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Neuropsychological Function in a Child with 18p Deletion Syndrome: A Case Report

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Abstract

We report the neuropsychological profile of a 4-year-old boy with the rare 18p deletion syndrome. We used a battery of standardized tests to assess his development in intellect, language, visuospatial integration, academic readiness, socialization, and emotional and behavioral health. The results showed borderline intellectual function except for low average nonverbal reasoning skills. He had stronger receptive than expressive language skills, although both were well below his age group. He had impaired visuospatial integration and pre-academic skills such as letter identification. Emotional and behavioral findings indicated mild aggressiveness, anxiety, low frustration tolerance, and executive function weaknesses, especially at home. Interestingly, he showed social strengths, responding to attention and sharing enjoyment with his examiner. With its assessment of development in many domains, this case report is among the first to characterize the neuropsychological and psychiatric function of a young child with 18p deletion syndrome. We discuss the implications of our findings for clinical practice.

Keywords

18p deletion syndrome; neuropsychology; genetic syndrome; developmental disorder; neuropsychological assessment

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Individuals with 18p deletion syndrome (also known as monosomy 18p or 18p- syndrome) have a deletion of a part, or the entire short arm, of chromosome 18. This syndrome was first described by Jean de Grouchy and colleagues in 1963. It is now a well-established chromosomal syndrome that is estimated to affect about 1 in 50,000 live births worldwide (Babovic-Vuksanovic et al, 2004; Thompson et al, 1986; Wester et al, 2006).

The most common phenotype of 18p deletion syndrome includes growth retardation, short stature, facial deformity (eg, low nasal bridge, protruding ears), and developmental delay (Babovic-Vuksanovic et al, 2004; Maranda et al, 2006; Portnoi et al, 2007; Thompson et al, 1986; Wester et al, 2006). The phenotypes of individuals with this syndrome vary widely, however, because the expression of characteristics depends on the deletion size and specific breakpoints. The larger the deletion and the closer to the centromeric region of the chromosome, the more severe the medical and developmental anomalies (Wester et al, 2006).

Most empirical studies and case reports on 18p deletion syndrome have focused on its medical correlates, such as growth retardation and cardiac problems. Only a handful of studies have concentrated on the developmental aspects, and, to our knowledge, none have fully characterized patients' neuropsychological function. Thus, until now, the literature has lacked a description of the syndrome's cognitive, language, motor, social, academic, and emotional aspects.

Intellectual impairment is common in case reports of 18p deletion syndrome (Babovic-Vuksanovic et al, 2004; Thompson et al, 1986; Wester et al, 2006). Intelligence quotient is typically in the borderline to mentally retarded range, although a few reported individuals have had average intellect because the breakpoint of their deletion was distal to the chromosome's centromeric region (Wester et al, 2006).

For instance, in a molecular study characterizing 7 patients aged 7 to 34 years, the 2 patients with breakpoints farthest from the centromere showed normal intellect (Wester et al, 2006). One patient with a breakpoint near the centromere had borderline intelligence. The other 4, all with a breakpoint close to the centromere, had mild to moderate mental retardation. This and other previous case studies of 18p deletion syndrome have typically relied on the Wechsler scales of intelligence or the Stanford-Binet Intelligence Scale to assess intellect (eg, Thompson et al, 1986; Wester et al, 2006).

Regarding the linguistic capabilities of children with 18p deletion syndrome, we could find only 1 study that focused specifically on receptive and expressive language skills (Thompson et al, 1986). In this study of 3 young children aged 4 to 9 years, 2 had severe receptive and expressive language delays at both initial testing and follow-up several years later. The language impairment reflected the children's cognitive capacity: Those with very low intellectual function also had very low language skills. All 3 children had severe articulation difficulties.

