Case Report

Idiopathic Central Precocious Puberty Associated with 11 Mb De Novo Distal Deletion of the Chromosome 9 Short Arm

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We report a girl with a de novo distal deletion of 9p affected by idiopathic central precocious puberty and intellectual disability. Genome-wide array-CGH revealed a terminal deletion of about 11 Mb, allowing to define her karyotype as 46;XX,del(9)(p23-pter). To our knowledge, this is the second reported case of precocious puberty associated with 9p distal deletion. A third case associates precocious puberty with a more proximal 9p deletion del(9)(p12p13,3). In our case, more than 40 genes were encompassed in the deleted region, among which, DMRT1 which is gonad-specific and has a sexually dimorphic expression pattern and ERMP1 which is required in rats for the organization of somatic cells and oocytes into discrete follicular structures. Although we cannot exclude that precocious puberty in our del(9p) patient is a coincidental finding, the report of the other two patients with 9p deletions and precocious puberty indeed suggests a causative relationship.

1. Introduction

Central precocious puberty (CPP) is classically defined by the appearance of sexual secondary characteristics before the age of 8 years in girls and 9 years in boys [1]. It is caused by a premature activation of the hypothalamus-pituitary-gonadal axis. CPP may be either idiopathic or associated with occult intracranial lesion, mainly hypothalamic hamartoma or astrocytoma and noncancerous CNS disorders [2, 3]. This condition may cause early epiphyseal maturation with compromised final height as well as psychological stress [4, 5].

Chromosome 9p deletion syndrome (OMIM#158170) is a well-recognized entity, caused by a constitutional monosomy of a portion of 9p of different sizes in different patients. It was first described by Alfi et al. in 1973 [6]. Until now, approximately 180 cases have been published [7].

The most common features of monosomy 9p syndrome, as described by Swinkels et al. [8], include developmental and psychomotor delay, trigonocephaly, flat midface, short palpebral fissures, highly arched eyebrows, low-set ears, short flat nose with anteverted nostrils, thin upper lip, long philtrum, high palate, micrognathia, short neck, nipple hypertelorism, tapering fingers, flat feet, hypotonia, and developmental sex disorders in XY subjects. The critical region for a consensus phenotype has been reported to be located in a 300 Kbp region on 9p22.3 [8]. Approximately half of the cases are due to de novo deletions of 9p, the remaining ones to unbalanced translocations with a derivative 9p chromosome. Few cases have been reported with 9p distal deletion concomitant to 9q distal duplication, with some of them due to a parental chromosome 9 inversion.

To our knowledge, only one case of distal 9p deletion [del9(p22pter)] [9] and a second case of proximal 9p deletion...
Here, we report a girl with distal 9p deletion with idiopathic central precocious puberty and mental impairment.

2. Case Presentation

The proband is a girl. We have been following her from the age of 7 years and 4 months. She is the only child of nonconsanguineous healthy Italian parents. At her birth, her mother was 29 years old, and her father was 31 years old. She was born at the 40th week of gestation after uneventful pregnancy and delivery. Her birth weight was 3350g (50th centile), her length was 50cm (50th centile), and her head circumference was 35cm (75th centile). She had neonatal jaundice requiring one-day phototherapy. Her psychomotor development was delayed: she began to walk by the age of 24 months. She suffered from chronic constipation for 2 and a half years. At the age of 6 years, she presented a left inguinal hernia which was surgically reduced.

She has a moderate intellectual disability with good social adaptation, and presently, she is enrolled in a public school with the aid of a tutor.

At 7 years and 4 months of age, she was referred to our unit of Pediatric Endocrinology for evaluation of precocious puberty since pubarche, axillarche, and axillary sweating were noted at the age of 7 years, followed by unilateral thelarche and pubertal spurt. Clinical evaluation showed several facial anomalies (Figure 1), including low anterior hair line, low-set ears, synophrys, short nose, long philtrum, and wide mouth with thin vermilions of the lower and upper lip. In addition, geographic tongue, dental crowding, slightly arched palate, bilateral short 4th and 5th metacarpal and metatarsal, and signs of ungual decalcification were noted. She was
The girl was then diagnosed as a case of distal 9p deletion which came to our attention because of idiopathic central precocious puberty. About 180 cases of monosomy 9p syndrome have already been described [7]. The cases that presented del(9p) as the sole anomaly usually have a de novo mutation [15], which was the case of our patient. In the majority of cases, the breakpoint occurs at 9p21 [16]; however, many clinical features are similar regardless of the length of the deletion [15].

Even if our patient is different from previous del(9p) cases in the absence of trigonocephaly, flat nasal bridge, and the large number of digital whorls, she has many features in common with classic 9p-syndrome such as developmental delay and moderate mental retardation, long philtrum, arched palate, low-set ears, low anterior hair line, cardiac defect, and inguinal hernia. Besides, she has some physical characteristics that are not classical features of 9p-syndrome such as short 4th metacarpal and metatarsal and geographic tongue (Table 1).

