19p13.3 Deletion With Polyotia: A Case Report and Literature Review

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Abstract

Mutations at chromosome 19 are rare, and reports in the literature are scarce and clinically variable. This chromosome has a high genetic density, and hence a given deletion can cause distinctive effects on body systems and, in addition, result in a characteristic phenotype.

We report the case of a patient who presented with distinctive signs and symptoms such as delayed psychomotor development, severe postnatal delay, dolichocephaly, polyotia, and ocular hypertelorism. Even though all cases with a chromosome 19 deletion do not present in the same way, they still share some clinical manifestations that should be considered, which prompted us to present a summary of the available literature on the subject. Additionally, to our knowledge, this is the first and only case with polyotia in its phenotype to be reported in Colombia to date.

Introduction

During the last few years, several new syndromes have been described in the field of clinical genetics thanks to the development and increasing use of tests such as comparative genomic hybridization (CGH) arrays. However, the information available regarding 19p deletions is still scant [1]. As of 2021, only 85 cases have been reported in the DECIPHER database [2]. The 19p13.3 deletion syndrome is usually sporadic, meaning it appears de novo, resulting from a chromosomal segment deletion during the formation of reproductive cells or in early fetal development. The majority of the affected individuals have no history of the disease in their families [3]. To our knowledge, only seven patients had documented parental origin [2].

The 19p13.3 region contains 6.9 Mb and several different genes within. Hence, depending on the number of bases compromised by a deletion, this will result in a specific clinical presentation. For example, this chromosomal region contains the serine/threonine kinase 11 (STK11) gene, associated with Peutz-Jeghers syndrome, which codes for a serine-threonine kinase protein that acts as a cell cycle metabolism regulator, cell polarity modulator, and tumor suppressor [3].

Additionally, other genes within this region are frequently affected by these deletions, such as the testicular haploid expressed gene (THEG), which plays an essential role in body development through its influence on hormone development, and whose absence may impact the height of the patients, who are generally short in stature [1]. The product of SHC adaptor protein 2 (SHC2) is responsible for the maturation of sensory, cortical, and sympathetic neurons [4], and hence its loss leads to impaired vision and hearing [1]. The actin alpha 1 (ACTA1) gene is expressed in neuronal tissue, especially in the cerebellum and hippocampus, where mutations in this gene have been associated with hypotonia and delayed motor skills development [5].

G protein subunit alpha 11 (GNA11) is related to normal craniofacial and cardiovascular development, and transducin-like enhancer protein 2 (TLE2), which is associated with neurogenesis and epithelial differentiation during embryonic development [6]. In addition, deletions at this level have been associated with different pathologies related to deficits in tumor suppression, such as breast cancer and lymphomas [7,8]. Given the broad clinical spectrum, the prognosis and life expectancy will depend on the manifestations in each patient.

In the silico genomic analysis of 19p13.3 microdeletion, breakpoints revealed numerous highly repetitive sequences, suggesting events mediated by long interspersed nuclear elements (LINEs) and/or short interspersed nuclear elements (SINEs) as the generators of these microdeletions [1]. These genetic alterations give rise to the phenotypic spectrum of the disease, which is still being defined. In this report, we explore the clinical features of a patient who presented for an appointment at the Hospital of the Universidad del Norte, and to the best of our knowledge, this is the first reported case of this clinical syndrome in Latin America.

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Case Presentation

A seven-year-old male patient presented to the clinical genetics office accompanied by his mother. She was concerned because her child had experienced learning difficulties and growth retardation since his first year of life. The patient had no relevant comorbidities, and his parents were of appropriate age and height, not consanguineous, and had four children (one deceased, who had suffered from Down syndrome). No prenatal history was available.

