately the quality of life.

Given this literature, general pediatricians may wish to consider co-morbid neurologic or developmental diagnosis if a child with DS presents with hypotonia, have asymmetric neurological findings or are significantly more motor delayed than most children with DS (for example not walking by 60-72 months).
Adaptive functioning

Adaptive behavior is essential to perform day to day activity independently and is comprised of conceptual, social, and practical adaptive skills. The understanding of the adaptive behavior profile of DS is evolving. So far, the adaptive behavior profile in DS is characterized by strengths in socialization and self-help with difficulties in motor and communication skills.

Progression in adaptive functioning is particularly seen in early childhood up to the age of 6 years; while in children and adolescents the gains in adaptive skills are not strongly correlated with age.

Children with DS find it difficult to keep up with their typical peers in adaptive skills and deceleration is observed across all ages. The domains continue to grow at a slower pace than typically developing children. Also, there is great variability in the attainment of skills in children with DS as compared to their typical peers such that adaptive scores are close together in neurotypical children in relation to their chronological age; while the scores have a larger spread in children with DS.

Speech and language (Communication)

There is a characteristic profile of communication with strengths and challenges in individuals with DS. Children with DS typically manifest significant delays in language development. There are deficits in both receptive and expressive language skills which are more pronounced than cognitive development. In general, expressive language is more affected than receptive language and/or language comprehension. Hearing loss and anatomical and functional differences in the oro-motor apparatus have been associated with speech delay.

Craniofacial differences including small oral cavity and narrow, vaulted palate, as well as hypotonia, contribute to the articulatory performance.

The motor speech difficulties have historically included Childhood Apraxia of Speech (CAS) and Childhood Dysarthria. One can have either or both.

The development of oral language is a complex process which requires cognitive, perceptual and language skills that begin to form in the prelinguistic stage. Similar to typical children, children with DS use gestures and vocalizations in the prelinguistic stage. Children with DS show better performance using gestural communication than is expected for their developmental age thus placing them in “gestural advantage”. Delays in certain aspects of prelinguistic vocalizations especially canonical babbling (repeating consonants and vowels) followed by delays to attain single words speech have been reported in the literature. There is a range in the acquisition of the first words such that for some children the first words have emerged at around 9 months while for others they didn’t come until 7 years of chronological age.

The issues revolve around language production, syntax (sentence structure) and poor speech intelligibility. Pragmatics (social use of language) is an area of relative strength for children with DS.

Studies have suggested that early linguistic stimulation employing speech and language interventions specially designed for children with DS individualized with each child’s characteristics can potentiate language development.

Therefore, from the literature, pediatricians may consider comorbid developmental diagnosis if a child with DS has more impairments in the pragmatics than compared to their overall developmental level or if the clarity of the expressive communication is significantly unintelligible after short sentence utterances have been achieved.

Social-emotional/behavioral development

Socialization is the strongest developmental
domain in children with DS.\textsuperscript{47} It has been supported by literature that children with DS with the same level of developmental delay as children without DS demonstrated better socialization skills.\textsuperscript{30} Also, different dimensions of social functioning such as social orientation, social engagement, and pro-social responsiveness are equally strong.\textsuperscript{48,49}

Children with DS have been characterized by decreased emotional expression and environmental response.\textsuperscript{50,51} Studies have shown that infants with DS displayed less intense emotions and increased latency to distress as compared to developmentally matched infants.\textsuperscript{52}

Research on the recognition of emotional expressions by children with DS has been a work in progress.\textsuperscript{53} Previous literature suggested that they have a better understanding of understanding emotions as expressed by facial expression as compared to other forms of intellectual disabilities.\textsuperscript{54} Later studies looking into emotional processing in children with DS concluded that there were emotional perception deficits.\textsuperscript{55}

A child with DS has been stereotyped to be affectionate, charming and friendly.\textsuperscript{48} Thus, the co-occurrence of Autism Spectrum Disorder (ASD) with DS was considered to be a rare phenomenon in the past. However, recent research estimates have shown the prevalence of co-occurring ASD to be 5 to 18\% in children with DS.\textsuperscript{56-58} The published literature has not shown comprehensive or “gold standard” diagnostic assessments for diagnosing ASD in children with DS.\textsuperscript{59} However, screening tools like Social communication questionnaire (SCQ) and Modified Checklist for Autism in Toddlers (M-CHAT)\textsuperscript{56} have been used followed by Autism Diagnostic Interview-Revised (ADI-R) and Autism Diagnostic Observation Schedule (ADOS).\textsuperscript{60} Keeping in view that many of the symptoms that constitute the autism screening checklists are also present in intellectual disabilities, this may result in increased sensitivity with decreasing specificity.\textsuperscript{61} A developmental approach to diagnose ASD has been recommended by various authors in children with intellectual disabilities where to diagnose an individual with ASD there should be significantly more impairment in social or communication domain than the overall intellectual capabilities.\textsuperscript{62}

Several studies have contributed in creating the behavioral profile of children with DS with a dual diagnosis of ASD which includes increased behavioral disturbance, increased repetitive and stereotypical behavior, poorer social, language and adaptive skills and greater regression.\textsuperscript{56} Another study demonstrated that individuals with a dual diagnosis of ASD-DS were less withdrawn than with idiopathic ASD.\textsuperscript{57}

Maladaptive behaviors in DS occur in varying intensities across the lifespan. About one-third of individuals with DS have behavior challenges.\textsuperscript{63} Behavior problems like inattention, stubbornness, non-compliance social-withdrawal and obsessive-compulsive behaviors have also been established in the profile.\textsuperscript{54,65} In children with DS who have behavioral problems, vocabulary has been found to be a major contributor.\textsuperscript{66} More externalizing behaviors have been observed in children with DS as compared to adolescents while both adolescents and adults have shown more propensity towards internalizing behaviors.\textsuperscript{48}

