Western European Journal of Medicine and Medical Science
Volume 2, Issue 8, August, 2024
https://westerneuropeanstudies.com/index.php/3
ISSN (E): 2942-1918 Open Access| Peer Reviewed

COGNITIVE DEFICITS AND ASSOCIATED NEUROLOGICAL COMPLICATIONS IN CHILDREN WITH DOWN SYNDROME

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Abstract
Down syndrome is a hereditary disorder that can result in varying degrees of cognitive impairment and a range of neurological problems. This condition is quite prevalent in neurodevelopment and affects approximately 1 in every 1000 live births globally. This study comprised a group of 120 children, aged 3 to 12 years, diagnosed with Down syndrome. These children were admitted to the clinic "ReaCenter Tashkent" between 2021 and 2023 for treatment of several neurological conditions. The diagnosis was confirmed through the examination of cytogenetic and clinical neurological investigations, which revealed the particular phenotype linked to this syndrome. This article examines specific tests that have been chosen for their capacity to emphasize significant considerations that practitioners should take into account when interpreting IQ test outcomes with this particular group. Statistically, in our research it has demonstrated that the predominant proportion of infants with Down syndrome are born to mothers aged between 26 and 35, accounting for 43 percent of cases. This is a result of the elevated fertility rate within this age group. Concurrently, the fathers' age at the moment of their child's birth ranged from 36 to 49 years. Individuals with trisomy had a greater degree of neurological damage in comparison to individuals with mosaic or translocation types. Verbal issues, hand fine motor impairments, deficiencies in the coordination sphere, and autonomic dysregulation were the ways in which these symptoms showed up.
Keywords: Down syndrome; neurological disorders; cognitive impairment; trisomy 21; children.

1. Introduction

Children diagnosed with Down syndrome (DS), sometimes referred to as trisomy 21, confront a variety of mental and physical disabilities, such as neurological challenges (including hearing, speech, visual, and cognitive difficulties) (1), cardiac abnormalities, and an altered immune response (2). DS is a common genetic abnormality that occurs in around 1 in every 1000 births and it is usually the result of an additional third copy of chromosome 21 (3).

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Individuals with DS often experience challenges in executive functioning, including issues in goal-oriented behavior and emotional regulation (4). These symptoms can present as heightened anxiety, melancholy, impulsivity, and difficulties with focus (5). Approximately 6-8% of children with this syndrome are officially diagnosed with attention deficit hyperactivity disorder (ADHD) (6). The syndrome also results in cognitive impairment, which exhibits significant variation across individuals and can range from mild to severe in areas such as motor development, memory, attention, and language (both oral and written) (7). The alteration in the expression of genes encoded by human chromosome 21 (Hsa21), such as amyloid precursor protein (APP), is a critical factor in the development of DS (2, 8).

The incidence of this syndrome has significantly increased in recent decades, possibly as a result of detrimental environmental variables (7) and a rise in the average reproductive age (2, 6). Advanced maternal age, specifically over 35 years, may be considered a risk factor (6).

Every individual with DS possesses distinct characteristics, including a range of potential health issues, learning problems, and other impairments commonly linked to the disorder (8). Based on analytical statistics, the birth rate of children with this syndrome is the same for both boys and girls (9).

Children with DS are more prone to developing a range of conditions, including hearing loss, recurring middle ear infections (otitis media) (10), thyroid problems (hypothyroidism) (11), speech disorders (12), instability in the cervical spine, visual impairment (13), sleep apnea (14), obesity, constipation (15), infantile spasms, seizures, dementia, and early-onset Alzheimer's disease (16, 17).

In addition, children with this syndrome may experience a notable decline in their ability to walk due to several factors (18), such as congenital heart abnormalities (19, 20), limited cardiovascular endurance (21), muscle hypotonia, reduced muscle strength, impaired coordination and balance (22), and intellectual disability (2, 8, 23).

