

# Microdeletion 3q13.31 and Agenesis of the Corpus Callosum in a Patient with Intellectual Disability and Autism Spectrum Disorder: A Case Report

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## Abstract

## Case Report

Total agenesis of the corpus callosum (ACC) is a rare condition characterized by the absence of corpus callosum formation during fetal development. It can occur in isolation or be associated with congenital syndromes, including the emerging microdeletion syndrome 3q13.31. This syndrome, caused by a deletion in the long arm of chromosome 3, presents with developmental delay, growth abnormalities, craniofacial dysmorphism, skeletal malformations, genital anomalies, and agenesis of the corpus callosum. The case of a 7½-year-old boy with microdeletion 3q13.31 is described, highlighting common clinical manifestations observed in this syndrome. The patient exhibited delayed psychomotor development, language delay, autism spectrum disorder, intellectual disability, facial dysmorphism, and agenesis of the corpus callosum. Comparison with existing literature showed similarities in features such as delayed development, language delays, intellectual disability, and brain anomalies. The 3q13.31 microdeletion syndrome encompasses a wide range of clinical phenotypes, and the identification of responsible genes contributes to understanding the condition, although treatment remains challenging.

**Keywords:** corpus callosum (ACC), congenital syndromes, chromosome, microdeletion.

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## INTRODUCTION

Total agenesis of the corpus callosum (ACC) is a rare cerebral malformation characterized by the complete absence of corpus callosum formation during fetal development. The corpus callosum (CC) normally facilitates information transfer and interhemispheric coordination. The prevalence of ACC varies in different studies, ranging from 0.05% to 0.7% in the general population and 2% to 3% in populations with intellectual disabilities [1].

Agenesis of the corpus callosum can occur in isolation or be associated with congenital syndromes. The development of high-resolution microarray techniques has facilitated chromosome studies, enabling the identification of genes responsible for known syndromes. Thus, more than 200 different congenital syndromes have been described to date, allowing the genetic etiology of ACC [OMIM 217990], often associated with chromosomal rearrangements, to be

identified [2]. A wide range of clinical phenotypes associated with agenesis of the corpus callosum have been described. Variable combinations of developmental delay, language disorders, intellectual disabilities, motor impairments, and epilepsy can be observed. The frequently associated cognitive and neurological phenotypic features of ACC include developmental delay, language disorders, motor impairments, intellectual disabilities, and epilepsy.

An "emerging" syndrome, newly recognized, was first identified in 2012, called microdeletion syndrome 3q13.31 (OMIM #615433). It is characterized by a proximal deletion of the long arm of chromosome 3, ranging in size from 0.58 Mb to 22.4 Mb, along with common clinical manifestations, including developmental delay, above-average postnatal growth, craniofacial dysmorphism, skeletal malformations, genital anomalies, and agenesis of the corpus callosum [3]. In some cases, attention deficits and autism

spectrum disorders have also been identified in affected individuals.

To date, there are only a few studies in the international literature on microdeletion syndrome 3q13.31. In this report, we describe the case of a 7½-year-old boy in whom a microdeletion 3q13.31 was identified by array comparative genomic hybridization (array-CGH), sharing common clinical manifestations observed in microdeletion syndrome 3q13.31.

### Clinical Vignette:

We present the case of a 7½-year-old child named SS, who is the youngest of two siblings from a non-consanguineous Moroccan couple. Regarding his medical and surgical history, our patient underwent resection of the right upper eyelid levator muscle. In terms of medical history, he has a cousin who is being treated for autism spectrum disorder. His pregnancy was marked by a post-term delivery with severe oligohydramnios, necessitating an emergency cesarean section, and resulting in neonatal distress with an Apgar score of 4/10 at birth. His birth weight was 2.5 kilograms, and he was breastfed for 6 months. His head circumference was within the normal range. His overall psychomotor development was delayed, with first words and walking acquired at the age of 4½ years, while first phrases and nighttime bladder control were only achieved at the age of 6½ years. From early childhood, the parents noticed hypotonia, language delay, difficulties in socializing with peers, restricted and stereotyped interests, lack of pointing, apparent noise intolerance, and academic difficulties. At the age of 4½ years, due to concerns raised by teachers regarding his language delay and socialization difficulties, he was referred to a speech therapist, who provided numerous speech therapy sessions for 2 years. Around the age of 6½ years, following inadequate progress, the parents took the child for a pediatric psychiatric evaluation, where a diagnosis of autism spectrum disorder and intellectual disability was considered. The child then underwent a clinical evaluation, including the administration of the Autism Diagnostic Observation Schedule (ADOS), revealing moderate autism, as well as the Autism Diagnostic Interview-Revised (ADI-R), with scores exceeding diagnostic thresholds in all domains. Subsequently, the child was referred for a neuropsychological assessment using the Wechsler Intelligence Scale for Children (WISC-IV), which revealed profound intellectual disability with an IQ of 44. The diagnosis of intellectual disability associated with autism spectrum disorder was made according to the diagnostic criteria of the fifth edition of the Diagnostic and Statistical Manual of Mental Disorders. From an academic perspective, his attention, learning, and writing difficulties worsened, leading to his repeating the first grade and later receiving educational accommodations to provide the necessary support for understanding and integration with other students.