Physical examination revealed delayed language and fine motor skills, as well as low height (112 cm; Z-score: -1.87; percentile: 3%) and weight (17 kg; Z-score: -1.61; percentile: 5%). There was a prominent sagittal suture with dolichocephaly, skull bulging, triangular facies, short and oblique fissures, epicanthus, telecanthus, ocular hypertelorism, low bridge, hypoplasia of the distal third of the eyebrows, and low-set, winged, and rotated pinnae, with bilateral polyotia (perceived as soft preauricular skin-covered nodules). No stereotypies (repetitive movements or sounds) were observed. No pictures of our patient’s phenotypical findings are shown here, as his mother did not give permission to publish them.

At the time, the patient’s mother brought an old report of her son’s bone age, which was found to be of 30 months, for a chronological age of five years. Additionally, she brought a karyotype test, with a normal result. Due to his learning disabilities, fragile X testing was requested. The fragile X study reported the presence of an allele of 28 CGG repeats in the analyzed region of FMR1, which was a normal result. Finally, a microarray analysis was ordered to rule out other possibilities.

The microarray report (Table 1) showed a 19p13.3 deletion of 1.22 Mb that involved 19 genes and stated that it was of uncertain significance given that only three similar cases had been described so far, all with smaller deletions (Figures 1, 2 in the Appendix). One case presented autism and intellectual disability, another had delayed psychomotor development, and the third one did not have an associated phenotype, according to the report.

| Variant in copy number | Chromosomal localization | Genomic coordinates (hg19) | Minimum size | OMIM genes contained | Clinical significance |
|------------------------|--------------------------|----------------------------|--------------|----------------------|----------------------|
| Deletion               | 19p13.3                  | Chr19:4148279_5373802      | 1.22 Mb      | See full report in Appendix (Figures 1, 2) | Variant of uncertain significance (VUS) |

TABLE 1: Microarray results

Due to his growth abnormalities, the patient was referred to endocrinology. Also, physical and occupational therapy every three weeks was selected as a therapeutic approach, and an abdominal ultrasound was ordered. However, there are no follow-up reports available because the patient stopped attending appointments.

Discussion

The information currently available on the 19p13.3 deletion syndrome is limited, and the reports mention variable clinical features. For example, de Smith et al. have described a patient with overgrowth, macrocephaly, obesity, mental retardation, and behavioral problems (self-and hetero-aggressions and temper tantrums) [9]. Sibberg et al. have described two patients, both with aberrations in chromosome 19. However, they had different manifestations. The first case was a two-year-old patient with macrocephaly, normal growth, and a 1.25 Mb deletion at the 19p13.3 site. The other was a nine-year-old patient with microcephaly, growth retardation, and duplication of 0.81 Mb at the same location. Nevertheless, both patients had dysmorphic features and delayed psychomotor development [10].

Another publication has reported hypotonia, congenital cardiac malformations, sensorineural and conductive hypoacusis, absence seizures, tonic-clonic seizures, difficulty in social development, short philtrum, thick eyebrows, keloids, immune dysregulation, dysmorphic features, and again, delayed psychomotor development, but with normal postnatal growth [11].

Lastly, Peddibhotla et al. have discussed a cohort of eight patients with 19p13.3 microdeletion, a high incidence of learning difficulties, hypotonia, and global developmental delay, along with the considerable presence of congenital anomalies such as feeding difficulties, congenital heart disease, and gastrointestinal, renal, urogenital, auditory, and visual anomalies. Other abnormalities found in the patients were ventriculomegaly, broad forehead, mid-facial hypoplasia, low-set ears, smooth philtrum, sunken eyes, and VACTERL association [1].