Previous studies have shed very little light on the motor, social, academic, and emotional development of children with 18p deletion syndrome. While some studies have described behavioral characteristics such as restlessness, anxiety, poor concentration, and mood

lability in affected individuals (eg, Zavala et al, 2010), these findings have yet to been reported in many other children. In terms of social development, no previous cases have reported whether the 18p deletion affects social interaction, eg, eye contact, reciprocal social smiling, and shared enjoyment.

We present results from an extensive neuropsychological evaluation of a young boy with 18p deletion syndrome. We tested his intellect, language, visuomotor integration, pre-academic abilities, socialization, and emotional and behavioral function. Because we evaluated the child 4 months before genetic testing established his diagnosis, the examiner knew nothing about his genetic disorder.

CASE REPORT

“J.K.,” a white boy aged 4 years, 1 month, was referred to us for a neuropsychological evaluation by his pediatrician. J.K. had multiple developmental concerns, including poor fine motor skills, low muscle tone, delayed language, and emotional and behavioral problems such as low frustration tolerance, stranger anxiety, and anger directed at his little sister.

J.K.'s parents gave written permission for us to review his medical records, evaluate him, and publish our findings. They were actively involved in his care and his evaluation.

Developmental History and Parents' Concerns

J.K. was born to a 37-year-old mother and father. After an uncomplicated 41-week pregnancy, J.K. was delivered by caesarean section, weighing about 10 pounds. No perinatal concerns were reported.

His early motor development was delayed. Because of low muscle tone, he did not start to crawl until he was 23 months old, and he did not walk independently until 25 months.

His language development was also delayed. Although he spoke his first words on time, his progress lagged behind his parents' expectations. He added vocabulary slowly: At around 35 months of age, he had only an estimated 30 words. When we assessed him at 49 months, he had only about 55 words and could at most put 2 or 3 together.

He had a medical history of constipation.

Available family developmental and psychiatric histories were unremarkable, with the exception of scoliosis in a maternal uncle. J.K.'s 2-year-old sister was developing normally. His mother was healthy and of Western and Northern European ancestry; his father was also healthy and of Scottish and Swedish ancestry.

The family became concerned about J.K.'s development early on, as he missed motor and language milestones. He began receiving Early Intervention services after his first birthday.

As J.K. got older, his parents noted that he was developing an “anxious and cautious” temperament.

At age 3 years, he transitioned from the Early Intervention Program to the public school system, receiving services through an Individualized Education Program. In his developmentally integrated preschool classroom, he received individualized speech therapy (3 sessions of 30 minutes per week), physical therapy (2 sessions of 30 minutes per week), and occupational therapy (2 sessions of 30 minutes per week). He also received 1-on-1 support from a classroom aide. According to his parents, school personnel characterized his difficulties as “global developmental delay.”

Because of emerging aggressiveness and anger aimed at his younger sister, he was started on outpatient psychological therapy. Socially, he was reported to be “slow to warm up to other kids,” although he was also said to relate better to other children once he became comfortable with them. He enjoyed social games, eg, laughing when tickled, but smiling was difficult because of his low facial muscle tone.

Neuropsychological Evaluation at Age 4 Years 1 Month

When J.K. was referred to us, he underwent observation and neuropsychological testing with author B.L.W. Below we describe the findings from their 2.5-hour session.

Informal Behavioral Observations—An anxious J.K. arrived with his parents for the appointment. Fearing being separated from them, he was hypervigilant about where they were in the room. He was most anxious when he first met B.L.W., but his fear eased noticeably as B.L.W. talked with his parents. Eventually, he calmed enough that his emotions did not interfere with the assessment.

His parents stayed in the office with him throughout the testing. When he became distracted, they helped to redirect his attention.

B.L.W. noted that J.K.'s speech and language skills, both vocabulary and grammar, were well below expectations for a child his age. He spoke only single words during the testing. His frequent misarticulations made his speech difficult to understand. He did not show excessive motor activity.

