Can we standardize sex assignment in 45,X/46,XY mixed gonadal dysgenesis (MGD)?

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Introduction

- Sex phenotype in patients with 45,X/46,XY MGD ranges from female, to ambiguous, to male; therefore individuals with 45,X/46,XY MGD can have both female and male sex assignments.
- Sex assignment involves a thorough evaluation by a multidisciplinary team and discussion with parents about the different components of sex.
- A standardized approach based on virilization and gonadal characteristics may provide objective guidance for the team as well as a tool for settings without a multidisciplinary team.

Objective

- To develop a standardized, sex assignment tool for individuals with 45,X/46,XY MGD and atypical genitalia.

Methods

Development of Virilization score

- Adapted from previously published score by Ahmed *et al.*
- A compounded score with emphasis on gonadal characteristics and function was used and is illustrated below.

	0	1	2
Genital Tubercle	Clitoris, < 1 cm	clitoromegaly/ or micropenis	> 2.5cm or within 2 SD for age
Genital Folds	Labia	Partial fusion	Complete fusion
Urethral position	Perineal hypospadias	Penile hypospadias	Normal male
Uterus	Formed	N/A	Absent
Right Gonad position	Abdominal	Inguinal	Labioscrotal
Right Gonad characteristics	Streak or ovary	Dysgenetic or both components	Testis-like
Left Gonad position	Abdominal	Inguinal	Labioscrotal
Left Gonad characteristics	Streak or ovary	Dysgenetic or both components	Testis-like
Androgen production	Absent	Present but low	Normal male

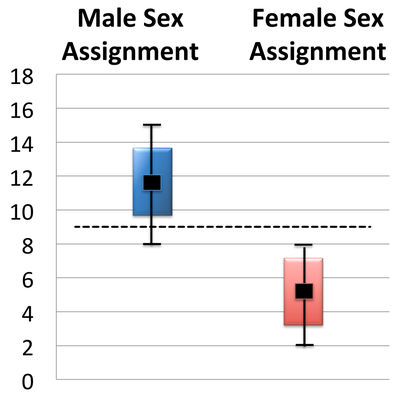
Testing of Score

- A retrospective chart review of patients with 45,X/Y component and ambiguous genitalia was performed.
- Patients were assigned a virilization score which was then compared to their sex assigned as recommended by a multidisciplinary team from a single institution (n =22).
- ROC analysis to establish a cut off point for sex assignment.
- Validation of score using patients from a second institution who also had sex assigned by a multidisciplinary team (n=8).
- Data from both institutions combined for final analysis.

Results

Distribution of scores

	Male Sex Assignment	Female Sex Assignment
Y cell line in peripheral karyotype	59.15% 95% CI 0.45-0.73	41.78% 95% CI 0.18-0.66
Score		
Mean	11.5	5
Median	12	5
Range	8-15	2-8
SD	1.9	2.0



Score Analysis

		Institution #1 n=22	Institution #2 n=8	Combined n=30	95% CI
Area under the Curve (AUC)		**0.991**	**1.00**	**0.995**	0.98-1.0
Cut off value: ≥9	**Consistent with sex assignment**	**95% (21/22)**	**100% (8/8)**	**97% (29/30)**	0.83-0.99
	Sensitivity	92%	100%	**94%**	0.73-0.99
	Specificity	100%	100%	**100%**	0.75-1.00
	PPV	100%	100%	**100%**	0.81-1.00
	NPV	90%	100%	**92%**	0.66-0.99

Clinical Application: Use of score

- A representative patient is seen in the figures along with the corresponding score indicating that a male sex of rearing would be appropriate for in this case.

	Score	Description
Genital Tubercle	1	2.2 cm (micropenis)
Genital Folds	2	Fused
Urethral position	0	Perineal
Uterus	2	Absent
Right Gonad position	2	Scrotal
Right Gonad characteristics	2	Testis-like per US
Left Gonad position	1	Inguinal
Left Gonad characteristics	2	Testis-like per US
Androgen production	2	Baseline Testosterone: 58 ng/dL Stimulated Testosterone: 291 ng/dL
Compounded Score	**14**	**Male sex assignment**

Conclusion and Future Directions

- A score using objective, non-invasive parameters that reflect the degree of gonadal dysgenesis may be used to simplify and standardize sex assignment in patients with 45,X/46,XY MGD.
- The score proposed, with a cut off value of 9 matched the sex assigned by a multidisciplinary team in 29 out 30 patients.
- Prospective, multicenter studies with long term outcomes are needed to validate its utility.
- This study represents a first step at standardization of sex assignment in DSDs.

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