The clinical presentation of our patient was compatible with what has been presented in the literature,
which is summarized in Table 2 [1,3,6,9-17]. Particularly, he showed learning difficulties (language delay) and postural and motor abnormalities (delayed fine motor skills). However, our literature search did not yield any reports of the polyotia that our patient presented, since, to our knowledge, this is the first reported case of polyotia related to a 19p13.3 deletion.

| General symptoms | Specific symptoms | Peddibhotla et al., 2013 [5] | Souza et al., 2011 [2] | Al-Kateb et al., 2010 [8] | de Smith et al., 2011 [9] | Siggeberg et al., 2015 [10] | Archer et al., 2015 [11] | Sgardioli et al., 2015 [12] | Campeoredte et al., 2015 [13] | Nevada et al., 2015 [14] | Kurada et al., 2014 [15] | Rilleg et al., 2013 [16] | Scolet et al., 2013 [17] |
|------------------|------------------|-----------------------------|------------------------|---------------------------|-----------------------------|-----------------------------|-----------------------------|-----------------------------|-----------------------------|-----------------------------|-----------------------------|-----------------------------|-----------------------------|
| Intellectual delay | -                | Yes                         | Yes                    | Yes                      | Yes                         | Yes                         | Yes                         | Yes                         | Yes                         | Yes                         | Yes                         | Yes                         | Yes                         |
| Developmental delay | Yes (7/8)       | Yes                         | Yes                    | Yes                      | Yes                         | Yes                         | Yes                         | Yes                         | Yes                         | Yes                         | Yes                         | Yes                         | Yes                         |
| Speech delay      | Yes (4/8)       | Yes                         | Yes                    | Yes                      | Yes                         | No                          | Yes                         | -                           | Yes                         | Yes                         | Yes (9/11)                  | Yes                         | Yes                         |
| Motor delay       | Yes (1/8)       | Yes                         | Yes                    | No                       | Yes                         | Yes                         | -                           | -                           | Yes                         | Yes                         | Yes (1/3)                   | Yes                         | Yes                         |
| Learning disabilities | Yes (7/8)       | Yes                         | Yes                    | Yes                      | Yes                         | Yes                         | Yes                         | Yes                         | Yes                         | Yes                         | Yes (4/8)                   | No                           | Yes                         |
| Memory impairment | No               | No                          | -                      | No                       | -                           | No                          | -                           | -                           | -                           | -                           | No                           | No                           | No                           |
| Seizures          | Yes (1/8)       | Yes                         | -                      | No                       | Yes                         | Yes                         | -                           | Yes                         | Yes                         | Yes                         | Yes (4/8)                   | No                           | Yes                         |
| Hydrocephaly      | Yes (6/8)       | Yes                         | Yes                    | Yes                      | Yes                         | Yes                         | Yes                         | Yes                         | Yes (1/2)                   | Yes                         | Yes (1/2)                   | Yes                         | No                           |
| Unilateral gait   | No               | No                          | Yes                    | No                       | No                          | Yes (1/2)                   | Yes                         | Yes                         | Yes (1/2)                   | Yes                         | Yes (1/2)                   | Yes                         | No                           |
| Attention deficiency | No              | No                          | -                      | No                       | -                           | No                          | -                           | -                           | Yes                         | Yes                         | Yes (1/2)                   | Yes                         | No                           |
| Behavioral problems | No              | No                          | -                      | Yes                      | -                           | -                           | Yes                         | -                           | -                           | No                           | No                           | No                           | No                           |
| Anxiety           | Yes (1/8)       | No                          | -                      | No                       | -                           | Yes                         | -                           | -                           | No (1/2)                    | Yes                         | Yes (1/3)                   | No                           | No                           |
| Macrocephaly      | No               | No                          | Yes                    | Yes                      | Yes                         | No                          | Yes                         | -                           | Yes                         | Yes                         | Yes (1/3)                   | No                           | Yes                         |
| Facial dysmorphia | Yes              | Yes                         | Yes                    | Yes                      | Yes                         | Yes                         | Yes                         | Yes                         | Yes                         | Yes (1/3)                   | Yes                         | Yes                         | Yes                         |