Physical Characteristics—J.K. was a well-groomed, proportional child. His head circumference was at the 75th percentile, weight at the 47th percentile, and height at the 83rd percentile. His ears were normally set, with typical architecture. His face was round, with prominent cheeks and a small jaw (mild micrognathia). His mouth and philtrum looked normal. His nose was low set, with an upturned tip. He had a mild fifth finger clinodactyly. His muscle tone was notably low, most strikingly in his face. As noted, earlier, he had trouble smiling.

Intellectual Function—We assessed J.K.'s intellectual function using the Wechsler Preschool and Primary Scale of Intelligence, 3rd edition (Wechsler, 2002). Table 1 shows his composite and subtest scores. Overall, his intellectual function was in the borderline range (Wechsler Scale Full Scale Intelligence = 70; 2nd percentile), with no significant discrepancy between verbal and nonverbal domains. His verbal skill scores were borderline for abilities to answer factual questions (Information), name pictures and define words

(Vocabulary), and reason verbally (Word Reasoning). In testing of nonverbal skills, his performance was borderline when he tried to imitate B.L.W. in building structures out of blocks (Block Design). He scored in the low average range for abilities to identify pictures sharing a common characteristic (Picture Concepts) and identify the missing piece of a visual pattern (Matrix Reasoning).

Language—B.L.W. used standardized assessments and informal behavioral observations to evaluate J.K.'s receptive and expressive language skills (Table 1). For receptive language, B.L.W. used the Peabody Picture Vocabulary Test, 4th edition (Dunn and Dunn, 2007). For each test item, he showed J.K. 4 pictures, spoke a word, and then asked J.K. to point to the 1 picture that the word described. J.K. scored in the low average range.

He had more difficulty on a test of expressive language, the Expressive Vocabulary Test, 2nd edition (Williams, 2007). For this test, he was asked to name objects shown in a picture. He performed in the borderline range.

When he spoke during these tests, he had difficulty making himself understood. Although his speech articulation was not assessed formally, B.L.W. noted that he left out medial and final consonants in words.

Visuomotor Integration—J.K. took the Beery-Buktenica Developmental Test of Visual-Motor Integration (Beery et al, 2005) to assess his visuomotor development, perceptual discrimination ability, and skill at integrating perceptual and motor processes. This test consists of geometrical forms that the child is shown and asked to copy with pencil and paper, in a sequence from simpler to more complex. B.L.W. asked J.K. to copy several of the geometrical figures. He scored in the very low range (Table 1), in part because he had trouble grasping the pencil.

Academic Readiness—Academic readiness is a child's knowledge of basic elements of early learning, such as colors, letters, and numbers. To measure J.K.'s academic readiness, B.L.W. gave him the School Readiness subtests of the Bracken Basic Concepts Scale: Expressive (Bracken, 2006). He was asked to name colors, shapes, letters, and numbers, and to make comparisons based on size. His difficulties with these tasks put his pre-academic skills in the borderline range (Table 1). He had trouble naming certain colors (eg, purple) and he could not name any letters. Likewise, he had trouble comparing sizes (eg, longer versus shorter) and identifying shapes (eg, a rectangle). His difficulty with early academic concepts was not surprising given his problems using language.

Socialization—B.L.W. evaluated J.K.'s social function with the Autism Diagnostic Observation Schedule, Module 1 (Lord et al, 2000). This semi-structured observation tool assesses social and communicative behaviors in young children whose speech is limited to single words. This assessment also involves a child's parents or caregivers.

B.L.W. encouraged J.K. to play with various toys and to engage with him in a series of social interactions, eg, playing jack-in-the-box and holding a make-believe birthday party. J.K. showed many instances of age-appropriate socialization. He imitated B.L.W., read

B.L.W.'s face to gauge his emotions (facial referencing), and did his best to smile in response to B.L.W. His joint attention (the ability to follow another person's gaze to a distant object and back again) was also within expectations. He communicated well with gestures, showed appropriate nonverbal ways of asking for help, and responded adequately to being called by name. Most notably, he clearly enjoyed interacting with B.L.W. and showed several instances of social-emotional reciprocity (shared enjoyment). For example, he laughed and asked to continue social games such as peek-a-boo. He made clear overtures to sustain the interaction, eg, by pointing to objects and giving toys to B.L.W. or his parents. He did not engage in restricted or repetitive behaviors.

