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An Outline on Rare Disorder : The Prader Willi Syndrome

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ABSTRACT

"PRADER LABHART WILLI SYNDROME" also known as Prader Willi Syndrome is an inbred genetic syndrome caused due to a lack in the expression of chromosome number 15q11.2-q13. It is followed by psychiatric, endocrinal, neurological as well as cognitive disturbances. Epidemiological data states that it is a rare syndrome affecting 1/15000-1/30000 population. Its major symptoms are hypotonia; which causes poor feeding and nourishment, hypogonadism which is characterized by underdeveloped pubertal development and gonads, adrenal insufficiency caused due to hypothalamic dysfunctions, hyperphagia and obesity caused by overeating, short stature, irresistible traits, and temper tantrums usually seen in the patients suffering from Prader Willi syndrome. Management of the syndrome by utilization of human growth hormone, continuous positive airways pressure, and Tube Feeding would help the patient in relieving the related symptoms.

KEYWORDS: Genetic, Growth Hormone, Hypogonadism, Prader-Willi Syndrome, Tube Feeding.

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KEY MESSAGES:

Prader Willi Syndrome is a very rare disorder occurring due to loss in functionality in parent-acquired chromosome no. 15. Growth hormone is the treatment option for GH deficiency, obesity and related complications; tube feeding is for infants who have poor sucking capacity; Continuous Positive Airways Pressure for sleep related disturbances.

INTRODUCTION

Prader–Willi syndrome is a rare genetic condition prevalently observed in 1/15000-1/30000 liveborn, occurring due to deficiency in expression of paternally acquired chromosome 15q11.2-q13 [(1)(2)(3)]. Its major symptoms include hypotonia, hypogonadism, improper secretion of growth hormone, psychological disturbances and, obesity(3).

Significant improvement in the long-term health and developmental growth of infants /children with PWS is possible if detected earlier by acquiring predictive guidance, expanding resources and recombinant human growth hormone (hGH) [(2)(4)].

The only technique that will diagnose and specialize PWS from Angelman syndrome is DNA Methylation Technique(5), which is performed using DNA methylation procedure targeting SNURF-SNRPN gene [(6)(7)(8)].

1. Clinical investigation:

Neonatal hypotonia, hypoplasia of the clitoris/labia minora in girls, and small penis/testis normally remain in the abdomen instead of descending normally into the scrotum in boys are the characteristics shown by the infants suffering from Prader Willi Syndrome. Infants are often found in the breech position at the time of delivery, with much reduced fetal activity when developed in the mother's womb.

Additional clinical features include dolichocephaly, almond-shaped eyes, declined angles of the mouth along with large amount of thick saliva, small hands and feet, neonatal head:

chest circumference ratio is elevated, confined bifrontal diameter(6).

Its major symptoms include

- Hypogonadism,
- Adrenal Insufficiency,
- Hyperphagia and Obesity,
- Short Stature,
- Diabetes and Glucose Metabolism,
- Sleep disturbances,
- Gastric disturbances.
- Hypotonia and abnormal neurological function

2.1. Hypogonadism:

Hypogonadism is an indication of underdeveloped pubertal organs, infertility which is clinically observed in both males as well as female[(1)(9)]. The common observation seen in males is hypoplastic wrinkled scrotum and generally have a small penis. About 80-90% of males show unipartite or bipartisan cryptorchidism. Hypo plasticity in a female is observed in the labia majora, labia minora as well as in clitoris. For about 20% of both males and females, precocious puberty occurs due to a rise in adrenal manifestation. Hypogonadism is an abnormal decrease in gonadotropin secretion affecting folliculogenesis in females due to low LH and estradiol levels and increased FSH and testosterone levels after puberty in males(1).

2.2. Adrenal Insufficiency:

In PWS, infants and adults are at higher threat to develop adrenal insufficiency with unclear recurrence. Unpredictable deaths occurring in PWS revealed detection with febrile or acute illness in 3 out of 4 children who had smaller adrenal glands except for the fourth child , whose adrenal weight was below normal.(2) (10).

It was stated that a pubescent male with Prader Willi syndrome may lead to adrenal insufficiency during a spine surgery which was resolved immediately after glucocorticoid administration(2)[2,11]. Growth hormone impedes the conversion of cortisone to cortisol through 11B-hydroxysteroid dehydrogenase type-1 (11ßHSD-1). A study on adrenal insufficiency revealed that almost 60% of children suffering from PWS were inadequately tested by overnight non-recurrent metyrapone testing. There were no changes in the baseline hormones of the one who tested sufficient but had a deficiency in the response to stress for the one who tested insufficiently(2) [2,12]. When tested with other approaches including different dosing of synacthen and the insulin tolerance test showed rare adrenal insufficiency with the highest percentage of about 14-15% [2,13-17].

