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Romanian Prader-Willi Association

ASOCIACIÓN MADRILEÑA
PARA EL SÍNDROME DE
PRADER-WILLI



MORTALITY IN PRADER-WILLI SYNDROME: ROLE OF GENOTYPE, GENDER AND GH THERAPY

Graziano Grugni, MD¹, Antonino Crinò, MD², Laura Bosio, MD³, Andrea Corrias, MD⁴, Marina Cuttini, MD², Teresa De Toni, MD⁵, Eliana Di Battista, MD⁵, Adriana Franzese, MD⁶, Luigi Gargantini, MD⁷, Nella Greggio,⁸ Lorenzo Iughetti, MD⁹, Chiara Livieri, MD¹⁰, Arturo Naselli, MD⁵, Claudio Pagano, MD⁸, Giovanni Pozzan, MD⁸, Letizia Ragusa, MD¹¹, Alessandro Salvatoni, MD¹², Alessandro Sartorio, MD¹, Giuliana Trifirò, MD¹³, Roberto Vettor, MD⁸, Giuseppe Chiumello, MD³ (*Genetic Obesity Study Group of the Italian Society of Pediatric Endocrinology and Diabetology*).

¹Italian Auxological Institute, Verbania; ²Bambino Gesù Hospital, Palidoro-Rome; ³S. Raffaele Hospital, Milan; ⁴University of Turin; ⁵University of Genoa; ⁶University of Naples; ⁷Civic Hospital of Treviglio (BG); ⁸University of Padua; ⁹University of Modena and Reggio Emilia; ¹⁰University of Pavia; ¹¹Oasi Maria S.S., Troina (EN); ¹²University of Varese; ¹³S. Giuseppe Hospital, Milan; Italy.

INTRODUCTION: Complications associated with obesity are the recognized main risk factors for death during the entire lifespan of patients with Prader-Willi syndrome (PWS), while infectious disease seems to be the major cause of unexpected sudden death in children below the age of 5 years. In addition, some patients with PWS may be susceptible to additional diseases unrelated to obesity, which may compromise health further. As far as genetic mechanisms are concerned, it has been reported that UPD15 seems to be an independent risk factor for death in adult patients with PWS. On the other hand, no data about the effects of gender on mortality risk of PWS are currently available. Moreover, the role of GH/IGF-I axis dysfunction and its treatment in the poor health outcomes of PWS adults remains to be fully established, whereas the benefits of GH therapy (GHT) were well documented both in children and in adolescents. In spite of these beneficial effects, fatal events after the start of GHT have been reported in paediatric patients with PWS, raising the possibility that a causal link may be present. The aim of our study was to analyse the role of genotype, gender and GHT as factors contributing to the mortality of Italian patients with PWS.

PATIENTS AND METHODS: In collaboration with the Italian PWS Association and in a national collaborative study, all known cases with genetically confirmed PWS were collected. Clinicians were asked to report genetic tests, age, sex, weight, length/height, presence or absence of GHT, dosage and duration of GH treatment, and cases of death. Multivariate Cox proportional hazards analysis was used to explore the factors potentially associated with survival.

RESULTS: On 30 June 2006, 425 subjects with PWS, 209 males (M) and 216 females (F), were identified. Two hundred and thirty-eight patients had a del15, 104 subjects had a UPD15, and 4 individuals showed a translocation affecting chromosome 15q11-q13. Positive methylation test was demonstrated in the remaining 79 patients (18.6%). The median age was 13.7 (range 0.5-45.4) for males, and 19.0 (range 0.4-46.7) for females. One hundred and thirty (62.2%) of the males and 103 (47.7%) of the females were below 18 years of age. The difference of age distribution between males and females was statistically significant (p 0.03). Overall, the proportion of obesity was 62.6%. A total of 212 subjects have performed GHT (49.9%, 106 M): 141 cases were currently receiving GHT (33.2%, 80 M), while 71 individuals have stopped the treatment (16.7%, 26 M). Eighteen patients deceased during the



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past 20 years. The frequency of death was higher in M than in F (12/209= 5.74% vs. 6/216= 2.77%). On the other hand, no difference was detected between the different genotypes (del15= 4.6%; UPD15= 4.8%). Three children (2 M) died while receiving GHT. The frequency of death during GHT was 1.41% (3/212), while 15 out of 213 patients with PWS died without GHT (7%). When the effect of GHT, obesity, genetic defect and gender were considered together in a multivariate Cox model, only the latter showed a marginally significant ($p=0.05$) relationship with survival, with a decreased risk of death for females compared to men (OR 0.38, 95% CI 0.14-1.02).

CONCLUSIONS: 1) no correlation was found between death and UPD15; 2) mortality is higher in M than in F. This finding may indicate random variation in small populations. Alternatively, the possibility that, with PWS, as in general population, women outlive men cannot be excluded. However, such variations may also suggest an increased mortality rate in M patients with PWS; 3) GHT in patients with PWS, as a group, does not seem to rise the risk of death.