Epidemiology of diagnoses of Sex Development Disorders based on the Registry of Rare Diseases, in a large area of North-Eastern Italy

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Sex chromosome DSD	46,XY DSD	46,XX DSD
(A) 45,X (Turner syndrome and variants)	(A) Disorders of gonadal (testicular) development 1. Complete gonadal dysgenesis (Swyer syndrome)	(A) Disorders of gonadal (ovarian) development 1. Ovotesticular DSD 2. Testicular DSD (eg, SRY+, dup SOX9)
(B) 47,XXY (Klinefelter syndrome and variants)	2. Partial gonadal dysgenesis 3. Gonadal regression 4. Ovotesticular DSD	3. Gonadal dysgenesis
(C) 45,X/46,XY (mixed gonadal dysgenesis, ovotesticular DSD)	(B) Disorders in androgen synthesis or action 1. Androgen biosynthesis defect (eg, 17-hydroxysteroid dehydrogenase deficiency, 5α reductase deficiency, StAR mutations	(B) Androgen excess 1. Fetal (eg, 21-hydroxylase deficiency, 11-hydroxylase deficiency)
(D) 46,XX/46,XY (chimeric, ovotesticular DSD)	2. Defect in androgen action (eg, CAIS, PAIS) 3. LH receptor defects (eg, Leydig cell hypoplasia, aplasia) 4. Disorders of AMH and AMH receptor (persistent mullerian duct syndrome)	2. Fetoplacental (aromatase deficiency, POR) 3. Maternal (luteoma, exogenous, etc)
	(C) Other (eg, severe hypospadias, cloacal extrophy)	(C) Other (eg, cloacal extrophy, vaginal atresia, MURCS, other syndromes)

While consideration of karyotype is useful for classification, unnecessary reference to karyotype should be avoided; ideally, a system based on descriptive terms (for example, androgen insensitivity syndrome) should be used wherever possible.
AMH, anti-mullerian hormone; CAIS, complete androgen insensitivity syndrome; DSD, disorders of sex development; MURCS, mullerian, renal, cervicothoracic somite abnormalities; PAIS, partial androgen insensitivity syndrome; POR, cytochrome P450 oxidoreductase.

Fig. 1 2005 Chicago Consensus Conference classification of developmental sex disorders (DSDs)

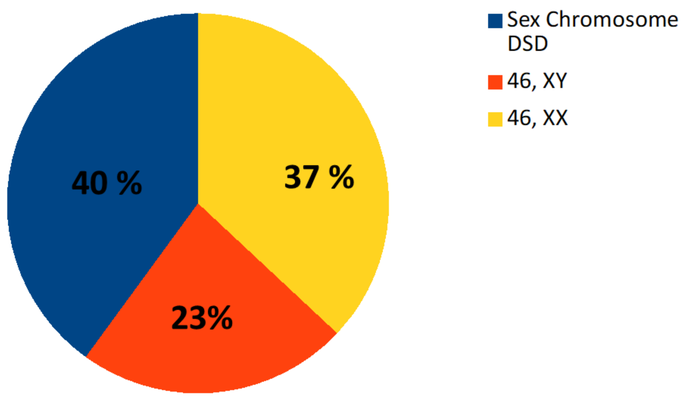

Fig. 2 147 patients with known Cariotype

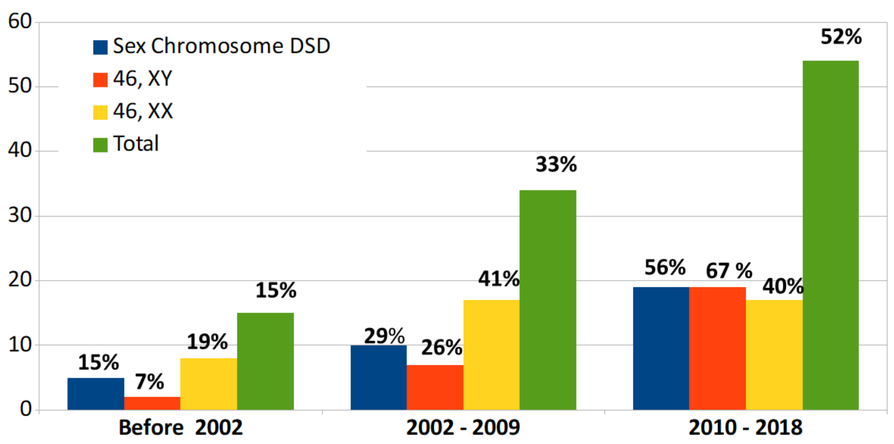

Fig.3 The distribution of the diagnoses among the three time periods. In 2010-2018 period an higher increase of XY DSD diagnoses , albeit not significant, is evident.

