# MULTIPLE MALFORMATIONS IN A PATIENT WITH UNBALANCED TRANSLOCATION 46,XY T(7;16) AND AMBIGUOUS GENITALIA

ILARIA LOMBARDO - ALICE LE PIRA - STEFANIA SALAFIA - PIERO PAVONE* - TERESA MATTINA
University of Catania - Department of Paediatrics - Unit of Clinical Paediatrics (*Director: Prof. L. Pavone)*
*University of Catania - Unit of Paediatrics - Hospital "Vittorio Emanuele"

*[Malformazioni plurime in un paziente con traslocazione sbilanciata 46,XY t(7;16) con genitali ambigui]*

**SUMMARY**

We report on a male infant with unbalanced translocation 46,XY t(7;16) with multiple malformations.

Our patient is the first reported in literature with unbalanced translocation with partial monosomy 7qter and 16p duplication in an overlapping phenotype including intrauterine growth retardation, facial abnormalities, congenital heart defect, pachygyria, syndactylya, and ambiguous genitalia.

Unbalanced translocation 46, XY t(7;16) must be considered one of the several causes of ambiguous genitalia.

**Key words:** Unbalanced translocation, ambiguous genitalia, facial dysmorphisms, pachygyria, syndactylya

***RIASSUNTO***

*Riportiamo il caso di un bambino con traslocazione sbilanciata 46,XY t(7;16) con malformazioni multiple.*

*Il nostro caso è il primo riportato in letteratura con traslocazione sbilanciata con monosomia parziale 7qter e duplicazione 16p con fenotipo con ritardo di crescita intrauterino, dimorfismi facciali, difetti cardiaci congeniti, pachigiria, sindattilia e genitali ambigui.*

*La traslocazione sbilanciata 46, XY t(7;16) deve essere considerata tra le cause di genitali ambigui.*

**Parole chiave**: *Traslocazione sbilanciata, genitali ambigui, dimorfismi facciali, pachigiria, sindattilia*

## Introduction

Ambiguous genitalia is one of the most distressing problems found at birth[1].

Today, the terms "intersexuality", "pseudohermaphroditism" and "sex reversal" have recently been renamed "disorders of sex development" (DSD)[2].

Any condition involving genes, transcription factors and hormones implicated in sexual differentiation of the child during fetal life, may lead to a disorder of sex differentiation.

Anomalies resulting from the errors in the differentiation process of the reproductive system during fetal life can be grouped in[3]:

• errors in the differentiation of the gonads caused by numerical chromosomal abnormalities (S. Klinefelter, S. Turner, mixed gonadal dysgenesis, chimerism);

• disorders of gonadal development of structural abnormalities of chromosomes: complete or partial gonadal dysgenesis, true hermaphroditism (ovotestis DSD);

• errors of differentiation due to disorders in sex hormones synthesis or to a defect in signaling such as resistance to the action of sex hormones (pseudohermaphroditism);

• other causes: post-receptor defect at the nuclear level, with changes in the synthesis or metabolism of mRNA; syndromic associations.

We report the case of a patient with unbalanced translocation of chromosomes 7 and 16 with multiple malformations and a sex development disorder.

## Case report

BB, is the first born of non-consanguineous parents, from a mother who had a balanced reciprocal translocation t(7;16) with normal phenotype and a father with normal karyotype, 46, XY.

He was delivered by caesarean section after a 38-week pregnancy, complicated by oligohydramnios and intrauterine growth retardation. Apgar score was 8 at 1' and 10 at 5'. The birth weight was 2450 g (<3°C), birth length 43 cm (<3°C)., cranial circumference 30.5 cm (<3°C).

The patient was admitted to the department of neonatal pathology for ambiguous genitalia, syndactyly of the bilateral 2nd and 3rd toes, cleft of soft palate and facial dysmorphisms: sloping forehead, eyebrows up and rade, long eyelashes, blepharophimosis, nose pointing down, small mouth, retrognathia, hands with tapering fingers.

At the physical examination he appeared in poor condition with lethargy, and generalized hypotonia. Crying was weak and feeble. Heart tones were muffled, and frequency was 127 b / min.

The genitalia were ambiguous (Fig.1) with, hypospadias, shawl scrotum and cryptorchidism.

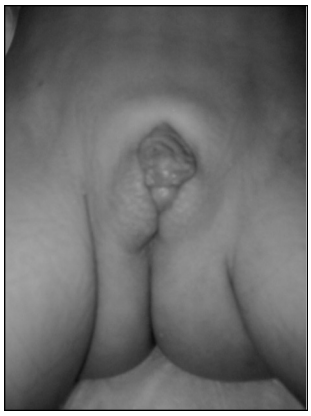

**Fig. 1:** Ambiguos genitalia with hypospadias and shawl scrotum.

Neurological examination revealed mild hypotonia, symmetrical and hypoactive neonatal reflexes were present.

The routine laboratory tests, and PCR and TORCH, were normal.

Hormonal evaluation showed FSH: 7.8 mIU/ml, LH: 8.3 mIU/ml; Testosterone: 2.62 ng/ml, DHT 0.5 ng/ml; Cortisol: 422 nmol/L; ACTH: 32 pg/ml, 17-OH-Progesterone: 9.8 ng/ml, DHEA-S: 0.4 µg/ml; Androstenedione: 0.9 ng/ml; plasmatic Aldosterone: 1151.1 pg/ml, renin activity, plasma: 102.5 pg/ml. The HCG test stimulation showed a normal testosterone-dihydrotestosterone ratio.

