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Hypothyroidism in a 45, X phenotypic male with a Y/18 translocation

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CASE STUDY

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ABSTRACT

This is the first case report of a 45, X male with autoimmune thyroid disease. Chromosome analysis revealed that all cells were 45, X without chromosome Y. The entire short arm and the centromere of Y chromosome were translocated onto the short arm of chromosome 18. Fluorescence in situ hybridization revealed that the SRY gene was present in all cells. At the age of 3 years he was diagnosed with hypothyroidism, and treatment was initiated.

In the rare event of 45, X karyotype in a male, hypothyroidism should be considered so that early treatment could be initiated.

Key Words
Hypothyroidism, 45, X male phenotype, Y/18 translocation

Implications for Practice:

1. What is known about this subject?
A phenotypic male associated with a 45, X karyotype is rare. Translocations involving the Y chromosome and autosomal chromosomes occur in approximately 1/2000. Hypothyroidism had never been reported in a phenotypic male with 45, X karyotype.

2. What new information is offered in this case study?
Hypothyroidism should be considered in a phenotypic male with 45, X karyotype.

3. What are the implications for research, policy, or practice?
In the rare event of 45, X karyotype in a male, hypothyroidism should be considered so that early treatment could be initiated.

Background

A phenotypic male associated with a 45, X karyotype is a rare condition.[1] It could be due to undetected mosaicism or translocation of Yp material. Translocations involving the Y chromosome and autosomes are very rare, occurring in approximately 1/2,000 of the general population. The most frequent translocation of this type occurs between the heterochromatin of the long arm of chromosome Y and the short arm of chromosome 15.[2-3] This is the first report of hypothyroidism in a phenotypic male with a 45, X karyotype.

Case details

A 3-year-old boy, born by cesarean section at 30 weeks gestation due to severe preeclampsia was admitted to the neonatal intensive care unit due to respiratory distress syndrome and prematurity. The birth weight was 1,450g. Physical examination was unremarkable except for bilateral undescended testes, with normal penis. After an uneventful course he was discharged home at 36 weeks corrected gestational age, weight at discharge was 1,900 g.

At the age of nine months he was investigated for failure to thrive and delayed mile stones. Growth parameters, were below 2 SD. Chromosome analysis showed 45, X karyotype. Detailed analysis of each chromosome at a resolution of 400-550 bands per haploid set indicated that the entire short arm and centromere of the Y chromosome were translocated onto the short arm of chromosome 18, resulting in an unbalanced dicentric chromosome. This was confirmed by Fluorescence in Situ Hybridization (FISH) probes for CEP Y and SRY. The SRY gene was present in all

cells. The father had a normal 46, XY karyotype (Figures 1 and 2).

At the age of one year he suffered recurrent infections, and was found to have IgA deficiency. Thyroid function was tested at different intervals (Table 1). At the age of 3 years, FT4 was 8.7pmol/L, TSH was 10.1mIU/L, and anti-thyroid peroxidase antibodies (anti-TPO antibodies) was 95 (negative <50, borderline 50–70, positive >75). He was diagnosed with autoimmune hypothyroidism, and was started on levothyroxine (5mcg/kg/day). Thyroid function became normal within 4 weeks. Bilateral orchidopexy was performed.

Discussion

There are rare case reports of 45, X in phenotypic normal males. The risk of multiple comorbidities, such as obesity, hypothyroidism and hypertension may be amenable to therapy.[4]

Cassorla et al. reported a case of 45, X, t (Y;18) (p11;p11) associated with congenital heart disease, mental retardation, mild virilization and gonadal tumors. Testosterone level was elevated. Thyroid function was not tested.[5]

Khodr et al. reported a case of a five-year-old female with mosaic Y-autosome translocation involving Y and 18 chromosomes, 45, X, t (Y;18) (q11;p11)/45,X. In addition to her short stature, she was found to have bilateral gonadoblastoma.[6]

El Kalla et al. reported a case with Y-autosome translocation (Y;18) involving the long arm of the Y chromosome, that presented with multiple congenital anomalies caused by chromosome 18p deletion syndrome, with no mention of the endocrine status.[7]

Oliveira et al. in their review of the Y chromosome in Turner syndrome, specifically about tumor etiology, concluded that the presence of Y-chromosome material in patients with dysgenetic gonads increases the risk of gonadal tumors, especially gonadoblastoma, with no reports of autoimmune hypothyroidism.[8]

The index-patient showed no evidence of gonadoblastoma at the time of assessment. This issue is too addressed at follow-up.

Hypothyroidism in children is associated with impaired physical and cognitive development. Thyroid hormone levels change during childhood. Age and sex-specific reference intervals are important prerequisites for interpreting thyroid hormone measurement in children. Furthermore, differences in reference intervals between studies may be caused by different characteristics of antibodies used in various analytical methods, and geographic covariates of iodine and selenium in different populations.[9]

Primary hypothyroidism is diagnosed on the basis of raised TSH rather than low free T4 and T3 levels, as they may be normal in subclinical hypothyroidism. Furthermore, low free T4 can be found in central hypothyroidism, and free T3 is not particularly useful in the evaluation of primary hypothyroidism.