| High and/or wide forehead | Yes (5/8) | No                      | Yes                    | Yes                      | Yes (1/2)                   | Yes                         | Yes (1/3)                   | Yes                         | Yes (1/2)                   | Yes                         | Yes (1/3)                   | Yes                         | Yes (1/3)                   |
| Otic malformations | Yes (6/8)       | No                          | Yes                    | No                       | Yes (1/2)                   | Yes                         | Yes                         | -                           | Yes                         | Yes                         | Yes                         | Yes (1/3)                   | Yes                         |
| Deathness         | Yes (4/8)       | No                          | Yes                    | No                       | No                          | Yes                         | Yes                         | Yes                         | Yes (1/2)                   | Yes (1/3)                   | Yes (1/2)                   | Yes                         | Yes (1/8)                   |
| Hair implantation anomalies | No      | No                          | Yes                    | Yes                      | Yes (1/3)                   | Yes                         | Yes                         | Yes (1/3)                   | Yes (1/3)                   | Yes (1/2)                   | Yes (1/3)                   | Yes                         | Yes (1/2)                   |
| Wide nostrils     | -                | -                           | No                      | -                        | Yes (1/2)                   | Yes (1/3)                   | Yes                         | Yes (1/3)                   | Yes (1/3)                   | Yes (1/3)                   | Yes (1/3)                   | Yes (1/3)                   | Yes (1/3)                   |
| Long face         | Yes (1/8)       | No                          | No                      | Yes (1/2)                 | Yes                         | Yes (1/3)                   | Yes                         | Yes (1/3)                   | Yes (1/3)                   | Yes                         | Yes (1/3)                   | Yes (1/3)                   | Yes (1/3)                   |
| Pointed chin      | Yes (1/8)       | No                          | No                      | -                        | -                           | -                           | -                           | Yes                         | Yes                         | Yes                         | Yes (1/3)                   | Yes                         | Yes (1/3)                   |
| Thin lips         | No               | No                          | No                      | -                        | Yes                         | -                           | Yes                         | Yes (1/2)                   | Yes                         | Yes (1/2)                   | Yes (1/3)                   | Yes                         | Yes (1/3)                   |
| Smooth philtrum   | Yes (4/8)       | No                          | No                      | -                        | Yes (1/2)                   | Yes                         | Yes                         | Yes                         | Yes (1/3)                   | Yes (1/3)                   | Yes                         | Yes (1/3)                   | Yes (1/3)                   |
| Low hanging columna (nasal columna) | No | No                          | No                      | Yes (1/2)                 | -                           | -                           | Yes (1/2)                   | Yes                         | Yes (1/3)                   | Yes (1/3)                   | Yes (1/3)                   | Yes (1/3)                   | Yes (1/3)                   |
| Epicanthal folds  | Yes              | Yes                         | Yes                    | No                       | -                           | Yes                         | -                           | Yes                         | Yes                         | Yes                         | Yes (1/3)                   | Yes                         | Yes                         |
| Nasal dysmorphia  | Yes (2/8)       | Yes                         | Yes                    | Yes (1/2)                 | Yes                         | Yes                         | Yes                         | Yes (1/2)                   | Yes                         | Yes                         | Yes (1/3)                   | Yes                         | Yes (1/3)                   |
| Mouth dysmorphia | No               | No                          | Yes                    | Yes (1/2)                 | Yes                         | -                           | Yes                         | -                           | Yes                         | Yes                         | Yes (1/3)                   | Yes                         | Yes (1/3)                   |
| Nasal abnormalities/vestibulopharyngeal insufficiency | Yes (4/8) | No                          | No                      | Yes (1/2)                 | Yes                         | -                           | Yes (1/2)                   | Yes                         | Yes (1/3)                   | Yes (1/3)                   | Yes (1/3)                   | Yes (1/3)                   | Yes (1/3)                   |
| Gastroesophageal reflex | Yes (2/8) | No                          | Yes (1/2)               | No                        | Yes (1/2)                   | Yes                         | Yes (1/2)                   | Yes (1/2)                   | Yes (1/3)                   | Yes (1/3)                   | Yes (1/3)                   | Yes (1/3)                   | Yes (1/3)                   |
| Dysphagia         | Yes (1/8)       | No                          | -                      | Yes (1/2)                 | Yes                         | Yes                         | Yes (1/2)                   | Yes                         | Yes (1/3)                   | Yes (1/3)                   | Yes (1/3)                   | Yes (1/3)                   | Yes (1/3)                   |
| Hypertonusus at birth | No        | No                          | -                      | Yes (1/2)                 | -                           | Yes                         | -                           | Yes (1/2)                   | Yes                         | Yes (1/3)                   | Yes (1/3)                   | Yes (1/3)                   | Yes (1/3)                   |
Unfortunately, the patient's attendance during the follow-up period was poor, which limited his clinical follow-up. Therefore, some clinical features of this syndrome that were not detected may still be present in our patient.

