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Prader-Willi Syndrome: A Comprehensive Review

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Abstract: *Prader-Willi syndrome (PWS) is a multisystem genetic disorder caused by the loss of paternally expressed genes on chromosome, that can lead to a wide array of symptoms, including obesity and developmental delays. It is caused by genetic changes on an "unstable" region of chromosome 15 that affects the regulation of gene expression. It has mostly occurred in babies whose mothers age is over 35 years of age. It mostly causes developmental delay and intellectual disability, behavioural difficulties, hyperphagia and obesity with food behavioural anomalies. It only diagnosed with genetic counselling. There is currently no treatment for this syndrome, treatment focussed on managing symptoms and improving quality of life through early intervention and with behavioural therapies.*

Key Words: *Prader-Willi syndrome (PWS), Genetic Disorder, Children.*

1. INTRODUCTION

Prader-Willi syndrome (PWS) is a rare, multisystem genetic disorder caused by the loss of paternally expressed genes on chromosome.[1] The disease was first described in 1956 by Swiss doctors Andrea Prader, Heinrich Willi and Alexis Labhart. The description concerned nine patients, who were diagnosed with growth deficiency, obesity, mental retardation, and small hands and feet[2].

PWS has a prevalence of 1 in every 20,000 to 30,000 births.[3] Worldwide, around 400,000 individuals are affected, with 20,000 residing in the United States. This condition stands as the most prevalent genetic cause of life-threatening obesity.[4] Both females and males are equally affected, with no discernible differences noted among racial and ethnic groups.[5]

PWS is a complex multisystem disorder, characterized by neonatal hypotonia and feeding difficulties in early infancy, short stature, behavioural problems, cognitive impairment, psychiatric illness, dysmorphic features (characteristic facial appearance, small hands and feet, narrow hands with straight ulnar border, scoliosis), multiple endocrine abnormalities (hypogonadism, growth hormone [GH]/insulin-like growth factor-I axis dysfunction, hypothyroidism, central adrenal insufficiency), early development of hyperphagia with food seeking behaviour, and progressive development of severe obesity, unless eating is not promptly restricted.[6]

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2. OBJECTIVES:

Objective of the study was to review available information regarding definition, causes and risk factors, pathogenesis, clinical manifestations, diagnostic evaluation, management and prognosis of Prader -Willi syndrome.

DEFINITION:

Prader-Willi syndrome (PWS) is a genetic disorder that can lead to a wide array of symptoms, including obesity and developmental delays. It results when there is a problem with a portion of chromosome 15.7

3. CAUSES AND RISK FACTORS

Causes

Prader-Willi syndrome is caused by genetic changes on an "unstable" region of chromosome 15 that affects the regulation of gene expression, or how genes turn on and off. The genetic changes that cause Prader-Willi syndrome occur in a portion of the chromosome, referred to as the Prader-Willi critical region (PWCR), around the time of conception or during early foetal development. Although Prader-Willi syndrome is genetic, it usually is not inherited and generally develops due to deletions or partial deletions on chromosome 15.[8]