2.3. Hyperphagia and Obesity:

The onset of obesity occurs between 1-4 years of age where the hypothalamic imbalance results in hyperphagia which led to the loss of hunger [3,18-21]. Centrally obesity occurs if the food intake is not controlled externally. In many cases, morbidity and mortality (death) occur due to the obesity-related complications including obstructive sleep apnea, thrombophlebitis, cardiorespiratory insufficiency, and chronic leg edema. 25% of obese adults were found with type-II diabetes mellitus (NIDDM) due to extreme obesity [3,22].

2.4. Short Stature:

Short Stature presented in childhood also remains after late childhood due to absence of growth hormone and lack of pubertal growth as well resulting in a typical height of 1.55 m and 1.48 m for males and females respectively. A reduced growth hormone secretion was observed according to 13 data from multiple studies that involved over 300 children and adults with PWS [3,23].

2.5. Glucose metabolism and Diabetes:

At age of 20 years, almost 25% of adults with BMI around 37kg/m2 suffering from PWS were reported with Type II diabetes mellitus [2,22]. Children with PWS were less frequent to develop diabetes, but 4% showed impaired glucose tolerance by Oral Glucose Tolerance Test in a study [2,24]. For diabetes and features of the metabolic syndrome, periodic scrutiny should be undertaken in obese individuals. Before initiating of hGH treatment in obese patients over 12 years of age, evaluation of diabetes risk is endorsed with periodic monitoring for those taking hGH treatment [2,25].

2.6. Sleep disturbances:

Trouble in sleep is common in all PWS patients regardless of their age and weight. Multiple sleep disturbances like Disrupted sleep organization, daytime sleepiness, extended nocturnal sleep, and sleep- disordered breathing (SDB) are generally observed in patients with Prader Willi Syndrome. Infant SDB is a sleep disorder with diminished or retarded ventilatory responses and arousal to asphyxia and hypercarbia [6,26-29]. While adult PWS patients have obesity-hypoventilation syndrome and obstructive sleep apnea [6].

Clinical Features of Sleep Disturbances:

Sleep-related problems include Daytime drowsiness and SDB as well as Abnormal sleep-wake organization but disordered REM cycle and SDB that occurs in early childhood [6, 30-32].

2.7. Excessive daytime sleepiness:

The most ubiquitous feature in PWS patients is Excessive daytime sleepiness (EDS) is reported in more than 90% of observed patients [6, 33-35]. Temper tantrums during the day were exhibited in patients who were found with EDS.

2.8. Sleep Disordered Breathing (SDB)

Sleep-disordered breathing including central apneas and recurrent breathing is being evidenced in the four months old infants suffering from Prader Willi Syndrome [6,30,31]. Sleep apnea of the obstructive type becomes more usual when obesity occurs for two years. Obstructive sleep apnea in PWS patients is directly linked to the stage of obesity and

conversely associated with age [36]. Even a slight elevation in Apnea-hypopnea index (AHI), oxygen desaturation is observed. The level of sleep-related oxygen desaturation may be serious with increasing BMI of PWS patients [37].

2.9. Gastrointestinal Issues:

Anomalous effluxes in ghrelin may lead to hyperphagia is normally observed in PWS. Low caloric and rational diet with attentive supervision and restriction to excessive food intake together with regularly programmed meals and activities are suggested [6,38]. Children with PWS has been found to have lower energy demand as compared to healthy adult [6,39-41]. Elevation in caloric load during the commencement of muscle-building phase may be needed when growth hormone replacement therapy is initiated, but once the lean mass gathering is balanced, reduction in caloric intake may again be required [6].

Decreased muscle tone, Poor oro-motor control, and uncontrolled eating with a restricted time for proper mastication of food may further result in choking or suffocation. Approximately 8% of all PWS deaths are accounted for due to choking incidents [6].

2.10. Hypotonia and abnormal neurological function:

Hypotonia is indicated by decreased and deviant fetal position, and increased abdominal delivery. Hypotonia may lead to poor sucking capability in infants, so feeding is promoted by an external tube or special nipples is mandatory. Hypotonia may get better, but with time a decrease in muscle tone is seen [3,42,43].

3. TREATMENT AND CARE

3.1. Growth Hormone:

The PWS patients have GROWTH HORMONE deficiency which covers from 40-100% according to the diagnostic criteria [2,24,44]. The clinical indications of GROWTH HORMONE(GH) deficiency include irregular body construction, short stature with obesity, decreased secretion of Growth Hormone, low insulin levels like IGF-1(insulin-like growth factor 1) [2,25]. Increased fat mass and decreased LBM are observed in PWS infants even after having a normal BMI when compared to normal children [2,45,46]. Recombinant human growth hormone (hGH) is used in the management of growth failure due to PWS, which was FDA approved in the US in the year 2000. Human growth hormone therapy can be utilized to increase motor performance as well, for which guideline for hGH therapy was published [2,25]. A cohort-controlled study collated children of age group 6-9 years who are on hGH therapy for up to 6 months to the same aged-matched children who are not treated with hGH [2,47]. The study revealed that the group which had been treated has significantly more lipid profiles, good motor strength and function, improved muscle mass, and lower body fat percentage (36% versus 45%). A remarkable enhancement in body structure and height was seen in the infants which are on hGH therapy for 30 months [2,48-54]. In studies up to 4 years of duration, improvements in hand and foot size, lipid profiles, motor function, fat utilization, and inspiratory muscle forces has been observed. Progressive hGH dosage is not dependent upon the total body fat [2,48,55,56,57].