Thus, J.K. did not meet the clinical cutoff for an autism spectrum disorder. For him, socialization was an area of strength. Table 1 lists his scores.

Emotional and Behavioral Function—B.L.W. used standardized parent and teacher reports to assess J.K.'s emotional and behavioral function (Table 2). On the Behavior Assessment System for Children, 2nd edition (Reynolds and Kamphaus, 2004), J.K.'s mother had reported that he had difficulties with hyperactivity (eg, “has poor self-control”), anxiety (eg, “is nervous”), depression (eg, “is easily upset”), and somatization (eg, “has stomach problems”). By contrast, his teacher had rated him as having only somatic problems. During the clinical interview, his parents noted his mild aggressiveness.

On the parent version of the Behavior Rating Inventory of Executive Function (Gioia et al, 2000), J.K.'s mother had reported that her son had great difficulty in shifting smoothly from 1 activity to another, controlling his emotional and behavioral responses, mentally manipulating information (working memory), and planning ahead and organizing. His teacher had also noted difficulties in these domains, as well as with inhibition, although a majority of her ratings were less extreme than the mother's.

Only the teacher had rated J.K. on the Social Responsiveness Scale (Constantino and Gruber, 2005) a standardized rating scale of autism spectrum symptoms. She considered J.K. to be within the normal range in every domain.

Recommended Interventions and Follow-Up

Based on J.K.'s neuropsychological evaluation, we made these recommendations for his education and outpatient treatment:

- We recommended that he continue in the developmentally integrated preschool class with individualized attention from a classroom aide. His speech, occupational, and physical therapy should continue at their current frequency, as outlined in his Individualized Education Program.
- We recommended that a special education teacher help him learn colors, letters, shapes, sizes, and other pre-academic skills.
- We recommended that the child psychologist keep seeing J.K. as well as help support his parents and sister, reduce the whole family's anxiety, and guide behavioral interventions.

- We urged the parents to consider getting J.K. a psychopharmacological consultation when he reached age 5, to look into treatment options for inattention, hyperactivity, and anxiety.
- Because of his significant delays and low muscle tone, we recommended genetic testing and consultation.

Genetic Testing

About 4 months after his evaluation, J.K. underwent genetic testing at our hospital. Array comparative genomic hybridization using the Agilent 4x180K SurePrint G3 CGH+SNP microarray (Agilent Technologies, Santa Clara, CA) revealed a hemizygous deletion on chromosome 18 (18p11.32-p11.21), involving 469 oligonucleotide probes and spanning 12.493MB (genomic coordinates based on hg19 reference: 148,963 - 12,642,430). The deletion meant that J.K. had only 1 copy of the deleted region. J.K.'s parents were given genetic counseling.

DISCUSSION

While case reports characterize most people with 18p deletion syndrome as having impaired intellectual function and other developmental delays, little has been written about their language, visuomotor, academic, social, emotional, and behavioral function. This case report lets us fill in some of the gaps, to help characterize these people's neuropsychological function and guide clinicians in choosing and interpreting neuropsychological, emotional, and behavioral tests for their patients.

Consistent with previous findings of intellectual impairment in people with 18p deletion syndrome (Babovic-Vuksanovic et al, 2004; Maranda et al, 2006; Portnoi et al, 2007; Thompson et al, 1986; Wester et al, 2006), patient J.K. had borderline intellectual function among his multiple areas of developmental delay. However, he scored in the low average range on the Picture Concepts and Matrix Reasoning test of the Wechsler Preschool and Primary Scale of Intelligence, 3rd ed. His relative strengths in nonverbal, abstract reasoning matched an earlier case study reporting stronger nonverbal than verbal skills in 3 girls with 18p deletion syndrome (Thompson et al, 1986).