In terms of morphology, the patient exhibits a prominently wide forehead, spaced eyes, and ptosis of the right upper eyelid. Upon clinical presentation, our patient underwent a neurological examination, which revealed preserved muscle strength, brisk and polykinetic osteotendinous reflexes with clonus in the left foot, as well as congenital right ptosis. The remainder of the neurological examination was unremarkable. Electroneuromyography (ENMG) showed normal motor and sensory nerve conduction in the lower limbs, ruling out peripheral neurological involvement. A brain MRI revealed complete agenesis of the corpus callosum. Subsequent blood analyses, including erythrocyte pyruvate kinase assay (with normal activity), lactate-to-pyruvate acid ratio (not increased), elevated lactate dehydrogenase, and amino acid chromatography (without anomalies), ruled out amino acid deficiency. The patient was then referred to a specialized genetic consultation, where constitutional karyotyping revealed no chromosomal abnormalities. Molecular cytogenetic analysis using the CGH array identified a heterozygous interstitial deletion in 3q13.31, encompassing 10 RefSeq genes, including the pathogenic OMIM gene ZBTB20.

Through this case, we aim to compare the clinical manifestations observed in our patient with those described in the medical literature.

## DISCUSSION

In the literature, until today, few cases of 3q13.31 deletion syndrome have been identified, but four groups have been established [4]:

- In group 1, affected individuals have lost DNA between 3q13.2 and 3q13.31 with breakpoints around 112-115.5 Mb. This group includes 9 individuals reported by Shuvarikov (2013), 5 individuals reported by Molin (2012), one in Shimojima (2009), as well as 6 in Decipher [4].
- In group 2, affected individuals have a larger deletion than in group 1. This group includes 14 individuals mentioned by Ogilvie (1998), Lawson-Yuen (2006), Malan (2010), Molin (2012), Wisniewiecka-Kowalnik (2013), as well as 4 Unique members, and 3 in Decipher.
- In group 3, individuals have a deletion overlapping the repetitive deletion but extending towards the upper part of the long arm. This group includes 4 individuals mentioned by Hou (2004), Kosaki (2005), Sato (2007), Simovich (2008), Molin (2012), 3 Unique members, as well as 2 in Decipher.
- In group 4, individuals have a deletion overlapping the repetitive deletion but extending to the end of 3q. This group includes two individuals reported by Molin (2012) and Vuillaume (2013), as well as four unique members and 3 cases in Decipher.

Pregnancy generally progresses without complications, according to Molin (2012) [3]. In two patients from the aforementioned group 1, pregnancies were marked by oligohydramnios, but this complication did not cause renal problems, which was also found in the case of our patient.

Regarding delivery, it generally occurred at term. Newborns in group 1 were generally born at term with a good birth weight, averaging 3.36 kg, and some had a high cranial circumference. Four deliveries were performed by cesarean section. The babies experienced various neonatal difficulties, including low Apgar scores, respiratory difficulties, neonatal resuscitation in some cases, and feeding problems. These findings are consistent with those of our patient, who underwent an emergency cesarean section but with a lower than normal birth weight and a history of neonatal distress.

Genital anomalies appear to be slightly more frequent in boys than in girls. In the medical literature and in Unique, 15 out of 24 boys had genital anomalies, and in Decipher, 4 out of 9 boys had them. These anomalies included cryptorchidism, testicular atrophy, or hydrocele. No genital anomaly was reported in our patient.

Characteristic facial features have been described that are responsible for a distinctive resemblance among the affected patients. The most common features include a broad and prominent forehead, widely spaced and prominent eyes, or downward-slanting eyes, a short but wide and sometimes upturned nose, a short space between the mouth and the nose, a full lower lip, low-set ears attached to the sides of the head and sometimes having an unusual shape. Less frequent features have been described, such as hooded eyelids, sparse or absent eyebrows, a pointed chin, and midface hypoplasia. The most frequently encountered vision problems in the series of patients described in the literature are ptosis, myopia, or hyperopia. Thus, 12 out of 46 children reported in the medical literature have ptosis, and some have undergone levator muscle shortening [4]. Myopia and presbyopia have also been described in 3 out of 15 children in group 1, 6 out of 18 children in group 2, and one child each in groups 3 and 4. These findings align with the morphological description of our patient, who has ptosis in the right eye and facial characteristics similar to those described above.