**Conclusions**

Despite the paucity of literature available on this disease, the case presented still provides good insight into some of the manifestations found in these patients. Additionally, we found other clinical characteristics that may be present if a clinician encounters a patient with this challenging diagnosis, highlighting the importance of keeping this disorder in mind for a differential diagnosis in patients with dysmorphic features and developmental delay.

**Appendices**
**FIGURE 1: Microarray report in Spanish (description and methodology)**

Translation:

**Genome scan description:**

- Comparative genome hybridization array (ACGH) allows simultaneous detection of changes in the number of copies, on a genomic level, deletions (losses), duplications (increases), as well as unbalanced rearrangements. This technique does not detect balanced rearrangements (translocations), polyploidies, mosaic duplications, and deletions with a percentage below 40%. Neither does it detect punctual mutations in the analyzed regions.

- The commercial platform used contains approximately 120,000 CGH probes and 60,000 SNP probes; the resolution for detection of loss of heterozygosity (LOH) is approximately 10 Mb.

**Methodology:**

- Extraction of genomic DNA from a peripheric blood sample from the patient and the application of the corresponding quality checks.

- Marking of the patient’s DNA and reference DNA (masculine control) and hybridization using the array Sureprint G3 Human ICGH+SNP from Agilent 4x180k (array number: 25283051042), through previously established protocols.

- Data scanning through Surescan.

- Data obtention, quality analysis, and analysis of results using Agilent software Cytogenomics.
FIGURE 2: Microarray report in Spanish (results and interpretation)

Translation:

Results:

- Result of the array-CGH (ISCN 2016): arr[hg19] 19p13.3(4148279_5373802)x1

- The remitted sample presents a genomic pattern of masculine sex

Interpretation:

- An uncertain clinical significance deletion has been detected on the chromosomal region 19p13.3, genomic coordinates chr 19:4148279-5373802. This CNV affects 19 OMIM genes and is not reported in databases of benign variants such as the Data Base of Genomic Variants (DGV). On the other hand, the DECIPHER database (https://decipher.sanger.ac.uk/) describes three cases (304624, 316918, and nssv580436) of patients with smaller deletions inside the altered region in the proband of study, cataloged as VUS and probably pathogenic. The patient of case 304624 presents autism and intellectual disability, the case nssv580436 presents psychomotor delay. The case 316918 does not report an associated phenotype. Because there are only three described cases with several alterations whose pathogenic contribution is not clear, it is granted an uncertain clinical significance to the deletion detected in chromosome 19.

Additional Information

Disclosures

Human subjects: Consent was obtained or waived by all participants in this study. Conflicts of interest: In compliance with the ICMJE uniform disclosure form, all authors declare the following: Payment/services info: All authors have declared that no financial support was received from any organization for the submitted work. Financial relationships: All authors have declared that they have no financial relationships at present or within the previous three years with any organizations that might have an interest in the submitted work. Other relationships: All authors have declared that there are no other relationships or activities that could appear to have influenced the submitted work.

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