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Doctors help Israeli combat soldier with testosterone disorder start a family

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Dr. Karen Tordjman, a senior lecturer at Tel Aviv University's Sackler Faculty of Medicine didn't have an immediate diagnosis for the under-masculinized young man who walked into her office. A 25-year-old university student who had served in an elite commando unit in the Israeli navy, he was handsome in a fashion-model kind of way: rail thin, with a smooth face and delicate, feminine features. Closer inspection revealed no body hair other than sparse patches in his armpits and groin. His genitals were small and heavily scarred.

The young man had reluctantly agreed to visit the medical clinic at the insistence of his girlfriend, who wanted an explanation for his condition. He couldn't have known he was initiating a years-long medical journey that would lead Dr. Tordjman and a team of physicians to discover a new genetic mutation, bolster the case for a counterintuitive medical treatment, and push the limits of male fertility. "We offered treatment not for his future reproductive capabilities but for his appearance," says Dr. Tordjman. "We didn't guarantee him anything, but we said we'd try."

Her research, published in the journal *Andrologia* in June, will allow future genetic screening for the mutation.

Uncharted waters

Dr. Tordjman and her colleague Dr. Amnon Botchan, also a Sackler lecturer, began by obtaining the patient's medical records. The records

showed that two of his uncles had been diagnosed with androgen receptor insensitivity—a rare condition that results in the body under-responding to the androgen hormones that drive male sexual development. Usually caused by a mutation in the androgen receptor gene, the condition impairs the development of male genitalia in the womb and of secondary male sexual characteristics during puberty.

In cases of complete androgen insensitivity, no male sexual development takes place. The result is men who look like women on the outside but have testes rather than female genitalia inside their bodies. Such cases are often diagnosed only during puberty, when the individuals develop breasts and other female sexual characteristics but do not start menstruating. In cases of partial androgen insensitivity, which range from mild to severe, the individuals are born with ambiguous genitalia. If doctors determine that surgically creating male genitalia is infeasible, they tend to assign the female gender.

Dr. Tordjman's patient, who reported a consistent heterosexual orientation, had not had sex reassignment surgery or been given androgen treatments to try to enhance his sexual development at birth. But he had been diagnosed with the same condition as his uncles and undergone operations to correct genital malformations at age three and to remove breast tissue during puberty. Genetic testing, performed with the help of French researchers Dr. Serge Lumbroso and Prof. Charles Sultan, confirmed that he had a mutation of his androgen receptor gene—one that had not previously been reported.

A family affair

Hoping to masculinize the patient per his wishes, Dr. Tordjman started him on high-dose testosterone therapy. Theoretically, this type of therapy makes little sense for patients with androgen receptor insensitivity, because their bodies create plenty of testosterone—it's just

that they are unable to put it to use. But Tordjman had read about a case in which the therapy had worked and decided to give it a try.

After several months of weekly injections, the patient appeared dramatically more masculine. He gained 18 pounds—mostly of muscle—and grew hair on his face and body, leading him to shave for the first time in his life. His voice, which had always been high-pitched, did not change. (The voice, says Tordjman, is stubbornly resistant to hormone therapy.) The treatments continued for four years, during which the patient and his girlfriend got married and eventually began talking about having a baby.

Infertility in men with androgen receptor insensitivity is nearly universal, even in mild cases; and no one with a case as severe as the patient's was known to have successfully fathered a child. But having seen a significant improvement in his sperm count, Tordjman took another long shot and referred the couple for fertility treatment. When Tordjman next saw the patient several years later, he was pushing a baby girl into her office in a stroller.

Children have a 50-percent chance of inheriting a mutation for androgen receptor insensitivity from a parent. While fathers have typically been left out of the equation given the male sterility associated with the condition, this case will force a rethinking of that dogma and encourage the use of testosterone and fertility treatments in men with the condition, says Tordjman.

"My suggestion is in any case like this with partial androgen insensitivity, even if you don't know where in the androgen receptor gene the mutation lies, testosterone treatment is worth trying," she says.

Provided by Tel Aviv University