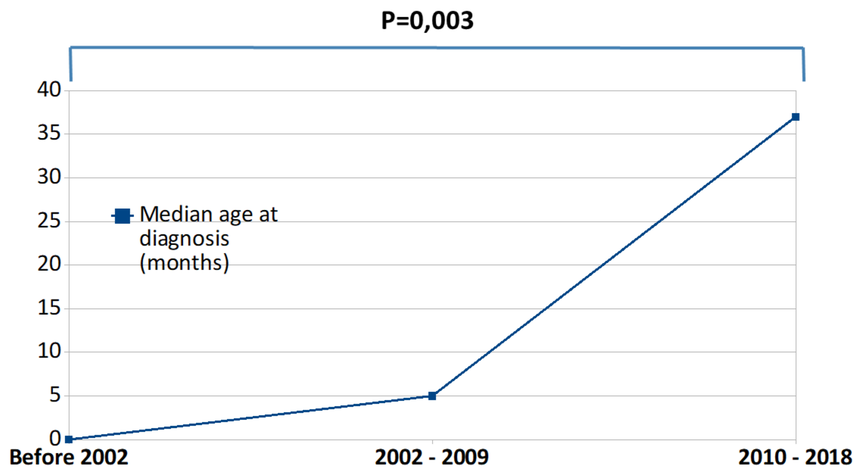

Fig.4 Median age at dagnosis of the patients diagnosed before 2002 and patients diagnosed after 2002. The median age at diagnosis was significantly higher in patients diagnosed after 2002 in comparison to patients diagnosed before 2002 (**p=0.003**)

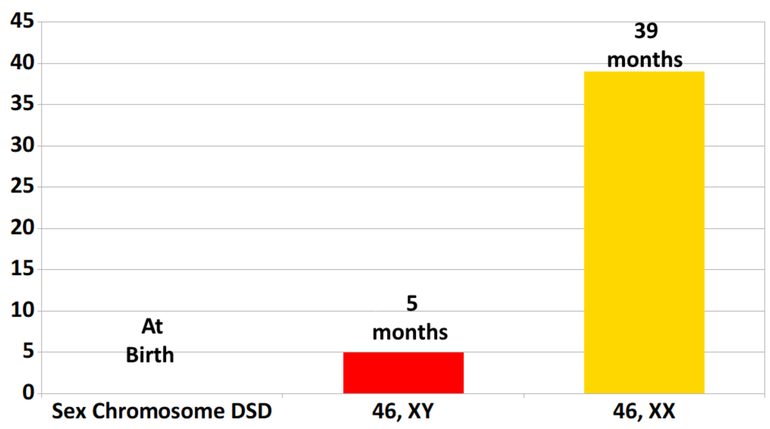

Fig. 5 The median age at diagnosis in the different types of DSD

BACKGROUND

Disorders of Sex Development (DSD) are a rare disease often caused by complex genetic mechanisms, with a wide spectrum of clinical manifestations that lead to a continuous evolution of diagnoses classification. From 2002, In the Veneto Region, all DSD diagnoses have been collected thanks to the creation of a Registry for Rare diseases.

Matherial and Methods

We retrospectively analyzed the DSD diagnosed by the Pediatric Endocrinological Unit of University of Padua, which most patients of a large area of the North-Eastern Italy refer to. To analyze the time trend of diagnoses, we considered 3 periods: before 2002, from 2002 to 2009 and from 2010 to 2018. We reviewed outpatients' available data to obtain the type of DSD diagnosis, the date and the age at diagnosis. We classified the patients following 2005 Chicago Consensus Conference.

RESULTS

In the whole reviewing Registry data we counted 374 new DSD certifications. Outpatients' data from only 147/374 were obtained for the classification of DSD etiology. Among them, the distribution was as follows: 58 Sex Chromosome DSD, 34 46,XY DSD and 55 46,XX DSD. In 104 patients, age at diagnosis was available. The median age at diagnosis resulted significantly higher in patients diagnosed between 2010 and 2018 in comparison with the other two periods (p=0.003) (Fig. 4), with an higher, albeit not significant, frequency of 46, XY DSD diagnosis (Fig.3) . Indeed, among the 28 patients with 46, XY DSD in which the date of diagnosis was available, 7% were diagnosed before 2002, 26% between 2002 and 2009 and 67% between 2010 and 2018. The median age at diagnosis of XY DSD was significantly higher in patients diagnosed after 2002 (85%) in comparison to patients diagnosed before 2002 (16%) (p=0.02).

CONCLUSIONS

Our analysis showed a trend towards an increase in the total number of DSD diagnoses over the years. With the limit represented by a lack of a Registry, before 2002 nearly all the diagnosis were made at birth, by the evidence of ambiguous genitalia, coming mostly from classical CAH (50%) and Sex Chromosome DSD (35%). In the other two periods taken into consideration, we observed a trend towards an higher age at diagnosis in the 2010-2018 period, with an increased in 46,XY DSD diagnosis. We suggest that this different distribution may be due to a progressively wider use of prenatal chromosomal sex determination and a better management of the early adolescence clinical signs by the Pediatric Endocrinologists. The ongoing study of all patient's data could better clarify these hypotheses.