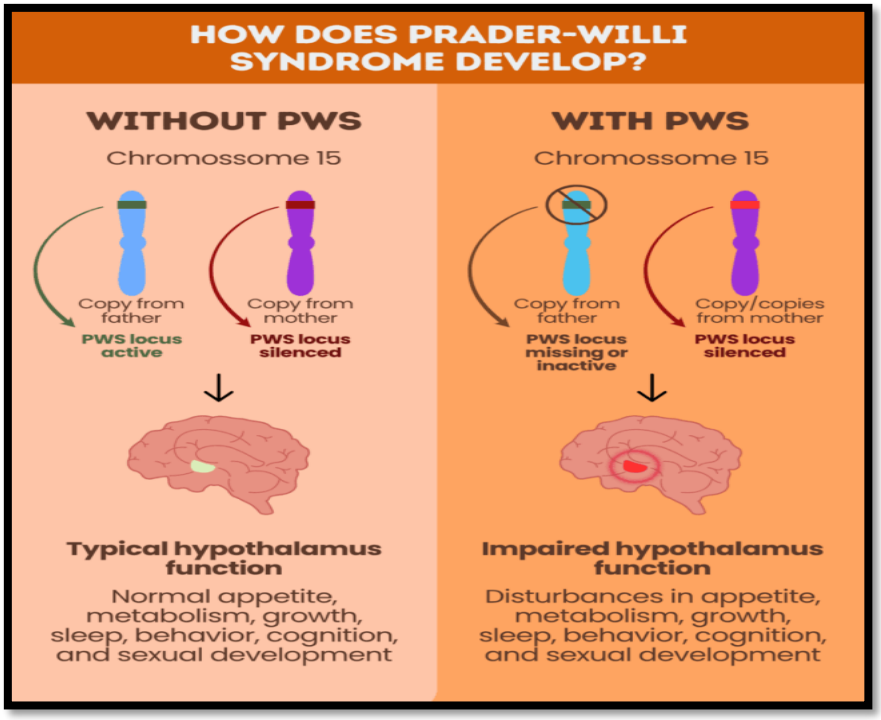

Figure-1 Picture showing changes in Chromosome 15

RISK FACTORS

Subtypes: Patients with PWS presenting with maternal disomy 15, having isodisomy or segmental isodisomy forms, are known to be at risk for the development of secondary genetic conditions that involve recessive genes on chromosome 15 if the mother is a recessive gene carrier.

Maternal Age: mothers over 35 years of age can also lead Prader-Willi syndrome.

Environmental Conditions: There is an increased risk for paternal chromosomal deletions due to environmental reasons, such as occupational exposure, drug use, and infections. Hydrocarbons are mostly known to induce chromosomal defects.

Assistive Reproductive Technology: Reported a significantly increased proportion of maternal disomy 15 and imprinting defects in the child conceived through ART.

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4. PATHOGENESIS:

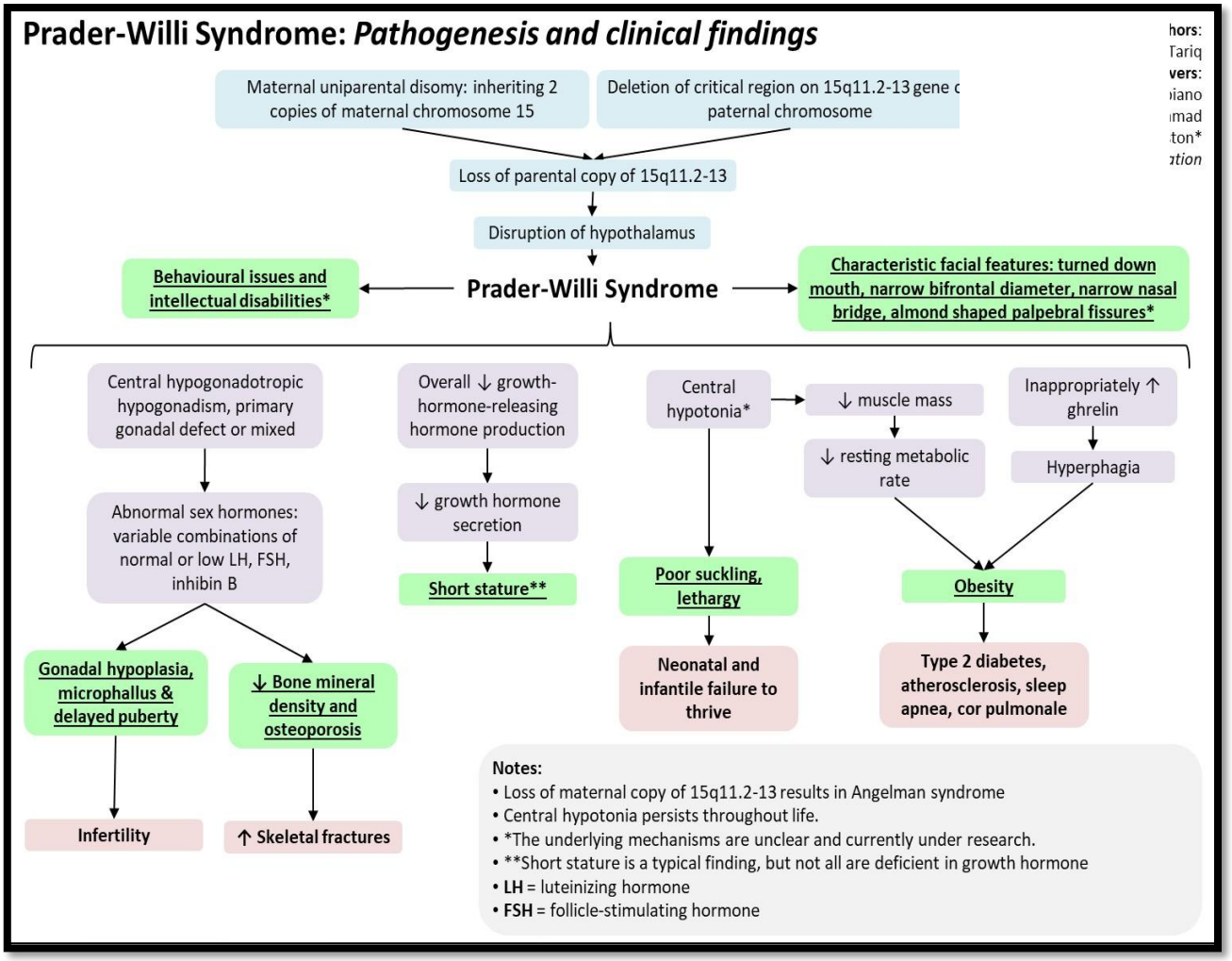

Figure2: Prader Willi syndrome pathogenesis[9]

