# TREMOR AND OTHER MOVEMENT DISORDERS IN PATIENTS AFFECTED BY KLINEFELTER SYNDROME

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**Background.** Klinefelter syndrome (KS) represents the most common sex chromosomal disorder in males, characterized by an extra X chromosome, with key finding of hypergonadotropic hypogonadism. Previous research suggests that psychiatric and neurologic disorders might be overrepresented in KS patients, although the specific evaluation of movement disorders appears largely unexplored.

**Objective.** In this study we aimed to evaluate the presence of tremor and other movement disorders in a population of KS patients and their clinical categorization.

**Material and Methods.** Consecutive male patients with genetically confirmed KS were enrolled. Each patient underwent a clinical evaluation including: demographic data, age at KS first signs onset and diagnosis, type of presenting symptoms, current medications and dosage, presence of comorbidity and psychiatric disorders. The correct identification by standard karyotype (chromosome analysis for presence of 47, XXY, 48, XXYY, mosaicism 47 XXY/46XY,) was registered for each patient. Each patient underwent a complete neurological evaluation, with special focus on presence of tremor and other movement disorders such as: bradykinesia, rigidity, dystonia, ataxia and myoclonus. Tremor and other parkinsonian symptoms were also evaluated with the UPDRS-III (items 20-26), the Essential Tremor Rating Assessment Scale (TETRAS) ADL subscale and an assessment tool specifically designed for this study. In KS patients with evidence of movement disorders a brain MRI was performed, while those with lateralized resting tremor undergo a brain [(123)I]FP-CIT SPECT. A control group of matched healthy subjects was also enrolled.

**Results.** Sixteen male KS patients with a mean age 40.1±15.4 years were included (Table 1). Mean KS history was 5,4 ±8.1 years. At chromosome analysis, 13 presented with 47, XXY, two with 48, XXYY, and one for mosaicism 47 XXY/46XY. Clinical signs are reported in Table 2. Nine patients presented tremor (Table 3), statistically increased compared to control group ( $p<0.001$). Tremor was of mixed type in six patients. More specifically, postural tremor was detected in 8 patients, intentional tremor in 6 patients (always concomitant with the postural component), while resting tremor was present in 4 patients (Table 4). One patient presented with dystonic tremor. Mean score of UPDRS-III (only items 20-26) was 5.1 ± 6.6, while TETRAS-ADL score was 8.0 ± 7.8. In patients with lateralized tremor, [(123)I]FP-CIT SPECT was positive in one of them with evidence of a dopamine nigrostriatal terminal defect (Figure 1a). In this patient, iron binding accumulation was also detected at brain MRI (Figure 1b). Bradykinesia and rigidity were detected in three patients. Finally, two patients presented with myoclonic movements.

**Conclusions.** Movement disorders are common in patients affected by KS and often underevaluated. Among them, tremor represents the most frequent and the role of testosterone administration, often worsening this symptoms, should be adequately investigated.

*Table 1*

| Caratteristiche esaminate | Pazienti KS (16) | Popolazione controllo (16) | P< |
|---|---|---|---|
| Sesso maschile, N (%) | 16 (100) | 16 (100) | NS |
| Anni all'osservazione, anni (DS) | 40,06 (15,4) | 41,56 (12,77) | NS |
| Età alla diagnosi, anni (DS) | 31,31 (19,7) | NA | |
| Pazienti in terapia sostitutiva, N (%) | 12 (75) | NA | |
| Testosterone Gel, N (%) | 7 (43,75) | NA | |
| Testosterone Orale, N (%) | 1 (6,2) | NA | |
| Testosterone IM, N (%) | 4 (25,0) | NA | |
| Cariotipo 47,XXY, N (%) | 13 (81,2) | NA | |
| Cariotipo 48,XXYY, N (%) | 2 (12,5) | NA | |
| Cariotipo 46,XY/47,XXY, N (%) | 1 (6,2) | NA | |

*Table 2*

| Segni clinici e patologie | Pazienti KS (16),N (%) | Popolazione controllo (16), N(%) | P< |
|---|---|---|---|
| Ipotrofia testicolare | 16 (100) | 0 (0) | 0,000 |
| Azoospermia | 16 (100) | 0 (0) | 0,000 |
| Osteopenia/osteoporosi | 4 (25,0) | 0 (0) | NS |
| Ginecomastia | 3 (18,7) | 0 (0) | NS |
| Varicocele | 2 (12,5) | 0 (0) | NS |
| Deficit erettile | 1 (6,2) | 0 (0) | NS |
| Patologie cardiovascolari | 6 (37,5) | 1 (6,2) | NS |
| Disturbi comportamentali/psichiatrici | 7 (43,75) | 0 (0) | 0,0003 |
| Disturbi metabolici | 4 (25,0) | 0 (0) | NS |
| Altri disturbi neurologici | 3 (18,7) | 1 (6,2) | NS |
| Patologie gastrointestinali | 1 (6,2) | 0 (0) | NS |
| Patologie oculari | 1 (6,2) | 0 (0) | NS |
| Patologie respiratorie | 1 (6,2) | 0 (0) | NS |
| Patologie prostatiche (IPB) | 1 (6,2) | 1 (6,2) | NS |

*Table 3*

| Disordini del movimento | Pazienti KS (16) | Popolazione controllo (16) | P< |
|---|---|---|---|
| Tremore, N (%) | 9 (56) | 1 (6,2) | 0,006 |
| Mioclonie, N (%) | 2 (12,5) | 0 (0) | NS |
| Mirror, N (%) | 1 (6,2) | 0 (0) | NS |
| Rigidità, N (%) | 4 (25,0) | 0 (0) | 0,051 |
| Bradicinesia, N (%) | 4 (25,0) | 0 (0) | 0,051 |
| Postura distonica, N (%) | 1 (6,2) | 0 (0) | NS |
| Atassia, N (%) | 2 (12,5) | 0 (0) | NS |

*Table 4*

| Caratteristiche cliniche del Tremore (9 pazienti KS totali) | |
|---|---|
| Tremore posturale, N (%) | 8 (88,9) |
| Tremore intenzionale, N (%) | 6 (66,7) |
| Tremore di riposo lateralizzato, N (%) | 4 (44,4) |
| Tremore distonico, N (%) | 1 (11,1) |
| Familiarità per tremore, N (%) | 1 (11,1) |
| Predominanza a destra, N (%) | 5 (55,5) |
| Predominanza a sinistra, N (%) | 1(11,1) |
| Risposta positiva a dosi moderate di alcol, N (%) | 0 (0,0) |
| Età d'insorgenza tremore, anni (DS) | 5,3 (8,1) |
| Miglioramento con testosterone, N (%) | 0 (0) |
| Peggioramento con testosterone, N (%) | 1 (11,1) |

**Figure 1.** A peculiar KS patient with lateralized tremor, [(123)I]FP-CIT SPECT was positive with evidence of a dopamine nigrostriatal terminal defect (Figure 1a) and presence of iron binding accumulation was detected at brain MRI (Figure 1b)

**Figure 1a**

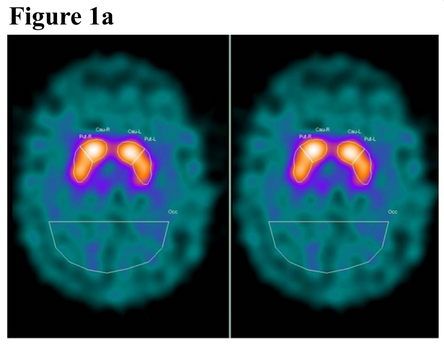

**Figure 1b**