The karyotype revealed 46, XY with unbalanced translocation and partial monosomy 7qter and 16p duplication arising from a maternal balanced translocation.

The DNA study for the microdeletion of the Y chromosome presented no alterations in as much as the molecular analysis carried out on the SRY, AZF and DAZ genes.

Ultrasound scans of the abdomen and the adrenal glands were normal; the pelvic ultrasound did not detect female genital organs and showed the testes in the inguinal channel.

A cerebral ultrasound (US) study showed the brain ventricular system in line, but not the posterior knee of the corpus callosum.

The EEG showed spike waves in the centre-temporal regions of the right hemisphere.

Brain-MRI showed a dysmorphic skull, with marked expansion of subarachnoid and subtentorial spaces and of the cisterna magna with pachygyria most evident in the left hemisphere, a slight asymmetric expansion of the side ventricles and hypoplasia of the posterior horn of the corpus callosum were also present.

The Angio-RM, the ECG and the ophthalmologic consultation did not show pathological findings. The echocardiograph showed small atrial septal defects, patent foramen ovale, with a left-to-right shunt at high velocity and a small interventricular defect with a transseptal gradient of 32 mmHg. Impedancemetry (Ty plate) and otoemissions showed the absence of noise on the right and left, indicating moderate-severe hearing loss.

The startle reflex was symmetrical, other reflexes slightly hyperactive, four limbs were slightly hypertonic with trunk hypotonic at the dorsal and ventral suspension, and inability to raise his head in the prone position and keep it to the traction maneuver; the response to visual and auditory stimuli was low and spontaneous movements were significantly reduced. His conditions were always compromised, and the course was marked by frequently recurring respiratory tract infections, growth deficiency and nutrition by nasogastric tube. Subsequently, the patient at the age of 2 years began to present multiple daily seizures characterized by eye deviation and hyperextension of the right arm to the left. EEG showed a typical pattern of epileptic encephalopathy with suppression-bursts, frequent tonic spasms and sporadic myoclonic seizures, therefore valproic acid and topiramate therapy was initiated.

## Discussion

Our patient had a set of chromosomes 46, XY with unbalanced translocation with partial monosomy 7qter and 16p duplication, and multiple malformations with facial dysmorphisms, pachygyria, diaphragmatic relaxation, cardiac defect, syndactyly of the 2nd and 3rd fingers and ambiguous genitalia, which was the most evident clinical sign.

The combination of malformations associated with ambiguous genitalia does not allow a rapid identification of sex, which was only possible after the karyogram, which highlighted the karyotype 46, XY, and the pelvic ultrasound that showed the presence of testes in the inguinal channel, as well as the absence of female genital organs in the pelvic cavity.

The chromosome analysis performed on peripheral blood lymphocytes from the patient was the first diagnostic step, and once the correlation between sex chromosomes and gonads was confirmed, the presence of ambiguous genitalia indicated a state of male pseudohermaphrotidism.

There are many causes of pseudohermaphrotidism such as default of formulation of a functional testis, of a testosterone synthesis, of a conversion of testosterone into dihydrotestosterone, of a peripheral sensitivity to androgens[4].

Our diagnostic approach was based on the determination of the karyotype (46, XY with unbalanced translocation t (7, 16)) that allow us to exclude numerical chromosomal abnormalities and the normal result of the DNA study for the microdeletion of the Y chromosome that allowed us to exclude complete or partial testicular gonadal dysgenesis.

Moreover, the formation of functional testis with normal production of androgens, the normal testosterone-dihydrotestosterone ratio and male karyotype, suggested the diagnosis of peripheral resistance to androgens. This can be confirmed by testicular biopsy, though it has not yet been carried out. The present report is clinically worthwhile to be published since the unbalanced translocation 46, XY t(7;16) must be maintained one of the several causes of ambiguous genitalia.

In our patient the unbalanced translocation of chromosomes (7;16) has caused the presence of several, significant and complex malformations causing of ambiguous genitalia, facial dysmorphisms, pachygyria, diaphragmatic relaxation, cardiac defect and syndactyly of the 2nd and the 3rd finger.

## References

1) Gollu G., Yildiz RV, Bingol-Kologlu M., Yagmurlu A., Senyucel MF, Aktug T., Gokcora IH, Dindar H. *Ambiguous genitalia: an overview of 17 years' experience*. J Pediatr Surg 2007, 42 (5): *840-4*.

2) Hughes IA, Houk C., Ahmed SF, Lee PA, *LWPES consensus group, ESPE consensus group. Consensus statement on management of intersex disorders.* Arch Dis Child, 2006; 91: *554–63.*

3) Ieuan A. Hughes. *Disorders of sex development: a new definition and classification.* Best Practice & Research Clinical Endocrinology & Metabolism, 2008 22 (1): *119–134.*

4) Rohtgi M., Menon PS; Verma IC, Iyengar JK. *The presence of intersexuality in patients with advanced hypospadias and undescended gonads*. J Urol, 1987; 137(2): *263-7.*

*Request reprints from:*
Dott.ssa ILARIA LOMBARDO
Piazza Duca Di Camastra, 18/8
95126 Catania
*(Italy)*