Reviewer’s report

Title: Chinese Patient with a 46,XY/47,XYY Karyotype and Female Phenotype: A Case Report

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Reviewer: Flavio Cadegiani

Reviewer's report:

This is a must-present case that deserves particular attention, since:

1. Which particularity may explain the fact that this patient with mosaic XY/XYY karyotype have a female phenotype, in opposition to virtually all cases reported in the literature?

2. Despite slight differences, she seems to have more phenotypical similarities to Turner syndrome (45,XO) than to XYY syndrome.

3. How did she have normal breast development for women, in the absence of estradiol?

Title: Unless relevant for the case, the nationality of the patient shouldn't be in the title.

Abstract: Infertility is only present in the minority of the patients with XYY syndrome.

Background:

Page 3 lines 39-42 - reference 2 is about a retrospective study performed in patients with XYY syndrome and infertility, but it does not mean that infertility is necessarily present. Indeed, the MAJORITY of the patients with XYY are FERTILE, even when non-mosaic, as mentioned in reference 2.

Besides, XYY in fertile men is likely underdiagnosed, given the lack of typical syndromic features in most cases, which means that the proportion of XYY males with infertility may be even lower. Also, other more typical features of the XYY syndrome should be either presented together with the possibility of fertility abnormalities (not all non-fully fertile XYY males are infertile), or both should be excluded.

In its current format, the sentence gives the idea that infertility is the only major characteristic of XYY abnormality.

Page 3 lines 52-59 - small penis, cryptorchidism and hypospadias was described in 1968, when chromosomal abnormalities were analyzed only when patients had more syndromic features. These characteristics have cited in the introduction of the reference 5, but were not further confirmed. These characteristics are absent in the almost totality of XYY patients, therefore are not typically present. Instead, XYY patients have macrocephalia, hypotonia with normal genital development and actually enlarged testicles (please read the full reference 5, until the discussion section), asthma and ADHD. Above all, symptoms VARY GREATLY. This should be highlighted and sentences must be corrected.

The paragraph in Page 7 lines 30-44 (in discussion section) should be used to describe the XYY in the
introduction. Authors should either provide a briefer (without detailed description of the characteristics) or a more precise description since the introduction. In the current format, XYY syndrome is imprecisely described in the introduction, giving an idea of an entirely different condition than the actual one. (In discussion it is well described, but may be too late for readers, and confound them).

Case presentation -

This is a very interesting case to be reported, but its presentation in the current manuscript deserves rewriting, as it is "too narrative". It should be more objective to the points.

Examples:

- "loud crying at birth" is unnecessarily told since "Apgar" was "normal".

- "She was breast-fed after birth" - unless there was any contra-indication for breast feeding, this is presumable. Conversely, the duration of exclusive breast feeding is more important, and a possible difficulty to breast feed could be an early sign of hypotonia.
- Particularly choosy for food is irrelevant without a contextualization.

Was this girl only investigated, and not treated? Did she undergo any hormonal treatment for female pubertal development? Please describe the clinical and therapeutic decisions, outcomes and follow-up (at least in the short term)? Ethically, she cannot be "used for investigation" without a description of the counterpart from the health providers.

Page 4 lines 50-52 -
Did the patient have a slow growth rate or a decrease in the speed of the growth rate?
Did the patient have a decline in intelligence, understanding and learning abilities, or she had a decline on the speed of development of the cognitive functions? Or she Involuted?

Page 5 lines 1-7

- Wasn't this patient tested for karyotype in the moment of the diagnosis of "dwarf syndrome"? Please specify.

- 1-2 months of GH therapy is not enough time to stop GH based on lack of response (lack of increase of growth speed)

- Was her father karyotyped, since the unique phenotype of this XYY patient may be possibly due to a pre-conception transmission of "YY", in opposition to the typical

Page 5 lines 37-42 - what allowed her to have a "normal breast development" for females, once she had undetectable estradiol?

Page 5 lines 46-48 - "Laboratory tests were unremarkable" - this is not true. She had altered gonadotropinic and steroid productions, due to the lack of gonadal development.
Page 6 lines 1-7 - please include the reference ranges for each hormone

Page 6 line 6 - was prolactin dosed directly in the pituitary? Which source of prolactin other than "pituitary prolactin" could she have?

Page 6 line 10 - why was the 24-hour free urinary cortisol particularly dosed in this case? What were authors/doctors suspecting when they ordered this exam?

Page 6 line 26 - what allowed this girl reach a bone age of 13 y/o, in the absence of any pubertal development? This should be explained in the discussion.

Discussion -

Authors should better discuss this case, due to its impressive particularities. Please:

1. Hypothesize the possible underlying molecular mechanisms that led to an opposite phenotype than expected for XY/XYY mosaicism, particularly because the most important genes related to sex-development were shown to be normal, and SRY is present.

2. Explore the similarities between the phenotype of this girl and Turner syndrome, when compared to what she was expected to present as having 46,XY/47,XYY. Perhaps a sort of "self-Y annulation"?

3. Suggest what may have led this girl to have normal breast developments, despite the lack of estradiol.

Conversely, authors extend too long with repeated information and not so relevant aspects.

Page 7 lines 17-21 - which reference did authors use to mention that this population has shorter life expectancy? This is not necessarily true, except in the syndromic patients. A large number of undiagnosed XYY males that have no alterations could show that life expectancy is not necessarily affected in this population.

Page 7 lines 38-40 - please provide reference for the increased risk of epilepsy

Page 7 lines 40-53 - this information is presumed and therefore unnecessary.

Page 7 line 60 - page 8 lines 1-10 - this information is unnecessary, at least as it has been detailed, since readers must be aware of how to differentiate primary from secondary hypogonadism (and their respective causes).

Page 8 lines 40-43 - symptoms may not only be "simply due to chromosomal abnormalities", otherwise other similar XY/XYY would have similar features, which is not the case. Please reconsider/exclude this possibility.

References:
Are the methods appropriate and well described?
If not, please specify what is required in your comments to the authors.

No

Does the work include the necessary controls?
If not, please specify which controls are required in your comments to the authors.

Unable to assess

Are the conclusions drawn adequately supported by the data shown?
If not, please explain in your comments to the authors.

No

Are you able to assess any statistics in the manuscript or would you recommend an additional statistical review?
If an additional statistical review is recommended, please specify what aspects require further assessment in your comments to the editors.

Not relevant to this manuscript

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