The youngsters in question exhibit a delay in the development of their speech (24), which is marked by significant impairment to their ability to articulate words and a tendency to stammer (25). This can occasionally conceal their genuine emotional state, leading to the belief that they have poorer cognitive capacities (26). However, some children with DS may achieve similar outcomes as typically developing individuals in non-verbal activities, such as object classification and counting operations (27). Children face difficulties while trying to transfer their skills and knowledge from one context to another (28). Moreover, dealing with real-life problems that arise may also present difficulties (29). DS may struggle to acquire knowledge in specific academic topics due to limitations in their brain's ability to generate ideas and draw firm conclusions (30).

Individuals with DS commonly experience conductive hearing loss (31), with a high occurrence of otitis media with effusion (32). Due to the higher likelihood of refractive errors, congenital and developmental cataracts, keratoconus, and amblyopia in individuals with DS (33), it is recommended to conduct an ophthalmological examination immediately after birth and at frequent intervals throughout their life, preferably every 1-2 years (34).

Most children with DS commonly display hypomnesia, instability of active attention, heightened fatigue, and exhaustion (35). As a consequence, they require more time to learn and proficiently acquire new skills, as well as to recall fresh information (36). It is crucial to acknowledge that these youngsters suffer from deficiencies in their auditory short-term memory and their ability to receive information through the ear (37).

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An individual with DS may encounter a broad spectrum of challenges (2, 17, 38). This complicates the ability to form broad conclusions about their overall well-being or life expectancy (39). Effectively addressing any problems and associated health conditions can increase the average lifespan (40). The objective of this study was to investigate the neurological and physical traits, as well as the cytogenetic profile, of individuals diagnosed with DS.

The Wechsler Preschool and Primary Scale of Intelligence (WPPSI) (41) and the Stanford-Binet scale (42) are the most effective and dependable assessments for evaluating cognitive ability in individuals with Down syndrome.

The WPPSI is a cutting-edge assessment tool designed to evaluate cognitive development in preschoolers and young children (41). The Stanford Binet IQ test is commonly employed to assess an individual's cognitive abilities (30, 42).

2. Methods

Between 2021 and 2023, we conducted research on 120 children diagnosed with DS who were admitted to the clinic "ReaCenter Tashkent" for medical treatment and rehabilitation. These children had numerous neurological and developmental abnormalities, including impaired motor coordination, speech difficulties, hyperactivity, and generalized seizures. The diagnosis was established by analyzing the cytogenetic and clinical neurological examinations, which included evaluating the DS phenotype. The children were classified into two groups based on their age: the first cohort included children aged 3 to 6 years old, while the second group comprised individuals aged 7 to 12 years' old who exhibited varying degrees of cognitive impairments and intellectual disabilities. The mean age was 6.2±2.8 years (Table 1).

Table 1

Distribution of children by gender and age.

Children's age	Boys		Girls		Total	
	n	%	n	%	n	%
3-6 years	55	45.8	32	26.7	87	72.5
7-12 years	20	16.7	13	10.8	33	27.5
Total	75	62.6	45	37.5	120	100.0

Among the whole group of children examined, 87 (72.5%) were the age range of 3 to 6 years and 11 months, with an average age of 4.3±1.2. In addition, there were 33 children, which accounted for 27.5% of the total, who were between the ages of 7 and 12 years. The average age of these children was 8.5 ± 1.3 years. Depending on the age of the participants, we were split into two groups and used the Wechsler Preschool and Primary Scale of Intelligence (WPPSI) to assess cognitive function in the second group and the Stanford-Binet scale in the first.

The mean duration of follow-up was 3 years. There was a combined total of 45 girls and 75 boys that were observed. Out of the sample, 97 neonates, making up 80.8% of the total, were born at full-term, while 23 infants, representing 19.2% of the sample, were born preterm at an

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average gestational age of 35.3±1.1 weeks. The number of male patients exceeded the number of female patients, with a ratio of 1.7:1.

Furthermore, the children with DS were classified into various categories based on their cytogenetic karyotyping results to determine the severity of their neurological condition (Table 2). The main group consisted of 88 children with trisomy on chromosome 21, making up 73.3% of the total. The control group consisted of 11 children (9.2%) with mosaicism and 21 children with translocation (17.5%).