Attention Deficit Hyperactivity Disorder (ADHD) has been reported in 9- 34\% of children with DS.\textsuperscript{67,68} Similar to ASD, making a dual-diagnosis of ADHD in a DS child is more difficult because some signs of ADHD and other comorbid disorders may be attributed to the child’s intellectual disability.\textsuperscript{69} Hyperactivity–impulsivity–inattention have been regarded as parts of the typical DS behavioral phenotype thus increasing the dilemma of diagnosing and treating ADHD in them even further.\textsuperscript{70} The diagnosis is clinical and there are no standardized tests available to detect ADHD in children with DS. However, a neurodevelopmental assessment using clinical observation and
general rating tools like Aberrant Behavior Checklist (ABC), Child Behavior Checklists (CBCL), Conner’s rating scale and/or Strengths and Difficulties Questionnaire (SDQ) etc. could be considered in all children with DS during clinical visits when there is a concern about inattention or impulsivity. This may facilitate in implementing therapeutic interventions (both pharmacologic and behavioral) which decrease symptoms of hyperactivity and irritability.

Cognition

The neurocognitive profile of DS is characterized by psychomotor delay with significant deficits in learning, memory, executive functions, and language abilities that define the intellectual disability.

The intelligence quotient (IQ) in individuals with DS vary widely from below 20 to at least an IQ of 69 depending on the age, environment and the genotype. A progressive declining trend has been demonstrated in individuals across childhood ranging between 60-70s in the preschool age group with a subsequent decrease to between 40-50s in kindergarten and further decline dropping to between 30-40 in school-aged children. This declining cognitive growth rate correlates with declines observed in the rate of development of functional skills during childhood in DS. However, the psychometric testing available does not account for the wide range of challenges experienced by this population.

Few cognitive differences have been observed in infants with DS from neurotypical controls on standardized tests which may be due to a probable lack of sensitivity to detect them but, with increasing age, the gap becomes more obvious as the rate of intellectual development in DS slows considerably. Deficits in verbal information processing are the most apparent which is also associated with verbal working memory have been reported in the literature which was historically known to be associated with the deficits in the auditory short-term memory.

Executive functioning has also been found to be impaired in individuals with DS. Impairments in fluency, cognitive flexibility (shifting), planning, and inhibition were found in youth and middle-aged adults with DS when compared with adults with other developmental disabilities (DD). Interestingly, there is also heterogeneity in performance even after acquiring skill with rigorous training. This is supported by studies that tested and retested children with DS and found the tasks which were successfully done during one test could not be replicated in the other instance. These deficits in memory can be explained by impairment in hippocampal function which is linked to the explicit memory.

In contrast, visuospatial functioning and social relatedness are areas of relative strength.

Academics

Academic skills in individuals with DS have garnered a lot of attention in the last few decades. From the perspective of quality of life, literacy, the ability of reading and writing as well as numeracy, the concept of the number are important in day to day life and facilitate the vocational opportunities as well as chances of independent living in individuals with DS.

There is a spectrum of attainment of literacy skills in children with DS. When compared with mental age-matched children, the language was a stronger predictor of reading ability in contrast to cognition in the group with DS. There is evidence to suggest that there are strengths in word identification, possibly secondary to relative strengths in visual processing. However, there are challenges in verbal processing skills that lead to deficits in word attack skills.

Individuals with DS can attain simple skills in numeracy but a study suggested that unlike reading this cannot be retained into adolescence and adulthood. Research has also shown that children with DS can improve on these skills if appropriate strategies are used that employ
their stronger visual learning skills. Learning Numeracy has been suggested to be associated with real practical scenarios with concrete materials or computers.82

The learning process is said to be hindered by deficits in the working memory and executive functioning.83,84 Another study that looked at the predictors of academic attainment elucidated that severity of learning disability, child’s ability to sustain attention, mainstream education, mothers using a practical approach to problem-solving and fathers’ feelings of having control over some parts of life positively impacted the achievement.85 Children whose mothers were more supportive of their autonomy showed more persistence in performing challenging tasks. Interestingly, the relative social strength hinders collaborative learning as students with DS use avoidance and refusing tactics to save themselves from performing challenging tasks.86,87 Researchers also observed higher levels of off-task behavior when children with DS were matched for mental age.70 Deficits in goal-directed behavior have also been reported in the literature.88

Educational policies that emphasized inclusion and teaching academic skills, resulted in better attainment of skills and higher expectations of teachers. Also, a report on the practice of including children with DS in regular classrooms in England showed a difference in the phenotypic profile in older children and adolescents with DS.89 They noted that children with DS attending school in special classrooms showed strength in socialization and activities of daily living while having marked deficits in adaptive communication.86 In contrast, children who were in inclusive classrooms, these marked deficits were not demonstrated, and these children had much higher scores on speech, language, and academic skills. The learning targets, however, were individualized with additional in-class and some outside instruction when necessary.89

Take-home points

- The neurocognitive profile of DS is characterized by psychomotor delay and a generalized with significant deficits in learning, memory, executive functions, and language abilities that define the intellectual disability.
- Children with DS are typically delayed in all areas of development throughout their lives.
- The gap in the developmental skills widens during school-age childhood and adolescence compared to their same-age peers widens due to the slower pace of skill acquisition.
- Language is a stronger predictor of reading ability in contrast to cognition in the group with DS.
- The use of the combination of visual and phonological strategies in preschool children to augment the long-term learning has been supported by the literature.

REFERENCES


