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How Much of the Phenotype of Prader-Willi Syndrome is due to Growth Hormone Deficiency?

Suzanne B. Cassidy1, Ellen Simpson1, Shauna Heeger2

1Division of Human Genetics, Department of Pediatrics, University of California, Irvine, 101 The City Drive, Bldg 2, Orange, CA 92868, (714) 456-6261, and 2Case Western Reserve University.

The classical physical phenotype of Prader-Willi syndrome (PWS) is most notable for hypotonia, characteristic facial appearance (narrow bifrontal diameter, almond-shaped and sometimes upslanting palpebral fissures, downturned mouth), short stature, central obesity, small hands and feet, genu valgus, decreased muscle mass causing characteristic body habitus, straight ulnar borders and straight calf borders, and hypoplastic genitalia. In recent years, the short stature has been associated with growth hormone deficiency (hGH), as has altered body composition. PWS is now an FDA approved indication for the use of hGH, and it is becoming standard of care. Most newly diagnosed individuals are being treated from the time of diagnosis or shortly thereafter, which is often infancy. Observation of treated patients has suggested a significant impact on physical phenotype.

In the general population, growth hormone deficiency causes not only short stature, but also hypotonia, decreased muscle mass and increased fat mass (i.e., altered body composition), central obesity, osteopenia, small hands and feet, delayed bone age, and low IGF-1. All of these are present in PWS. Reports based on recent double-blind crossover studies of hGH treatment in PWS have indicated dramatic increase in growth rate (especially in the first year of treatment) and a variety of other effects, including: 1) improved body composition (higher muscle mass, lower fat mass), 2) improved weight management; 3) increased energy and physical activity; 4) improved strength, agility and endurance; and 5) increased respiratory muscle forces. These studies have also shown no adverse effects on behavior, and in fact suggest improvement in depression.

We have been conducting an ongoing detailed multi-system standardized phenotypic evaluation of individuals with PWS over the past several years for the purpose of genotype-phenotype comparison. Given the recent shift to hGH treatment, recently enrolled patients with hGH replacement can be compared phenotypically to earlier enrolled patients, who were not hGH treated. These comparisons, as well as review of patients followed in a multi-disciplinary PWS management clinic and of studies by others, indicate a number of effects on physical phenotype. Such effects include changes toward normal in body habitus, limb form, hand & foot length, facial appearance, bone density, body composition, and genital size. These changes are most impressive if hGH is started within the first year of life.

These impressive effects from replacement of a single hormone raise interesting questions about the relative importance of genetic alterations in causing at least this one dysmorphic syndrome.

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