man, vrouw en kind

Universitair Ziekenhuis Gent

Males with 45,X/46,XY have similar cardiovascular problems as females with Turner syndrome

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Introduction

Turner syndrome (TS) is a common genetic disorder, occurring in girls. Structural heart defects are found in 25-50% of the patients and include bicuspid aortic valve, coarctation and progressive dilation of the ascending aorta. In about 7% of TS girls, 45,X/46,XY mosaicism is documented. Sex chromosome mosaicism (45,X/46,XY and variants) is sometimes diagnosed in apparently normal males presenting at infertility clinics, in boys consulting for short stature or in neonates born with genital ambiguity. Many of those males show stigmata typically associated with TS (short stature, renal pathology and coarctation).
To our knowledge, no data exist on the frequency and nature of cardiovascular pathology in males with 45,X/46,XY.

Aim of the study

Investigate whether 45,X/46,XY males present with the same cardiovascular abnormalities as 45,X/46,XY girls with TS.
In view of the description of some cases of aortic dilation in males with 45,X/46,XY, this information is highly relevant, taking into account that current guidelines on regular cardiac follow-up exclusively implicate girls with TS.
If similar cardiovascular pathology is encountered in 45,X/46,XY boys adjustment of the guidelines is mandatory.

Study protocol

Identification of patients with 45,X/46,XY mosaicism through the Belgian Growth Hormone Database and the multi-disciplinary clinic for disorders of sexual development (DSD) of Ghent University Hospital.

Investigations performed in 1 day in a single centre (Ghent University Hospital):

- Blood pressure at the 4 limbs
- 12 leads ECG
- Echocardiography
- MRI (in 12 of 18 patients)
- Data on sexual phenotype and growth were collected from the files.

Overview of the results

Age (y)	Age diagnosis (y)	Karyotype	Raised	EMS	Associated features	Cardiovascular findings
21	15	45,X/46,XY	F	non-ambiguous female	short stature hypothyroidism	bicuspid aortic valve prolonged QTc (465ms) high heart rate (97/min)
30	9	45,X/46,XY	F	non-ambiguous female	short stature	prolonged QTc (471/min)
38	12	45,X/46,XY	F	non-ambiguous female	short stature	normal
13	Neonatal	45,X/46,X,i(Y)(q10)	F	non-ambiguous female	short stature	bicuspid aortic valve coarctation
15	8	45,X/46,XY	F	non-ambiguous female	short stature recurrent otitis ADHD	normal
13	10	45,X/46,XY	F	non-ambiguous female	short stature ADHD	bicuspid aortic valve prolonged QTc (457/min) high heart rate (92/min)
13	1	45,X/46,X, mar(Yq12)	F	non-ambiguous female	short stature	high heart rate (82/min)
26	Neonatal	45,X/46,XY	F	virilisation	short stature	right arteria lusoria
21	10	45,X/46,X,der(Y)	M	12	short stature	normal
24	7	45,X/46,X,idic(Y)(q11.21)	M	12	short stature mild mental retardation	bicuspid aortic valve
11	10	45,X/46,X,idic(Y)(p11.32)	M	12	short stature, scoliose ADHD recurrent otitis	bicuspid aortic valve mildly dilated ascending aorta prolonged QTc (465/min) high heart rate (95/min)
1	Prenatal	46,X,i(Y) (pter→q11:q11→pter)	M	12	cleft lip and palate	Normal
10	1	45,X/46,XY	M	10	short stature recurrent otitis webbed neck	bicuspid aortic valve, dilated ascending aorta impaired systolic function prolonged QTc (482/min) high heart rate (94/min)
19	1	45,X/46,XY	M	10	short stature	right arteria lusoria
3	Prenatal	45,X/46,X,i(Y)(p10)	M	10	height SD -2.6 multicystic kidney recurrent otitis	bicuspid aortic valve mildly dilated ascending aorta
10	Neonatal	45,X/46,XY	M	8	short stature horseshoe kidney	VSD bicuspid aortic valve dilated ascending aorta high heart rate (99/min)
5	Neonatal	arrYq11.223q11.223/XO	M	6		Normal
2	Neonatal	45,X/46,X,isoYp	M	5		normal

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Results: study population

Number of patients

18
patients with 45,X/46,XY or variant

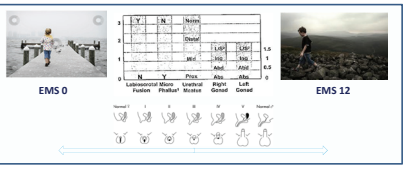
8
raised as female (F)
Age 13-31 y, median 19 y

- 7 with typical Turner features
- 1 with ambiguous genitalia at birth

10
raised as male (M)
Age 0-24 y, median 9,5 y

- 4 with normal external genitalia (EMS 12/12)
- 4 with mild undervirilisation (EMS 8-10/12)
- 2 with severe undervirilisation (EMS 5-6/12)

External masculinisation score (EMS) *the genital phenotype of the patients, if other than typically F, was described by the external masculinisation score, a clinical scoring system based on the position of the gonads, length of the phallus, presence of labioscrotal fusion and position of the urethreal meatus to quantitatively assess the degree of undervirilisation.*



Growth hormone treatment

14 patients (8 F, 6 M) received growth hormone for short stature. In 4 young males, although short for assigned sex, treatment was not started yet in view of their young age.

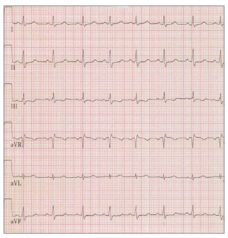
Results: cardiovascular findings

Cardiac history and clinical examination

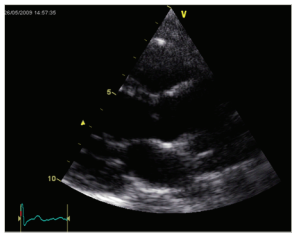
Five patients had previously visited a cardiologist. Routine echocardiography for TS was normal in 2 F and showed a bicuspid aortic valve (BAV) in one. One girl had a BAV and underwent neonatal cardiac surgery for coarctation of the aorta. One boy was known with a BAV and spontaneous closure of a VSD. None of the patients had a cardiac MRI.
Clinical cardiac examination was normal in all patients, except for the girl with previous cardiac surgery and a boy of 5 years old with a soft innocent murmur.
None of the other patients had any complaints or symptoms suggestive for underlying cardiovascular disease

Cardiac pathology

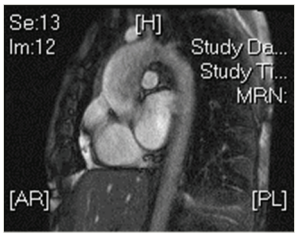
	Males (n=10)	Females (n=8)
VSD	1	0
Bicuspid aortic valve	5	3
Dilation of the ascending aorta	4	0
Coarctation	0	1
Right arteria lusoria	1	1
Prolonged QTc	2	3
Increased heart rate	3	3



ECG of a 11 year old boy with 45,X/46,XY showing prolonged QTc



Echocardiography of an 11 year old boy with 45,X/46,XY showing dilation of the ascending aorta



MRI of a 10 year old boy with 45,X/46,XY showing important dilation of the ascending aorta

CONCLUSION

Males with 45,X/46,XY mosaicism have the same type and frequency of cardiovascular pathology as 45,X/46,XY females with an incidence similar to what is found in classic Turner patients. Dilation of the ascending aorta can be important and might become life threatening. We advise cardiac screening and life-long monitoring in all males with 45,X/46,XY mosaicism according to the existing guidelines for Turner syndrome