Are human male patients with *DAX1/NR0B1* mutations infertile?

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**Abstract**

*DAX-1* stands for Dosage sensitive sex-reversal, Adrenal hypoplasia congenital (AHC), on the X chromosome. *DAX-1* mutations usually cause primary adrenal insufficiency or congenital adrenal hypoplasia in early childhood and hypogonadotropic hypogonadism (MIM # 300200). *DAX-1* protein is necessary to maintain normal spermatogenesis. In humans, male fertility has been studied in few patients carrying *DAX-1* mutations. Cases of azoospermia have been reported, as well as unsuccessful gonadotropin treatments. The clinician should be informed that TESE–ICSI technique carries a potential hope to father non-affected children, as shown in this review.

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**Keywords:** *DAX-1* mutations; Azoospermia; TESE–ICSI

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**Résumé**

*DAX-1* signifie inversion sexuelle dosage sensible, hypoplasie congénitale des surrénales sur le chromosome X. Les mutations de *DAX-1* entraînent une insuffisance surrénale primitive ou une hypoplasie congénitale des surrénales dans la petite enfance ainsi qu’un hypogonadisme hypogonadotrope (MIM#300200). La protéine DAX-1 est nécessaire au maintien d’une spermatogénèse normale. Chez l’homme la fertilité masculine a été étudiée chez quelques patients porteurs de la mutation. Des cas d’azoospermies ont été rapportés ainsi que des échecs de traitement par les gonadotrophines. Le clinicien doit être informé que la technique TESE–ICSI offre un espoir de paternité permettant la naissance d’enfants non atteints comme il est montré dans cette revue.

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1. Introduction

DAX-1 stands for Dosage sensitive sex-reversal, Adrenal hypoplasia congenital (AHC), on the X chromosome. DAX-1 gene is also named NR0B1. It is located on Xp21 and encodes for an orphan nuclear receptor. DAX-1 protein is expressed in tissues involved in steroid hormone production and reproductive function, such as adrenals, hypothalamus, pituitary and testis [1]. DAX-1 mutations usually cause primary adrenal insufficiency or congenital adrenal hypoplasia in early childhood and hypogonadotropic hypogonadism (MIM # 300200). In mice, Nrob1 null homozygous male mice have adrenal insufficiency as well as testicular disorganization, dilated seminiferous tubules and failed spermatogenesis [2]. Histological examination reveals a progressive degeneration of seminiferous tubule epithelium, hyperplasia of Leydig cells and sloughing of germ cells.

In humans, male fertility has been studied in few patients carrying DAX-1 mutations. Cases of azoospermia have been reported, as well as unsuccessful gonadotropin treatments [3,4]. Oligozoospermia has been observed in a rare case of late-onset AHC associated with a partial loss-of-function mutation [5].

Our group reported in 2011, the first birth after successful assisted reproduction technique (ART) using testis sperm extraction and intracytoplasmic injection (TESE-ICSI) in a patient with a DAX-1 mutation [6]. This mutation induced a stop codon (p.Gln404X) and therefore null activity in DAX protein function. Our patient had adrenal insufficiency at the age of 3 weeks. He was referred to us for hypogonadotropic hypogonadism at the age of 18, and was then treated by testosterone enanthate. As he desired paternity, 6 years later, his testosterone was replaced by gonadotropins (Menopur® 150 UI of FSH and 150 UI of LH 3 times per week with hCG 1500 Units twice a week). Twenty months after beginning gonadotropins, azoospermia was still present, although the patient’s compliance was good as his testosterone levels were normal and testis sizes reached 11 and 12 milliliters. Therefore, bilateral testicular biopsies were performed. Very few spermatozoa were extracted from the right posterior fragment. Three straws were cryopreserved, each containing 100 motile spermatozoa. Testis histological examination revealed severe hypospermatogenesis. The diameter of the seminiferous tubules was either normal or reduced. Tubules were limited by a thickened basement membrane and contained mostly Sertoli cells and a few germ cells arrested at the spermatocyte stage. No motile spermatozoa were recovered after thawing. However, pentoxifylline (1 mg/mL) was used to increase the motility of the few spontaneously immobile testicular spermatozoa. His wife was stimulated and 11 oocytes were recovered. They were fertilized and 4 embryos were obtained. Two Day-2 embryos were transferred and the remaining two were cryopreserved. No pregnancy followed. The following cycle, only one embryo remained viable after thawing and was used in a single-embryo transfer during a stimulated cycle. After this procedure, the patient’s wife became pregnant and gave birth — 9 months later, by Caesarean section — to a healthy boy.

In 2013, reproduction was studied in another patient with DAX-1 mutation [7]. He reported adrenal insufficiency at age 19. His puberty had been normal. He was referred at the age of 32 for infertility. Sperm samples showed severe oligozoospermia, although his testosterone was normal. The patient had previously fathered two children. A 20-year follow-up in this patient, showed persistent normal testosterone levels. This clinical case illustrates the fact that sperm alteration may occur even before alterations of gonadotropic axis.

Both cases illustrate the fact that DAX-1 protein is necessary to maintain normal spermatogenesis [6,7]. In patients with DAX mutations, hypogonadotrophic hypogonadism may be involved in sperm defects. However, as in male mice, oligozoospermia or azoospermia may be due to direct testis effects of DAX-1 protein, even in the absence of hormonal defects. A progressive defect in testicular function over the years is therefore suggested.

Genetic counselling in couples where the man is affected by an X-linked condition should mention that every male offspring will be unaffected and that every female offspring will be a heterozygous carrier of the mutation. Consequently, the risk of having an affected male is moved to the second generation.

In conclusion, physicians taking care of rare patients with DAX-1 mutations should inform them of a potential hope to father non-affected children after TESE–ICSI technique.

Disclosure of interest

The authors declare that they have no conflicts of interest concerning this article.

References