Table 2

Child distribution based on cytogenetic forms

Types of DS	The first group		The second group		Total	
	n	%	n	%	n	%
Trisomy 21	54	45.0	34	34.2	88	73.3
Translocation	7	5.83	14	11.7	21	17.5
Mosaic	8	6.67	3	2.50	11	9.2
Total	69	57.5	51	42.5	120	100.0

The Motor Assessment Scale (MAS) was used to assess the manual motor impairments in children diagnosed with DS. The scale comprises distinct categories that assess different types of motions, including the torso, arms, legs, balance, and spasticity (43). For our research, section H was utilized, which focuses on “fine motor skills” (Table 3). The segment has six upper limb motor activities (44), each of which is evaluated with one point per task. Hence, the segment is allocated a maximum of 6 points.

Table 3

Instructions for performing the MAS scale (subsection H)

№	Tasks	Score
1	Remove the pen cap and then replace it. The patient extends their arm, grasps the hat, and positions it on the table in closer proximity to themselves.	
2	Transfer a bead from one cup to another. The cup holds a total of 8 beads. Both cups are within easy reach. Using your left hand, transfer beads from the right cup to the left cup, and vice versa.	
3	Produce a straight line that extends horizontally until it connects with a vertical line on 10 separate occasions during a time span of 20 seconds. There must be a minimum of 5 lines that terminate precisely on a vertical line.	
4	Utilize a pencil to expeditiously position dots within the cells of the table. A minimum of two points within a time frame of five seconds. The patient autonomously grasps the pencil and positions it for writing, accurately creating dots without making contact with the page.	

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5	Consume a small amount of liquid with a dessert spoon and direct it towards your mouth. Avoid tilting your head towards the spoon and prevent any spillage.	
6	Utilize a comb to groom the hair located at the posterior region of your head.	

Simultaneously, the Nine Hole Peg Test (NHPT) was employed, it is a type of assessment that measures an individual's dexterity in manipulating pegs using their thumb and finger (45). Standardized hand function tests typically comprise three components: (a) assessments of arm and hand function, (b) evaluations of dexterity and fine motor skills, and (c) measurements of hand strength (46).

3. Results and discussion

In 2021, Uzbekistan marked the birth of 905 211 children, out of whom 264 were diagnosed with DS, resulting in a ratio of 1 in 3 429. In 2022, the number of births increased to 932 217, with 268 cases of DS reported, resulting in a ratio of 1 in 3 478. In 2023, out of 961 962 infants born, 312 were diagnosed with this syndrome, resulting in a ratio of 1 in 3 083 (47, 48).
The mother's age at the time of the proband's birth ranged from 19 to 25 years, which 36 (30%) women fell within this age range. Also, there were 52 women, accounting for 43.3% of the total, aged between 26 and 35. Furthermore, there were 32 women, representing 26.7% of the total, aged between 36 and 49. An analyzes of the ages of fathers at the time of delivery of infants with DS showed that 62 people (52%) were 36-49 years old. Among the parents of the 120 probands, 95% did not have any hereditary diseases.