J.K.'s language skills were delayed and his speech was notable for misarticulation. It is unclear whether his poor articulation was related to muscle weakness, motor control issues, or phonological problems. His receptive language skills were better developed than his expressive skills; still, both were about 1 year behind expected linguistic development for his age.

He had difficulty integrating visual and motor processes, and his fine motor skills were poor. His early academic skills were also below expectations for his age. While he could identify some colors, he had difficulty identifying letters and shapes, counting, and comparing sizes. Because of his borderline intellectual skills, we were not surprised by his wide-ranging developmental delays.

This is the first case report to study social function in a child with 18p deletion using a standardized observation. We assessed J.K. for possible autism spectrum symptoms using the Autism Diagnostic Observation Schedule (Lord et al, 2000).). He scored well in social reciprocity: He made good eye contact, engaged in facial referencing, had good joint attention skills, communicated by gestures, responded to hearing his name, and tried to smile in response to the examiner's smiles. He showed his pleasure when playing with the examiner, by trying to smile, seeking to continue the interaction, and sharing his excitement.

Although socializing with peers may be somewhat difficult for J.K. because of his deficient language and intellectual skills, the Autism Diagnostic Observation Schedule showed that his underlying social connectedness was intact. He did not meet the clinical criteria for autism or an autism spectrum disorder by either the Autism Diagnostic Observation Schedule or the standardized teacher report of autism symptoms, the Social Responsiveness Scale. Whether our findings in J.K. reflect intact social reciprocity in other children with 18p deletion syndrome will need to be tested in more cases.

Earlier case reports suggested that individuals with 18p deletion syndrome exhibit behavioral symptoms such as restlessness, stranger anxiety, poor concentration, and mood lability (Zavala et al, 2010). Our results support these findings.

At home, J.K. showed mild aggressiveness, anxiety, and low frustration tolerance. At home and in preschool, he had difficulties with executive function, namely, problems with set shifting, controlling his emotional and behavioral responses, mentally manipulating information, and organizing and planning ahead. These difficulties were less pronounced at school than home, leading us to suspect that the structure, routine, and individualized attention of the classroom helped him compensate.

The genotype-phenotype relationship in J.K. was much like that in other reported patients with 18p deletion syndrome. As reported by Wester et al (2006), individuals (like J.K.) who have smaller deletions originating at 18p11.21 are less impaired than those with larger deletions originating at 18p11.1. Patients with larger deletions closer to the centromeric region of the chromosome tend to have more severe motor disability, lower intellectual function, and more serious psychiatric disturbances (Babovic-Vuksanovic et al, 2004; Wester et al, 2006). Larger deletions have also been associated with more physical anomalies, such as severe brain malformations (eg, agenesis of the corpus callosum), short stature, and protruding ears (Wester et al, 2006). This was not J.K.'s phenotype.

Our study had some limitations. The findings from a single case report must not be over-generalized, especially when they provide only a snapshot of 1 individual with 18p deletion syndrome at 4 years of age. It is difficult to predict how J.K. will function later in life.

Further, we did not characterize all domains of J.K.'s neuropsychological function. In particular, although we obtained his mother's report of his attention and executive function, we did not assess them with standardized measures. We could not assess his memory or such aspects of language as sentence formation and pragmatics (socially appropriate speech). Although the processing speed subtests of the Wechsler Preschool and Primary Scale of Intelligence would have yielded important information about J.K.'s graphomotor

speed, we did not give them to him because the instructions were too complex for him to understand.

Within the context of these limitations and of earlier literature, our case report sheds light on some neuropsychological deficits specific to 18p deletion syndrome. Intellectual function is impaired, likely worse if the deletion is larger and closer to the chromosome's centromeric region. Language skills and visuomotor integration are also impaired, and also likely worse for larger lesions closer to the centromeric region. Emotional and behavioral findings show mild aggressiveness, anxiety, low frustration tolerance, and executive function weaknesses. Social reciprocity, however, may be generally intact.

