What are the indications for prenatal diagnosis in the androgen insensitivity syndrome? Facing clinical heterogeneity of phenotypes for the same genotype

Y Morel, F Mebarki, MG Forest

INSEER NR U329, Laboratoire de Biochimie endocrinienne et moléculaire, Hôpital Debrousse, 29, rue Soeur Bouvier, 69 322 LYON Cedex 05, France

Patients with androgen insensitivity (AIS) syndrome are 46,XY individuals presenting at birth with complete or incomplete masculinization of their external genitalia. It is now well established that AIS is an X-linked disorder due to structural or functional abnormalities in the androgen receptor (AR). However, a large spectrum of clinical phenotypes is observed, ranging from complete female phenotype to "mild" hypopadias.

This clinical diversity is associated with a biological heterogeneity, since a variety of quantitative and qualitative abnormalities in AR binding parameters have been found in cultured genital skin fibroblasts from AIS patients. In particular, there is a wide spectrum in AR binding capacity, from undetectable to supranormal numbers of binding sites with no apparent inverse correlation with the degree of virilization. These studies have been invaluable for the understanding of the physiopathology of AIS, but remain difficult assays to perform and time-consuming in cell culture, owing to the relatively large number of genital skin fibroblasts required.

The cloning of the cDNA for the AR has permitted the elucidation of an AR molecular defect in a number of families (1-3). However, there are cases in which no mutation of the AR gene was found. Today, it is difficult to evaluate the frequency of such situations because the entire AR gene was not sequenced in all AIS patients reported. In particular, the first exon. Indeed, in our laboratory, in which the strategy to sequence the entire gene was adopted, we found mutations in exon 1 in 5 out of our 40 families. In addition, in these well-documented AIS families, about 25% of the AR genes did not carry any mutation in the coding and bordering intronic regions (unpublished data).

Before the identification of molecular defects in the AR, prenatal diagnosis of AIS could not be performed accurately. Determination of the fetal karyotype associated with repeated ultrasonic examination of the fetal genitalia in the case of a male fetus was the only way of evaluating the risk of having an affected fetus in a family insistent about prenatal diagnosis. Now, prenatal diagnosis is possible when the molecular defect has been identified in the index case. In other cases, if no mutation is found, but the diagnosis of AIS well established, prenatal diagnosis can still be made by polymorphism studies. Indeed, the polymorphic number of trinucleotide CAG repeats located in the exon 1 can be used for prenatal diagnosis, providing prior study of the nuclear family. In our hands, this polymorphism has been informative in almost all cases (4), and can be used for prenatal diagnosis and carrier detection when the family story and segregation confirm a recessive X-linked inheritance. However, de novo mutations in AIS also occur, as is frequent in a recessive X-linked disorder (5).

In this issue, Lumbruso et al. (6) report a prenatal diagnosis in a partial form of AIS associated with a point mutation R840H of the AR gene. This paper raises the question: What are the indications for prenatal diagnosis in families with a complete or incomplete form of AIS? Moreover, the detection of heterozygotes in females raises another (ethical) question: How can we preserve patients' confidentiality and inform their heterozygote female relatives about their risk for this genetic disorder?

Can the performance of prenatal diagnosis and carrier detection be called to question? Currently, prenatal diagnosis is routinely performed for disorders that result in mental retardation and life-threatening diseases. In contrast, AIS results in physical defect and psychological stress. In the complete form, the subjects may believe that they have the appearance of a normal infertile woman. However, at any time they are at risk of discovering that they are genetic males (46,XY), in particular at gonadectomy or check-up for infertility. Thus, in families at risk for the complete form of AIS, it seems reasonable to let the parents decide whether they want a prenatal diagnosis after providing complete and unbiased information about the disease. At the same time, what should our attitude be regarding the detection of female carriers in the maternal family, if we want to preserve professional secrecy, patients' confidentiality, and disclose genetic diagnosis in relatives not asking directly for genetic counselling? There is presently no consensus among physicians. Thus, management of the situation largely depends upon the cultural background of both the patient and his family, as revealed in a recent study (answers of medical geneticists to a questionnaire about this situation) (7). Paradoxically, in less severe forms of AIS, prenatal diagnosis and carrier detection seem to be more appropriate. The problems, as illustrated by the report of Lumbruso et al. in this issue, are numerous: milder degree in genital ambiguity, debate about the choice of rearing (boy or girl), reiterate surgical procedures, poor virilization under androgen therapy or at puberty, are all arguments in favour of a prenatal diagnosis in order to make the correct decisions right after birth. Moreover, in incomplete AIS, disclosure of the genetic disorder to the patients and their relatives would appear easier than in complete AIS.