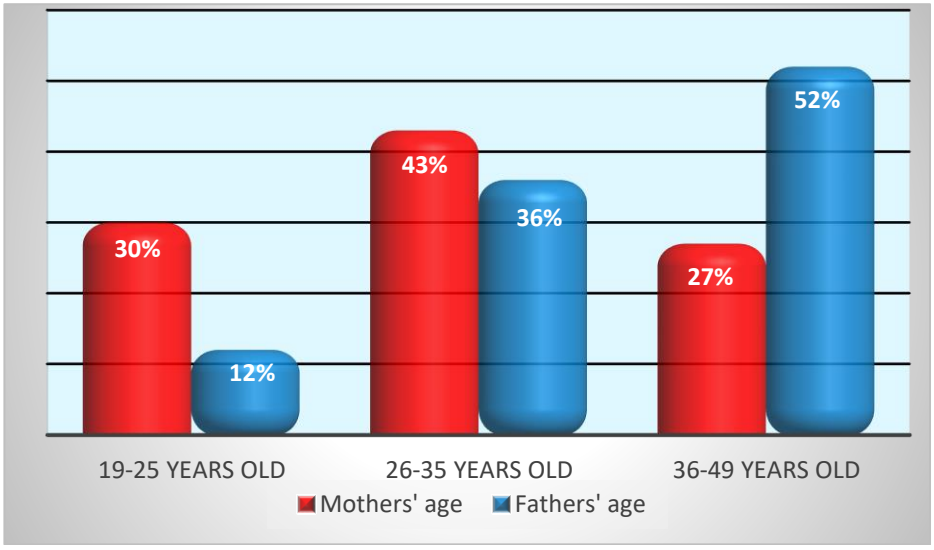

Fig.1. Parental age at birth of the proband

According to Figure 1, the highest proportion of mothers with DS was in the age range of 26 to 35 years, representing 43 percent of the total. This can be attributed to the elevated fertility rate among this particular age group. Simultaneously, the ages of fathers at the moment of their child's birth varied between 36 and 49 years.

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Furthermore, we performed a comprehensive analysis of the antenatal and perinatal medical records of all patients through the utilization of questionnaires, interviews with parents, and outpatient records. Children diagnosed with DS demonstrate a noticeable delay in their psychomotor development, especially those who have trisomy 21. The vast majority of newborns (98.3%) encountered extensive diffuse muscle hypotension and excessive joint mobility in the initial phases of their development. Consequently, the motor skills of the primary group of children with DS grew more slowly than those of the comparative group with mosaicism and translocation.

Table 4

Stages of cognitive development in children with Down syndrome

Skills	Main group (n=88)	Comparative group (n=32)	Healthy children
	Average age (months)	Average age (months)	Average age (months)
Started to smile	3.5±0.2	2.0±0.1	1.0±0.1
Started to turn over	8.1±0.1	7.2±0.4	5.7±0.2
Started to sit	11.3±0.2	9.4±0.8	7.5±0.8*
Started to crawl	16.2±0.3	13.2±1.0	8.3±0.2*
Started to get up	18.0±0.1	15.6±0.2	9.1±0.3
Started walking	25.7±0.2	20.5±0.3	13.4±1.0
Started talking	24.3±1.2	17.8±0.02	10.5±0.1*
Sentences were spoken	40±0.13	34.6±0.03	21.3±0.2*

** - P<0.05 interrater reliability*

Based on the evidence presented, it is clear that children with DS exhibited a delay in psychomotor development compared to their peers. These children had early indications of cognitive impairment, such as delayed achievement of developmental milestones such as rolling over, walking, sitting, and speaking in comparison to healthy children. The majority of these children achieved the ability to sit independently between the ages of 10 and 16 months. After a period of 12 to 20 months, the ability to crawl emerged and persisted for an extended duration. After a period of two years, the average individual has acquired the ability to walk independently (Table 4). Furthermore, we observed a delay in the development of fine motor abilities in children with this syndrome. Delayed psychomotor development in children with DS was found to be consistent with previous research, as evidenced by the reported delay in the capacity to grip a toy and grasp a spoon. Furthermore, an examination of medical records revealed that these children demonstrated restricted and inadequate manifestations of emotional reactions (such as a lack of excitement when seeing familiar folks or a lack of pleasure from a cherished object). Additionally, they demonstrated a postponed humming behavior, which was associated with a delay in the development of speech. It is important to highlight that verbal memory experienced the greatest decline across all cognitive abilities, while children with DS demonstrated the most advanced visual memory.

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Moreover, alterations in the correlations between emotional and behavioral challenges and sleep issues were observed in these children. Specifically, sleep-related breathing difficulties were found in 25.8% of the children, while parasomnias were present in 6.6%.
The findings of a neuropsychological study comparing the performance of children with DS who had cytogenetic variations, such as translocation and mosaicism, on both the Stanford-Binet and WPPSI, revealed that those with these deviations achieved superior outcomes compared to those with trisomy (Table 5). We observed more pronounced cognitive alterations in children with trisomy.