5. CLINICAL MENIFESTATION:

Neonate and infant

- Severe hypotonia (can also be present in the foetus and may present as reduced foetal movements).
- Poor sucking ability, lethargy and failure to thrive. Feeding difficulties generally improve by six months of age.

Childhood

- Developmental delay and intellectual disability.
- Behavioural difficulties (obsessive-compulsive disorder, temper tantrums, stubbornness).
- Hyperphagia and obesity, with food behavioural anomalies that include persistence in asking for extra food, food seeking, hoarding and stealing (either food or money to buy food) and the eating of inappropriate substances (not food).
- Weight increase can occur from two years to four and a half years, before the onset of hyperphagia.
- Hyperphagia increases between four and a half years and eight years and, if access to food is not controlled, there will be weight gain and morbid obesity.
- Hypothalamic hypogonadism (genital hypoplasia, incomplete pubertal development and usually infertility).

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- Short stature.
- Small hands and feet.

Facial features

Characteristic facial features include:

- almond-shaped eyes;
- thin upper lip and narrow nasal bridge;
- high prominent forehead; and
- narrow bifrontal diameter.[10]

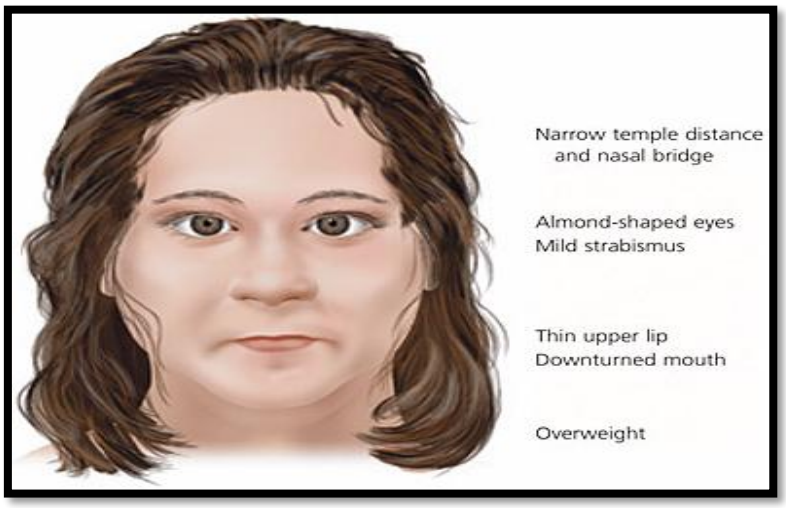

Figure3: Characteristic facial features in a person with Prader-Willi syndrome.[11]

6. DIAGNOSTIC EVALUATION:

Genetic testing is mainly done to check the chromosomes in a sample of a child's blood for the genetic changes known to cause Prader-Willi syndrome.[12]

The following criteria for a diagnosis of Prader-Willi Syndrome are based on Holm et al. (Paediatrics 91, 398, 1993). Because infants and young children have fewer symptoms than older children and adults with PWS, the scoring system differs by age group.

Major Criteria (Count as 1 point each)

1. Neonatal and infantile central hypotonia with poor suck, gradually improving with age.
2. Feeding problems in infancy with need for special feeding techniques and poor weight gain/failure to thrive.

3. Excessive (crossing two centile channels) or rapid weight gain on weight-for- length chart after 12 months and before age 6; central obesity in the absence of intervention.

4. Characteristic facial features with dolichocephaly in infancy, narrow face or bifrontal diameter, almond-shaped eyes, small-appearing mouth with thin upper lip, downturned corners of the mouth (three or more of these characteristics required).

5. Hypogonadism-includes any of the following, depending on age: a) Genital hypoplasia (in males: scrotal hypoplasia, undescended testes, small penis and/or testes; in females: absence or severe hypoplasia of labia minora and/or clitoris). b) Delayed or incomplete gonadal maturation with delayed pubertal signs after age 16 (in males: small gonads, decreased facial and body hair, lack of voice change; in females: no or infrequent menses).

