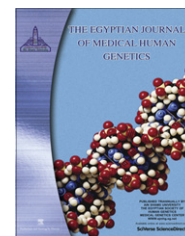




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ORIGINAL ARTICLE

Profile of disorders of sexual differentiation in the Northeast region of Cairo, Egypt

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Abstract This retrospective study has been conducted to determine the frequency, types, clinical presentation and associated genomic errors in patients with sex differentiation errors and their relatives. The present study comprised of 908 index patients with sex differentiation errors who were registered at the Medical Genetics Center (ASUMGC), Ain Shams University. Out of 28,736 patients attending the center and 660,280 patients attending the Pediatrics clinic during the interval of 1966–2009. Our results showed that, the frequency among all patients attending the Pediatrics Hospital was 0.14%. Disorders of sex chromosome (Klinefelter syndrome and Turner syndrome) were the commonest, followed by mullerian dysgenesis. The commonest age of presentation was adolescence (> 15–18 years) (36.56%), followed by patients aged 18 years or more (24.88%). In our study, 32.26% presented with primary female infertility, 27.86% adolescent girls presented with primary amenorrhea, 16.29% presented with male infertility, 10.35% presented with ambiguous genitalia at birth or soon afterward, 6.60% were females who presented with delayed 2ry sexual characters and short stature, 3.96% of our cases were boys who presented with microtestes and delayed 2ry sexual development and 2.75% presented with hirsutism. Central nervous system abnormalities were reported in 5.94% of our patients, ocular abnormalities in 4.29%, and cardiovascular system abnormalities in 2.86%. Three hundred and ninety-two multiple mutant genomic errors were defined

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among relatives of index cases of DSD families, where definable errors represented 35.24% and non-definable errors represented 7.92%. Cytogenetic findings of various DSD showed that, 33.46% of cases with Turner syndrome phenotype had (45,X), and 64.89% were mosaic (45,X/46,XX). While, among the 130 studied cases with Klinefelter syndrome phenotype, 83.84% had 47,XXY. Out of 75 patients with ovotesticular DSD, 85.33% possessed a 46,XX chromosome complement. To conclude, sex determination and differentiation are sequential processes that involve genetic, gonadal, phenotypic and psychological sex. Disorders of sexual differentiation, or syndromes of intersexuality, result when errors occur at any of these steps. Establishing a precise diagnosis in DSD is just as important as in other chronic medical conditions with lifelong consequences.

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1. Introduction

In the developing fetus, the genetic or chromosomal sex is determined at the time of fertilization. Thus a 46XX karyotype would normally give rise to a phenotypic female, and 46XY to a phenotypic male fetus. Differentiation of the gonads into either testes or ovaries determines the gonadal or hormonal sex and this occurs under the direction of an increasing number of identified genes and transcription factors which may be specific to either testicular or ovarian differentiation [1]. Gonadal hormone secretion determines the differentiation of the common genital tracts into either male (Wolffian) or female (Mullerian) internal tracts, and also the development of the external genitalia which results in the apparent or phenotypic sex. Subsequent development of the individual will result in the evolution of the psychological or behavioral sex, which is an important consideration in disorders of sexual development (DSD). The process of sex determination and phenotypic development begins as early as the 5th week of gestation and both internal and external genital differentiation are more or less complete by the end of the first trimester. Disorders of sex development arise as a result of a mismatch between the genetic, gonadal and phenotypic sex and are the result of early disruption in the programming of sex determination [2].

Disorders of sex development (DSD), previously referred to as intersex disorders, comprise a variety of congenital diseases with anomalies of the sex chromosomes, the gonads, the reproductive ducts and the genitalia. The term 'disorders of sex development' (DSD) is now proposed to define congenital conditions in which a disharmony between chromosomal, gonadal and anatomical sex exists [3]. A new classification system for the causes of DSD has been proposed based on the karyotype. This terminology, however, also includes the term "sex" in the description of the specific developmental abnormality with the inevitable associated connotation [4]. DSD is loosely classified into four groups on the basis of histological features of the gonadal tissue: XX-DSD with two ovaries (female pseudohermaphroditism), XY-DSD with two testicles (male pseudohermaphroditism), ovotesticular DSD with both ovarian and testicular tissue (true hermaphroditism) and gonadal dysgenesis either mixed (a testis and a streak gonad) or pure (bilateral streak gonads) [2].

Sex differentiation is comprised of many steps. Problems associated with sex differentiation, or syndromes of intersexuality, occur when errors in development take place at any of these steps. Problems can arise at fertilization when chromosomal sex is established. For example, girls with Turner syndrome have a 45,XO karyotype and boys with Klinefelter syndrome have a 47,XXY karyotype. It is also known that

some women have a 46,XY or 47,XXX karyotype and some men have a 46,XX or 47,XYY karyotype [5]. Disorders of sex differentiation can occur when a bipotential gonad is incapable of developing into a testis or an ovary. The inability to develop testes may occur if a gene such as SRY is absent or deficient. When this is the case, a 46,XY fetus will not receive the SRY signal to develop testes despite the presence of a Y chromosome. Additionally, 46,XY fetuses may begin to develop testes, but this development can be thwarted, and subsequently Mullerian-inhibiting substance (MIS) and androgen production may be absent or diminished [6].

Intersexuality can also result as a consequence of problems related to Mullerian or Wolffian duct development. For example, MIS secretion accompanied by the absence of androgens or the inability to respond to androgens can result in a fetus lacking both male and female internal duct structures. In contrast, the absence of MIS accompanied by androgen secretion can result in a fetus possessing both male and female internal duct structures to varying degrees [7].

Children born with deviations from normal development of the sex organs can be expected to grow up successfully and to lead enriched lives [8]. However, their problems must be considered carefully. In cases of abnormal sex differentiation, efforts should be made to determine the reason for the abnormality as treatment may vary according to the cause of the disorder [9].

Herein, we conduct a retrospective study to determine the frequency, types, clinical presentation and associated genomic errors in patients with sex differentiation errors and their relatives who were registered at Medical Genetics Center, in the Pediatrics Department, Ain-Shams University, Cairo, Egypt, in the period, 1966–2009. This hospital has a high standard of healthcare, so patients from nearly all governorates of Egypt attend this hospital to receive good health care.

2. Patients and methods

The present study comprised of 908 index patients with sex differentiation errors who were registered at the Medical Genetics Center (ASUMGC), Ain Shams University, out of 28,736 patients attending the center and 660,280 patients attending the Pediatrics clinic during the interval of 1966–2009.

All the patients were referred to the Medical Genetics Center for diagnosis, therapy and genetic counseling. Index cases were subjected to the following studies: Detailed history taking including personal history, age, sex, birth origin (paternal and maternal), treatment history (drugs or operations), perinatal history, age at presentation, main complaints and sex of rearing.

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