Table 5

Indicators of the cognitive sphere in the examined children

Scales	Forms of DS		
	Trisomy	Translocation	Mosaic
Stanford-Binet	34,98±9,35	36,75±9,85	42,22±6,43
WPPSI	36,38±11,28	50,14±10,57	58,00±7,94

Furthermore, the study examined the fine motor skills of all children aged 6 and older, utilizing the Motor Assessment Scale (MAS). Children diagnosed with mosaic and translocation types exhibited an average score of 5.5 points, whereas children diagnosed with trisomy demonstrated a score of 4 points, indicating a notable deficit in speech development (Table 6).

Table 6

Results of the assessment of fine motor skills of the hand in children with DS.

№	Test and Scale	Main group (n=88)	Comparison group (n=32)
1.	MAS(score)	4 score+	5,5 score+
2.	Nine-hole peg (sec.)-dominant right hand	Boys-60 seconds Girls-60 seconds	Boys-45 seconds Girls-40 seconds

According to the test findings of children aged six and older, it was discovered that children with trisomy exhibit lower fine motor skills in comparison to those with mosaic and translocation. Thus, these children displayed impaired motor coordination and a lack of precision in complex motor tasks, especially in the group with trisomy 21.
The study evaluated manual dexterity by quantifying the duration it took for children to insert 9 pegs using the 9-hole peg test. NHPT was administered to youngsters aged six years and older. During the analysis, our attention was directed towards the dominant hand, notably the right hand. Practically healthy girls who are right-handed usually finish the procedure in approximately 30±4 seconds (49).
Furthermore, all the children with Down Syndrome who were examined encountered varying degrees of challenges in the areas of feeding, swallowing, and verbal communication. The existence of a high arched palate, a small upper jaw, reduced muscular tone in the tongue, and weak muscles in the oral cavity were the factors that caused this. These children retained the ability to perceive phonemes, but their speech production was significantly impaired. Their

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main method of communication relied on using basic vocabulary and nonverbal signals. Children lacked continuous proficiency in precisely identifying objects, but they demonstrated their capacity to use these items through bodily activities.

Our research revealed a high prevalence of ear, nose, and throat diseases, including chronic tonsillitis, rhino-sinusitis, and otitis media, among children with DS. These children commonly had morbidity, characterized by frequent upper respiratory tract diseases that can lead to recurrent pneumonia. These episodes occasionally lasted for an extended period of time and had a negative effect on the psychomotor development of the children.