Our findings have implications for neuropsychologists who evaluate a child with 18p deletion syndrome. To get a full clinical picture of the patient and guide decisions about care, we recommend assessing the domains of intellect, pre-academics, receptive and expressive language, social function, and emotional and behavioral health. Patients may show relative strength in nonverbal reasoning and social interaction.

Patients should be followed long-term. It is likely that symptoms manifest differently at different developmental stages; the clinician should consider the patient's developmental context. The developmental trajectories of patients with 18p deletion syndrome are still unknown.

In conclusion, our neuropsychological evaluation of a child with 18p deletion syndrome showed that deficits in social reciprocity may not be a key feature and that patients present differently from those with autism, 16p deletion, and other clinical and genetic syndromes with associated delays in socialization.

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TABLE 1

This Patient's Neuropsychological Test Results

	Standard or Scaled Score	Percentile	Description
Wechsler Preschool and Primary Intelligence Scale-III¹			
Full Scale IQ	70	2nd	Borderline
Verbal IQ	74	4th	Borderline
Performance IQ	73	4th	Borderline
Information	5	5th	Borderline
Vocabulary	5	5th	Borderline
Word Reasoning	5	5th	Borderline
Block Design	3	1st	Borderline
Matrix Reasoning	7	16th	Low average
Picture Concepts	7	16th	Low average
Peabody Picture Vocabulary Test-4 (Form B)²			
Receptive Vocabulary	85	16th	Low average
Expressive Vocabulary Test-2 (Form B)³			
Expressive Vocabulary	78	7th	Low average
Developmental Test of Visual-Motor Integration⁴			
Visual-Motor Integration	69	2nd	Very low
Bracken Basic Concepts Scale: Expressive⁵			
School Readiness Composite	5	5th	Borderline
Autism Diagnostic Observation Schedule Module 1⁶			
Communication			Raw = 0 (2 indicates autism spectrum disorder)
Reciprocal Social Interaction			Raw = 0 (4 indicates autism spectrum disorder)
Play			Raw = 0 (no cutoff score)
Repetitive Behaviors			Raw = 0 (no cutoff score)

¹ Wechsler, 2002.

² Dunn and Dunn, 2007.

³ Williams, 2007.

- ⁴Beery et al, 2005.
- ⁵Bracken, 2006.
- ⁶Lord et al, 2000.

TABLE 2

Mother and Teacher Ratings of This Patient's Emotional and Behavioral Function

	Mother's Report			Teacher's Report		
	T-score	Percentile	Description	T-score	Percentile	Description
Behavior Assessment System for Children-2¹						
Hyperactivity	62	88th	At risk	57	79th	Normal
Aggression	59	83rd	Normal	50	67th	Normal
Anxiety	64	91st	At risk	55	76th	Normal
Depression	65	92nd	At risk	54	73rd	Normal
Somatization	63	90th	At risk	67	93rd	At risk
Aypicality	56	80th	Normal	54	77th	Normal
Attention Problems	58	77th	Normal	55	70th	Normal
Behavior Rating Inventory of Executive Function²						
Inhibit	57	74th	Normal	60	78th	Elevated
Shift	83	>99th	Clinical	61	80th	Elevated
Emotional Control	84	>99th	Clinical	60	76th	Elevated
Working Memory	60	80th	Elevated	64	84th	Elevated
Plan/Organize	71	97th	Elevated	61	78th	Elevated
Social Responsiveness Scale³						
Social Awareness				57	75th	Normal
Social Cognition				56	73rd	Normal
Social Communication				53	63rd	Normal
Social Motivation				51	53rd	Normal
Autistic Mannerisms				55	70th	Normal
Total Score				55	70th	Normal

¹ Reynolds and Kamphaus, 2004.² Gioia et al, 2000.³ Constantino and Gruber, 2005.