Review Article

Hypothyroidism in Paediatric Patients with Prader-Willi Syndrome; Regular Monitoring Is Recommended

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Abstract

Prader-Willi syndrome (PWS) is a genetic disorder described by multifaceted clinical features with implications on the endocrine system, metabolism, and behavior. Some symptoms of PWS syndrome can be confused with the relative clinical aspects of hypothyroidism, such as lethargy, muscular hypotonia, and poor sucking ability. In this review, we would like to enlighten the importance of checking thyroid function in PWS patients at birth, at least annually, in those on growth hormone (GH) treatment, in any child of PWS with growth failure, and in those in whom there is an insufficient response to GH therapy, to ensure that any aberrant thyroid function is not overlooked and adequately treated.

Keywords: Growth hormone, hypothyroidism, Prader-Willi syndrome, thyroid function

Background

Prader-Willi syndrome (PWS), first reported in 1956 by Prader, Labhart, and Willi, is a genetic syndrome with a variety of clinical manifestations[1] with implications on the endocrine system, metabolism, and behavior.[2] It is the most frequent form of syndromic obesity, and it influences both genders equally.[3] PWS results from a loss of a region of the 15q11-13 chromosome that is inherited paternally because of deletion, imprinting problems, maternal uniparental disomy, or chromosomal translocations.[4]

Clinical Features of PWS

PWS is distinguished by neonatal hypotonia that may continue through infantile age and feeding problems that result in a failure to thrive initially. Later, gaining an interest in food, followed by hyperphagia, which leads to weight gain at an early age that could easily progress to severe obesity. Other features include cognitive disorders, speech problems, psychiatric disorders, and characteristic dysmorphic features including facial manifestations such as small mouth associated with thin upper lip with downturned corners, palpebral fissures of upslanting nature, and small hands and feet.[5] The risk of PWS among a child's siblings with PWS is determined by the sort of molecular abnormality that causes PWS in that child. As a result, genetic testing is critical not only for confirming the diagnosis of PWS but also for determining the risk of recurrence in subsequent pregnancies.[6]

PWS patients have hypothalamic dysfunction, which can result in growth hormone (GH) deficit, central hypothyroidism, central adrenal insufficiency, hypogonadism, and low bone mineral density, among other endocrinopathies.[3] As a result, children with PWS need to be closely monitored by an endocrinologist throughout their lives, from the infantile period to adulthood.[2]

Hypothyroidism in PWS

The prevalence of hypothyroidism in PWS has been described in a variety of ways. According to some estimates, 20%–30% of patients are affected[7]; others,

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however, have observed that it is prevalent in just 2%–4% of the PWS population, which is comparable to healthy controls or the general population.[8,9] However, in a study of 18 children with PWS under the age of 2 years, Vaiani *et al.*[10] discovered low blood levels of total T4 and/or free T4 without a compensatory increase in serum thyroid stimulating hormone (TSH) in 72% of the studied infant patients, signifying that hypothalamic pituitary thyroid axis impairment is a prominent component in PWS throughout the infantile period.

Interestingly, when comparing PWS patients with healthy controls, Sharkia *et al.* reported no significant difference in total T4 and TSH levels on newborn screening of both groups. Furthermore, performing a thyrotropin-releasing hormone stimulation test in the same cohort of patients did not show any cases of central hypothyroidism.[9] According to this research, it is possible that central hypothyroidism does not exist at birth but develop later on; therefore, neonatal metabolic screening alone is insufficient to detect it[11] and it is strongly advised that thyroid function test ought to be performed during the first 3 months of child age and then every year after that, particularly if the patient was on GH medication.[12] Moreover, any PWS child with growth failure or decreased bone density, as well as those who do not respond well to GH therapy, should be tested for hypothyroidism.[12]

Thyroid hormone concentrations may be normal in PWS, but these observations could be confounded by the presence of obesity, which can cause a mild, reversible elevation of TSH,[7,13,14] and even later, anecdotal occurrences of congenital hypothyroidism in PWS neonates related to an ectopic sublingual thyroid gland and fetal goiter have been reported in the literature.[5]

From another point of view, as there is growing evidence that body composition has an impact on thyroid hormone levels,[15-17] thyroid function in PWS patients might be influenced by poor nutritional status, low body weight of children, and low body mass index, which are common in infants with PWS. As a result, during the infancy period, comparisons between PWS participants and healthy controls children may result in bias, leading to misreadings of thyroid function test in infants with PWS. Furthermore, because GH treatment has been reported to promote T4 to T3 conversion and lower T4 levels, a united evaluation of GH-treated and GH-untreated participants may result in thyroid hormone status misconceptions in PWS.[1]

Festen *et al.*[15] conducted a study of 79 children with PWS, which showed decreases in free T4 after starting GH treatment; however, TSH remained normal and total T3 levels were normal or in the high normal range implying that T4 to T3 conversion in PWS children has increased. This conclusion point sheds the light to the importance of assessing thyroid function before starting GH and regularly thereafter, while the patient is receiving GH treatment.

Conclusion

Hypothalamic dysfunction occurs in PWS patients, which can lead to a variety of endocrinopathies, including hypothyroidism. Moreover, some studies have reported the occurrence of congenital hypothyroidism in PWS. It is worthwhile to enlighten the importance of checking thyroid function in PWS patients at birth, at least annually, in those on GH treatment, in any child of PWS with growth failure, and in those in whom there is an insufficient response to GH therapy, to ensure that any aberrant thyroid function is not overlooked and adequately treated.

Ethical approval

Not applicable.

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Conflicts of interest

There are no conflicts of interest.

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