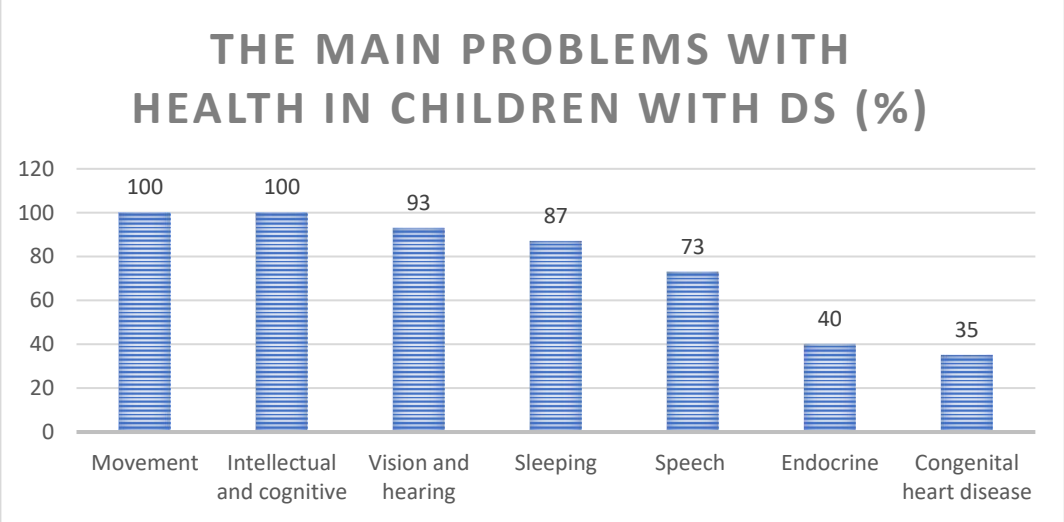

Figure 2. The main problems with health in children with Down syndrome

The data presented in Figure 2, clearly indicate that all children with DS (100%) exhibited movement difficulties such as muscle hypotonia, decreased tendon reflexes, impaired fine motor abilities, and delayed physical development. Additionally, intellectual disability and cognitive deficits were detected in all children. 111 youngsters (93%) were found to have hearing and vision impairments. Out of the total number of patients, 104 individuals (87%) were identified with sleep disorders and anomalies in the central nervous system during the perinatal period. The predominant speech impairments observed were dysarthria, affecting 64 patients (53.3%), and speech development delay, observed in 24 individuals (20%). Indicators such as speech comprehension, expressive speech, psycho-emotional state, sensory development, and self-care abilities were used to assess the severity of speech impairments and the condition of neuropsychiatric development. Moreover, a minority of individuals with DS were found to have endocrine system disorders, specifically hypothyroidism.

In addition, retrospective analyses indicate that echocardiography and ECG tests were conducted for all observed children. Forty-two children were diagnosed with congenital heart defects, representing 35% of the total. Atrial septal defect (ASD) was shown to be more prevalent in children with DS, namely in 38% (16/42) of instances. The Patent Foramen Ovale (PFO) was 28.6% (12/42), the Patent Ductus Arteriosus (PDA) was 23.8% (10/42). Other malformations, such as tetralogy of Fallot, pulmonary stenosis accounted for 9.5% (4/42).

The majority of parents in both the main and comparison groups reported observing signs of autonomic dysfunction in their children with DS. These signs included marbling of the skin,

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which was observed in 59.1% of children in the main group and 40.6% in the comparison group. Hyperhidrosis of the palms and feet was reported in 79.5% of children in the main group and 62.5% in the comparison group. Additionally, emotional impulsiveness and behavioral changes were observed in 90.9% of children in the main group and 26.3% in the comparison group. Signs of asthenization of the nervous system, such as increased fatigue, were reported in 81.8% and 62.5%, respectively. Irritability was also observed in 56.8% of children in the main group and 50% in the comparison group.

Indeed, impairments in vision and hearing, as well as hypothyroidism, had a notable influence on the cognitive abilities of individuals with DS. Our research findings indicate that girls had superior cognitive abilities compared to boys, with a statistically significant (p=0.05). Among the observed children, 53% of girls exhibited mild or moderate intellectual impairment, whereas the corresponding figure for boys was 46%. Therefore, a thorough analysis of the study's results indicated that both asthenization and autonomic dysfunction were more pronounced in the primary group of children with trisomy form.

4. Conclusion

Children with DS were born mainly from women who were aged 26-35 years, and fathers, on average, 36-49 years old. The research on clinical and neurological characteristics in children with DS revealed different degrees of severity of neurological problems, depending on the type of cytogenetic profile. Specifically, children with trisomy exhibited a more significant neurological, particularly cognitive impairment, including speech difficulties, fine motor impairments of the hand, coordination disorders, and autonomic dysregulation, as compared to children with mosaic and translocation types.

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Western European Journal of Medicine and Medical Science
Volume 2, Issue 8, August, 2024
https://westerneuropeanstudies.com/index.php/3
ISSN (E): 2942-1918 Open Access| Peer Reviewed

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Ethics approval and consent to participate
Not applicable

Consent for publication
Not applicable.

Availability of data and materials
The datasets used and analyzed during the current study are available from the corresponding author upon reasonable request.

Competing interests
The authors declare that they have no competing interests

Funding
This research received no specific grant from any funding agency in the public, commercial, or not-for-profit sectors.

Acknowledgements
We would like to thank and acknowledge all patients and their parents for their consent to participate in this study to improve research. The used figures are original, and belong to the authors of this manuscript.

Authors' contributions
SS and KS were the initiators of the proposed concept and made significant contributions to the final manuscript. The first author was responsible for the development of the theoretical framework and provided support in data collection. The second author conducted a thorough review of the final manuscript, played a role in the conceptual development, and made valuable additions. All authors made substantial contributions to the article and have given their approval for the submitted version.