6. Global developmental delay in a child younger than 6 years; mild to moderate mental retardation or learning problems in older children.

7. Hyperphagia (excessive appetite)/food foraging/obsession with food.

8. Deletion 15q 11-13 (>650 bands, preferably confirmed by fluorescence in situ hybridization) or other appropriate molecular abnormality in this chromosome region, including maternal disomy.[13]

Sum of Major Criteria Points:_____

Minor Criteria (Count as 1/2 point each.)
1. Decreased foetal movement or infantile lethargy or weak cry in infancy, improving with age.
2. Characteristic behaviour problems, temper tantrums, violent outbursts, and obsessive/compulsive behaviour; tendency to be argumentative, oppositional, rigid, manipulative, possessive, and stubborn; perseverating, stealing, and lying (five or more of these symptoms required).

3. Sleep disturbance or sleep apnoea.

4. Short stature for genetic background by age 15 (in absence of growth hormone intervention)

5. Hypopigmentation-fair skin and hair compared with other family members.

6. Small hands (less than 25th percentile) and/or feet (less than 10th percentile) for height age.

7. Narrow hands with straight ulnar border (outer edge of hand).

8. Eye abnormalities (esotropia, myopia).

9. Thick, viscous saliva with crusting at corners of the mouth.

10. Speech articulation defects.

11. Skin picking.

Sum of Minor Criteria Points:_____

SUM OF MAJOR AND MINOR CRITERIA POINTS: _____

Requirements for a Diagnosis of PWS: From Birth to Age 3: Five (5) total points are required, of which four (4) must be from the major criteria list. Age 3 to Adulthood: Eight (8) total points are required, including at least five (5) from the major criteria list.[14]

7.MEDICATIONS

Medications play a pivotal role in managing specific aspects of PWS, addressing both physical and behavioural challenges. Common medications that may be used to treat symptoms of Prader-Willi syndrome include:

Human Growth Hormone (HGH) Treatment

Human growth hormone (HGH) treatment is a cornerstone in the management of Prader-Willi syndrome. Children with PWS often exhibit growth hormone deficiency, leading to short stature and other associated issues. HGH treatment involves the administration of synthetic growth hormone, promoting linear growth and helping to normalize body composition. Beyond height improvements, HGH treatment contributes to muscle development and overall well-being.

Sex Hormone Treatment

As individuals with PWS enter puberty, sex hormone treatment may be considered. Hormonal imbalances can affect the development of secondary sexual characteristics, bone density, and overall reproductive health. Sex hormone treatment aims to address these imbalances, supporting a more typical pubertal development and mitigating associated complications.

Weight & Diet Management

Weight management is a critical aspect of caring for individuals with Prader-Willi syndrome. PWS is often characterized by an insatiable appetite, leading to excessive weight gain and obesity. Implementing a carefully monitored and

controlled diet is essential. Caloric intake must be regulated to prevent excessive weight gain, and dietary interventions are tailored to individual needs. The collaborative efforts of healthcare providers, nutritionists, and families play a crucial role in maintaining a healthy weight for individuals with PWS.

Educational Therapy

Education therapy takes centre stage in addressing the cognitive and developmental aspects of Prader-Willi syndrome. Tailored educational approaches are designed to meet the unique learning profiles of individuals with PWS. Educational interventions may include individualized education plans (IEPs), specialized educational services, and strategies to enhance academic success. The focus is on fostering cognitive development, optimizing learning potential, and providing a supportive educational environment.

Treatment Therapies

As with many disorders that affect physical and cognitive development, there are a number of therapies that emerge as options when looking for treatments for individuals with PWS. These therapies can help regulate a number of symptoms and may be recommended by a doctor or a specialist depending on your child's unique situation.

Cognitive Behavioural Therapy (CBT)

Cognitive behavioural therapy (CBT) is a valuable therapeutic approach for managing behavioural challenges associated with Prader-Willi syndrome. Individuals with PWS may exhibit obsessive-compulsive behaviours, anxiety, and difficulties with impulse control. CBT aims to identify and modify maladaptive thought patterns and behaviours, foster adaptive coping strategies and promote emotional well-being.

Physical Therapy

Physical therapy plays a crucial role in addressing the musculoskeletal challenges often present in individuals with Prader-Willi syndrome. Reduced muscle tone, joint laxity, and motor coordination issues can impact mobility and functional independence. Through targeted exercises and interventions, physical therapy contributes to improved mobility and quality of life.

Speech-Language Therapy

Speech-language therapy is essential for individuals with Prader-Willi syndrome who may encounter challenges in speech and language development. Speech therapists work to enhance communication skills, address articulation difficulties, and support overall language development.[15]

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