However, what we consider to be important in this case is the fact that our patient was affected by central precocious puberty, from the age of 7 years, requiring suppressive therapy. To our knowledge, this is the second reported case of precocious puberty associated to 9p distal deletion. The first case was a boy described in 1979 by Funderburk et al. [9] who carried a de novo [del(9)(p22->pter)]. The unusual features of the boy were precocious puberty from the age of 8 years and 10 months and hexadactyly. Precocious puberty was not mentioned in other cases with distal 9p deletion that should have already undergone pubertal development according to their age. Several del(9p) patients had anomalous external genitalia such as hypoplastic labia majora and prominent labia minora [9], as was observed in this case.

In our patient, more than 40 genes were encompassed in the deleted region. Some of these genes are involved in an insulin metabolism pathway. Increased insulin and IGF1 levels were found elevated in girls with CPP, suggesting a causal interrelation between CPP and insulin secretion [17, 18]. Unfortunately, the insulin secretion was not studied at...
Table 1: Clinical features of 9p-syndrome, as described in OMIM web site [11], compared to the clinical features presented by our patient affected of 9p-syndrome due to 9p24.3-p23 deletion.

| Category             | Features                                      | Present case |
|----------------------|-----------------------------------------------|--------------|
| Head                 | Trigonocephaly                                | No           |
| Face                 | Midface hypoplasia                            | No           |
|                      | Long philtrum                                | Yes          |
|                      | Micrognathia                                  | No           |
| Ears                 | Low-set ears                                  | Yes          |
|                      | Malformed ears                                | No           |
|                      | Posteriorly angulated ears                    | Yes          |
| Eyes                 | Upslanting palpebral fissures                 | Yes          |
|                      | Hypertelorism                                 | Yes          |
|                      | Epicanthal folds                              | Yes          |
|                      | Small palpebral fissures                      | Yes          |
|                      | Myopia                                        | No           |
|                      | High-arched eyebrows                          | Yes          |
| Nose                 | Flat nasal bridge                             | Yes          |
|                      | Anteverted nares                              | No           |
|                      | Choanal atresia                               | No           |
| Mouth                | Thin upper lip                                | Yes          |
|                      | Microstomia                                   | No           |
|                      | High narrow palate                            | Yes          |
| Neck                 | Short neck                                    | No           |
| Heart                | Heart murmurs                                 | Yes          |
|                      | Congenital cardiac malformations              | No           |
|                      | Atrial septal defect                          | No           |
|                      | Ventricular septal defect                     | No           |
|                      | Patent ductus arteriosus                      | No           |
| Breasts              | Widely spaced nipples                         | No           |
| Abdomen              | Inguinal hernia                               | Yes          |
|                      | Omphalocele                                   | No           |
| Skeletal             | Scoliosis                                     | No           |
|                      | Tapering fingers                              | No           |
|                      | Pes planus                                    | No           |
| Skin, nails, and hair| Pale skin                                     | Yes          |
|                      | Hyperconvex nails                             | No           |
|                      | High arched eyebrows                          | No           |
| CNS                  | Mental retardation                            | Yes          |
|                      | Delayed psychomotor development               | Yes          |
|                      | Speech delay                                  | Yes          |
|                      | Hypotonia                                     | Yes          |

| CNS                  | Central precocious puberty                    |
|                      | Short metacarpal                              |
|                      | Short metatarsal                              |
|                      | Wide mouth                                    |
|                      | Dental crowding                               |
|                      | Geographic tongue                             |
|                      | Ungual decalcification                        |
|                      | Low anterior hairline                         |
|                      | Synophrys                                     |
the time of the onset of CPP in our patient. The rearrangement included also DMRT1: this gene is found in a cluster with two other members of the gene family, having in common a zinc finger-like DNA-binding motif (DM domain). This gene exhibits a gonad-specific and sexually dimorphic expression pattern. Defective testicular development and XY feminization occur when this gene is hemizygous. Recent studies on its function revealed that DMRT1 protein controls Stra8 specifically, activating it in the fetal mouse ovary [19].

A gene that could be interesting in relation to the precocious puberty present in our del(9p) patient is ERMP1 (fxna rat homolog of KIAA1815). The protein product of this gene, in a rat, is required for the organization of somatic cells and oocytes into discrete follicular structures. No ERMP1 mutations have been reported in humans [20].

By differential display in the neonatal rat ovary, Garcia-Rudaz et al. [20] identified a novel cDNA, termed fxna (felixina), expressed during folliculogenesis.

Obviously, we cannot exclude that precocious puberty in our del(9p) patient is a coincidental finding; although, the report of other two patients with 9p deletions and precocious puberty (a male with a similar deletion and a female with a cytogenetically identified more proximal 9p deletion) indeed suggests a causative relationship.