A second point concerning the relationship between phenotype and genotype warrants discussion. It has been said that predicting the severity of genital ambiguity in partial AIS would be impossible solely on the basis of the evidence of a mutation in the AR gene (8). Recent reports in the literature show a heterogeneity in the phenotypic expression of a given mutation within the same family (8) or among unrelated families (9). In fact, if only the clinical phenotypes were
carefully described at birth, their difference would lessen. Almost all reported patients with incomplete AIS have a small degree of virilization described as either a microphallus, perineal hypospadias and a vaginal pouch or a clitoromegaly with a posterior labial fusion. It appears to us that phenotypic variations are often amplified by the choice of sex of rearing. Indeed, when the patient is raised as a girl, her phenotype is readily termed “a variant of complete AIS” or “incomplete testicular feminization”, a term disliked by some paediatricians for obvious psychological reasons. In contrast, when the patient is raised as a boy, his condition is usually referred to as Reifenstein syndrome. In almost all cases, there is a poor virilizing effect of an androgen treatment with a penis length barely increasing above 3.5 cm. As suggested by some authors, it would be more appropriate to call also these situations “partial AIS”. As mentioned above, the results of the AR binding studies correlate very much less than the clinical situations with the genotypes, because these studies are fraught with a number of influencing factors: culture conditions, imprecision on the site of the skin biopsy, variation in the expression of results (fentomol per µg of DNA or per mg of protein, or sites per cell). In order to illustrate this opinion, we can examine the phenotypes of the patients found to carry the point mutation R840H in their AR gene, as did the patient reported in this issue (6). This mutation R840H appears to be the most commonly found in partial AIS. It was associated with similar phenotypes—microphallus, perineal hypospadias and cryptorchidism—in two unrelated families (9), one family (10), four related patients (6), and seven other patients in four unrelated families (personal unpublished data). However, the choice of sex of rearing was not necessarily the same in a given kindred. Thus, among the 14 patients, 8 were raised as boys and classified Reifenstein syndrome; since they did virilize poorly after androgen treatment they had considerable psychological distress and poor functional results in their adult life. The other six patients were raised as girls, being classified as “severe partial AIS”. In this group of patients, findings varied in the AR binding studies. Yet, it is not possible to conclude whether this was related to technical variations or to factors other than the mutation in the AR itself.

This is why we believe that a careful re-evaluation of the clinical situation at birth should be carried out in the future in order to determine whether there is such a phenotypic variability for each mutation. For instance, the mutation V866M in the ligand binding domain of AR has been found in association with a qualitative defect in AR binding. Hence, the patients were described as complete AIS in three related patients (11) (9) and in one isolated patient (12), but described in another patient as having incomplete testicular feminization (9). We believe that the clinical data were not sufficiently described in these reports to help us understand their variability. To date, the point mutation Y763C is the only one which appears to be associated with a variable phenotype in partial AIS ranging from penile hypospadias with normal scrotum to a perineal hypospadias (8). Further collaborative studies are needed to re-evaluate the classical expression according to age and before surgical correction in order to help our understanding of the phenotypic variability of each mutation of the AR gene.

References


Y Morel, F Mebariki, MG Forest. INSERM U329, Laboratoire de Biochimie endocrinienne et moléculaire, Hôpital Debrousse, 29, rue Soeur Bouvier, 69322 LYON Cedex 05, France