Controlled studies of hGH therapy for about 1 -2 years aid in the development and perception of the brain. A marked increase in potency scores on progressive testing was observed in the patients who started hGH before 18 months [2,51]. Intelligent quotient (IQ) and Standard Deviation score (SDS) decreased in the normal group without treatment and remained steady in the hGH treated group, which is studied in a randomized controlled trial of prepubescent children and then increased when treated for four years [2,58].

There is no favorable or a specific age to start hGH, but the expert's concords to start it before the beginning of the obesity phase. Some experts advise starting hGH when the baby is newly born from almost three months [2,25]. A starting dose of 0.5 mg/m2/day. and further increase to 1 mg/m2/day is clinically recommended. For the positive effects in the body, a dose of at least 1 mg/m2/day hGH is required according to a randomized trial [2,38,59,25]. Even after the discontinuation of the hGH in childhood, its benefits may be carried on in adulthood. According to a study, improved body structure and metabolic status were observed in adults with a mean age of 25.4 years who were treated with hGH in childhood compared to the ones who were not treated. Lower mean hemoglobin A1c, lower mean insulin resistance index, less hypertension, a greater percentage with BMI <30 lower mean BMI were observed in the treated group [2].

The risk -benefit ratio of hGH treatment in this patient population is brought in light to recent studies. Depending on the agents used for the testing and the threshold GH level to define deficiency, the pervasiveness of GH deficiency in an adult with PWS ranges from 15%-95% [2,60,61]. A severe GH deficiency is 40%-50%, according to an average reported fact [2,62]. An increase in LBM, improved respiratory muscle function and decreased fat mass are the benefits of hGH therapy in adults with PWS when administered or treated for six months [2]. Edema was reported in several studies after the initiation of hGH, but it was not to a degree that led to the termination of the therapy. Regular testing is performed by agencies to diagnose GH deficiency before treating adults with PWS. A starting dose of 0.1- 0.2 mg/day in adults with the maintenance of IGF-1 levels between 0 and +2 Standard Deviation Score is recommended to attain beneficial effects of hGH with the lowest possible risk for unfavorable events [2].

Sudden death with hGH therapy in PWS has been observed. Almost 20 mortality cases were reported in children with Prader Willi syndrome who were treated with hGH but there is no such evidence proving the interconnection between sudden demise and hGH therapy

[2,63]. Within the 9 months of initiation to hGH therapy, almost 75% of the deaths occurred [2,64]. Sudden death due to hGH therapy may further lead to respiratory-related problems.

3.2. Tube Feeding:

Tube Feeding is done in new borns for approximately two months due to poor sucking capacity and hypotonia which may fail to thrive (FTT) . There is no concord regarding the use of tube feeding, whether it is compulsory or should be used only after intensive nursing fails. Long-term cardiovascular and metabolic problems are the cause of obesity during initial two years of life in non-PWS, proper care should be taken about overfeeding in PWS infants [65,66].

3.3. Superintending sleep disorders:

Because of the high ubiquity of sleep disturbances evaluation of sleep in all patients suffering from Prader-Willi syndrome should be regularly considered. Polysomnogram is required to rule out sleep- disordered breathing patients who are frequent snorers or sleepy during the day. The patients are more prone to the adverse effects of sleep-related breathing, who are been treated with growth hormone (GH) [6,67].

During the first nine months of GH treatment, SDB and respiratory tract related infection are salient in male patients [6,64]. So, an overnight sleep study is advisable before initiating GH therapy to eliminate sleep-disordered breathing.

Continuous Positive Airways Pressure (CPAP) or BiPAP is the gold standard treatment for sleep apnea in adults. While in children, first-time treatment would be adenoidectomy, tonsillectomy, or adenotonsillectomy. One of the approaches in Obesity hypoventilation syndrome is supplemental oxygen. Implementation of sufficient sleep hygiene, sleep-wake cycle management, and circadian rhythm refinement will help in managing sleep disturbances. A Multiple Sleep Latency Test (MSLT) is also indicated in patients who are suffering from excessive daytime sleepiness [6].

CONCLUSION

While there is no cure for Prader-Willi syndrome, developing quality of life is essential. The early usage of GH has ameliorated adult height, body structure, and muscle strength in patients. The main risk elements for death in patients with PWS are obesity and related consequences. So, by improvising the routine lifestyle of PWS patients, chances of associated complications would be less [6,68].

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