The association of moderate mental retardation and CPP has been described in patients carrying several genetic anomalies, other than the 9p distal deletion, detected with the CGH array technique and the fluorescence in situ hybridization analysis (FISH) [21–24]. The molecular basis of this association remains unknown, but it is likely that multiple gene aberrations are responsible for this association.

Conflict of Interests

All authors declare that they do not have a direct financial relation with the companies mentioned in the paper that might lead to a conflict of interests for any of the authors.

References

[1] A. Rogol and R. M. Blizzard, “Variations and disorders of pubertal development,” in Wilkins’ the Diagnosis and Treatment
of Endocrine Disorders in Childhood and Adolescence, M. S. Kappy, R. M. Blizzard, and C. J. Migeon, Eds., pp. 857–917, Charles Thomas, Springfield, Ill, USA, 1994.

[2] M. Cisternino, T. Arrigo, A. M. Pasquino et al., “Etiology and age incidence of precocious puberty in girls: a multicentric study,” Journal of Pediatric Endocrinology and Metabolism, vol. 13, supplement 1, pp. 695–701, 2000.

[3] M. Chalumeau, C. G. Hadjiathanasiou, S. M. Ng et al., “Selecting girls with precocious puberty for brain imaging: validation of European evidence-based diagnosis rule,” Journal of Pediatrics, vol. 143, no. 4, pp. 445–450, 2003.

[4] R. Brauner, L. Adan, F. Malandry, and D. Zantleifer, “Adult height in girls with idiopathic true precocious puberty,” Journal of Clinical Endocrinology and Metabolism, vol. 79, no. 2, pp. 415–420, 1994.

[5] G. B. Kletter and R. P. Kelch, “Clinical review 60: Effects of gonadotropin-releasing hormone analog therapy on adult stature in precocious puberty,” Journal of Clinical Endocrinology and Metabolism, vol. 79, no. 2, pp. 331–334, 1994.

[6] O. Alfi, G. N. Donnell, and B. F. Crandall, “Deletion of the short arm of chromosome # 9 (46,9p-). A new deletion syndrome,” Annales de Genetique, vol. 16, no. 1, pp. 17–22, 1973.

[7] R. Onesimo, D. Orteschi, M. Scalzone et al., “Chromosome 9p deletion syndrome and sex reversal: novel findings and redefinition of the critically deleted regions,” American Journal of Medical Genetics A, vol. 158, no. 9, pp. 2266–2271, 2012.

[8] M. E. M. Swinkels, A. Simons, D. F. Smeets et al., “Clinical and cytogenetic characterization of 13 Dutch patients with deletion 9p syndrome: delineation of the critical region for a consensus phenotype,” American Journal of Medical Genetics A, vol. 146, no. 11, pp. 1430–1438, 2008.

[9] S. J. Funderburk, R. S. Sparkes, and I. Klisak, “The 9p- syndrome,” Journal of Medical Genetics, vol. 16, no. 1, pp. 75–79, 1979.

[10] G. Eshel, E. Lahat, O. Reish, and J. Barr, “Neurodevelopmental and behavioral abnormalities associated with deletion of chromosome 9p,” Journal of Child Neurology, vol. 17, no. 1, pp. 50–51, 2002.

[11] OMIM, “Online Mendelian Inheritance in Man,” http://www.omim.org/clinicalSynopsis/158170.

[12] W. A. Marshall and J. M. Tanner, “Variations in pattern of pubertal changes in girls,” Archives of Disease in Childhood, vol. 44, no. 235, pp. 291–303, 1969.

[13] W. W. Greulich and S. I. Pyle, Radiographic Atlas of Skeletal Development of the Hand and Wrist, Stanford University Press, Stanford, Calif, USA, 2nd edition, 1959.

[14] N. Resta, R. Giorda, R. Bagnulo et al., “Breakpoint determination of 15 large deletions in Peutz-Jeghers subjects,” Human Genetics, vol. 128, no. 4, pp. 373–382, 2010.

[15] J. L. Huret, C. Leonard, B. Forestier, M. O. Rethore, and J. Lejeune, “Eleven new cases of del(9p) and features from 80 cases,” Journal of Medical Genetics, vol. 25, no. 11, pp. 741–749, 1988.

[16] D. W. Bianchi, “Chromosome 9, partial monosomy 9p,” in Birth Defects Encyclopedia, M. L. Buyse, Ed., pp. 353–354, Blackwell Scientific, Malden, Mass, USA, 1990.

[17] K. Sørensen, L. Aksglaede, J. H. Petersen, A. M. Andersson, and A. Juul, “Serum IGF1 and insulin levels in girls with normal and precocious puberty,” European Journal of Endocrinology, vol. 166, no. 5, pp. 903–910, 2012.