Hypothyroidism of autoimmune origin and thyroid peroxidase antibody titer may be elevated in 45, X phenotypic males. Early recognition and treatment would improve outcome and help boys with 45, X karyotype in their transition to adulthood.

Conclusion

45, X karyotype in males are rare. This is the first report of autoimmune hypothyroidism in a male with 45, X karyotype. Early recognition would promote the early initiation of therapy.

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PEER REVIEW

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CONFLICTS OF INTEREST

The authors declare that they have no competing interests.

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None

PATIENT CONSENT

The authors, *Khriesat W, Amarin Z, Raqad M, Al-Abbadi A,* declare that:

1. They have obtained written, informed consent for the publication of the details relating to the patient in this report.
2. All possible steps have been taken to safeguard the identity of the patient.
3. This submission is compliant with the requirements of local research ethics committees.

Figure 1: Karyotype result of 45, X male with unbalanced translocation between the short arm of chromosome Y and the short arm of chromosome 18

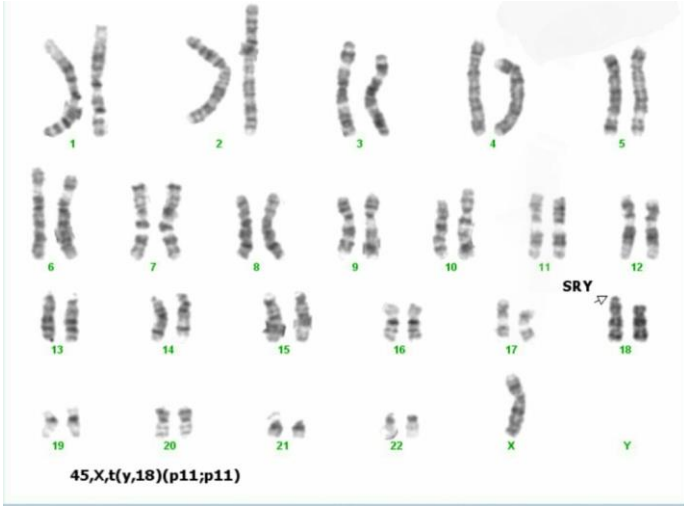

Figure 2: FISH result of 45, X male. All cells are X male with the SRY gene on short arm of chromosome 18

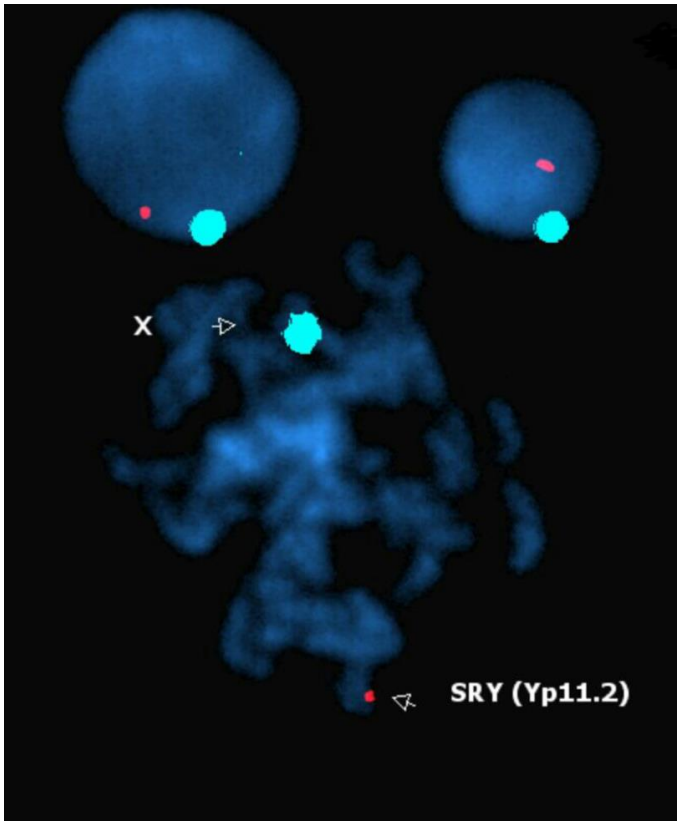

Table 1: Thyroid function test results of 45, X male with a Y/18 translocation at different stages

Age (months)	FT3 (pmol/L)	FT4 (pmol/L)	TSH (mIU/L)
1	5.6 (4.5-10.5)	17 (13.9-26.1)	2.1 (0.27-4.64)
12	4.3 (3.8-8.2)	19 (12.1-22.1)	2.3 (0.27-4.64)
18	4.2 (3.8-8.2)	13 (12.1-22.1)	3.4 (0.27-4.64)
24	4.7 (3.8-8.2)	15 (12.1-22.1)	4.2 (0.27-4.64)
30	3.9 (3.8-8.2)	12.3 (12.1-22.1)	4.4 (0.27-4.64)
36	3.7 (3.8-8.2)	8.7 (12.1-22.1)	10.1 (0.27-4.64)