Delayed development has frequently been described in the literature, including delayed sitting position, maintaining a standing position, weak muscle tone, loose or tight and contracted joints, and delayed fine motor skills. Toilet training is also generally delayed.

The majority of children has language delays, although some children in group 1 understand speech and learn to speak at the same age as children with normal development. Among children who experienced delayed speech, some caught up later. Babbling occurs around the second year, and the first words appear around 2-3 years. Some children speak in a confused manner, and two children stutter, as described by Molin and Shuvarikov [3, 7]. In group 2, children have a marked language delay and rely on body language to express their needs and feelings. Some use words for the first time around the age of 6-8 or even later. In three children, few or no meaningful words were used, and communication was primarily through signs or gestures at the ages of 4½, 8, and 18 years [3]. This is also the case with the patient we have described, who exhibited significant language delay.

Individuals with 3q13.31 deletion syndrome are likely to have an intellectual disability and therefore require support in their learning. Data from group 1 show significant variations, with a moderate level of difficulty [3, 7]. Children in group 2 require more learning support than those in group 1.

Seizures are quite common. In group 1, 5 children had one or more seizures; in group 2, 3 children had epilepsy; in group 3, 7 children developed generalized seizures from the age of one year, well controlled by antiepileptic drugs. In group 4, three children have associated epilepsy.

Brain imaging has revealed agenesis of the corpus callosum in 12 children, including 3 from group 1, 6 from group 2, and 3 from group 4. This condition involves a partial or complete failure of the development of the nerve tissue that connects the two cerebral hemispheres, with variable effects depending on the association with other brain abnormalities. Other brain anomalies have been described, including ventricular hypertrophy, cerebellar anomalies, delayed myelination, and atrophy of the white matter with scarring [4]. This is the case with our patient, whose brain MRI revealed a total agenesis of the corpus callosum.

In the literature, many children with 3q13.31 microdeletion syndrome have frequent concentration difficulties, and some have autism spectrum disorders. Parents of children in groups 1 and 2 report that their children are affectionate, have a sense of humor, and behave appropriately at home and in social situations. Literature reports describe anxiety, risk-taking behaviors, low energy levels, low capacity to cooperate and imitate others, aggression, easy frustration, and obsessive-compulsive behavior. Regarding autism spectrum disorder, repetitive behaviors, hand flapping, echolalia, and difficulties in coping with sensory overload have been described. Children in groups 3 and 4 exhibit a wide range of behaviors, from normal

behavior to significant difficulties, including lack of reaction and self-harm [3].

In the literature, four children were born with a cardiac problem, including a septal malformation, a persistent arterial duct, and one with a patent foramen ovale, which resolved spontaneously. The fourth child had Tetralogy of Fallot and required surgical intervention.

Renal anomalies are sometimes observed, with five children in groups 1 and 2 presenting these anomalies. These include a single kidney associated with compensatory hypertrophy [7], incomplete duplication of the collecting system on the right side, a hypertrophied kidney on one side, a small kidney [3], and swelling of the tubes connecting the kidneys to the bladder.

Spinal column anomalies have been described, including scoliosis, lordosis, or kyphosis. These anomalies affect 3 children in group 1, 4 children in group 2, 4 children in group 3, and 1 child in group 4.

It is believed that 3q13.31 deletion syndrome is due to the loss of one or more genes in the 3q13 region. The DRD3 gene is located in the 0.58 Mb DNA segment that all individuals with this syndrome have lost. It plays an important role in movement, learning, and emotions and likely contributes to developmental delay. The DRD3 gene could also be linked to obesity, impulsive personality traits, and addictive behavior [4].

The ZBTB20 gene is also located in the 0.58 Mb DNA segment that all individuals with this syndrome have lost, and it is believed to be responsible for developmental delay. It is involved in the production of an important protein in nerve cells, and disrupted production of this protein in mice leads to abnormal development of the corpus callosum. The ZBTB20 protein also regulates genes involved in growth and metabolism.

The LSAMP gene is involved in learning and behavior [3].

The GAP43 gene has been identified as potentially underpinning the development of autism characteristics, and it is suspected to be involved in corpus callosum formation. It is a strong candidate gene for developmental delay [3, 4, 6].

## CONCLUSION

The 3q13.31 microdeletion syndrome exhibits diverse clinical phenotypes, as mentioned in this article, and the identification of responsible genes is valuable and can aid future studies. However, it does not immediately lead to improved treatment. Furthermore, even if the presumed responsible gene is absent, it does not necessarily mean that the associated characteristics will be present. Other environmental and genetic factors play a role in the presence or absence of a particular feature.

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