IPWSO
International
Prader-Willi Syndrome
Organisation

Adolescents (12-18 years) with Prader-Willi syndrome

Medical care: Overview
Medical Care: Evaluation

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ADOLESCENT (12-18 years) MEDICAL CARE FOR PRADER-WILLI SYNDROME
Guidance for Physicians

Prader-Willi syndrome (PWS) is a rare, complex, multisymptomatic genetic disorder with many neurodevelopmental and behavioural manifestations that emerge during childhood and adolescence. PWS is due to loss of paternally inherited genetic information on chromosome 15, or the ability to express it, caused by one of three genetic changes (paternal deletion at chromosome 15q11.2-q13; maternal uniparental disomy 15; an imprinting defect on chromosome 15). A DNA methylation analysis confirms the diagnosis in >99% of cases. The main symptoms are severe neonatal hypotonia and need for tube feeding weeks to months, general developmental delay (motor and cognition) and symptoms related to hypothalamic dysfunction, including hyperphagia from early age, growth hormone deficiency, hypogonadism, and abnormal pain and temperature responses.

This document summarises the main challenges and health care needs for adolescents with PWS. Annual medical examinations and blood tests are essential. Contact with several specialists is often necessary. Adolescence is a critical period when hyperphagia and behavioural issues may emerge or worsen.

General Health Issues:

- Adolescents with PWS may not be able to accurately communicate that they are ill, and a change in level of alertness or behaviour may be the best indicators. Pyrexia and vomiting may be absent, and pain under-expressed.
- Hyperphagia, the drive to seek and eat food, leads to obesity unless food access is restricted. Managing such restrictions across all the environments where adolescents live their daily life can be challenging. To avoid obesity, environmental controls and/or supervised food access is necessary. FOOD SECURITY (the knowledge that food will be provided on a predictable schedule) helps with the psychological internalisation of controlled food access and decreases disappointment that can lead to tantrums. The goal is to achieve the understanding “I know what I will eat, how much I will eat and when I will eat it. I know that I will not obtain food at any other time. I accept these limitations and I am content.”
- Health risks associated with obesity include Type 2 diabetes, metabolic dysfunction-associated fatty liver disease (MAFLD), metabolic syndrome, obstructive sleep apnoea with hypoxemia and hypercapnia, obesity-associated hypoventilation, lymphedema, skin changes in the legs, cardiac insufficiency and dyspnoea on minor exertion. Unexplained impaired exercise tolerance should prompt cardiological assessment.
- Autonomic nervous system-related dysfunction includes temperature dysregulation, decreased pain perception, gastrointestinal dysfunction including dysphagia, emptying

of the bladder, reduced heart rate variability and decreased elevation of pulse and blood pressure during exercise.

Motor Function and Energy Needs:

- Fine and gross motor delays, first apparent during infancy and childhood. They persist through adolescence, especially gross motor function and balance, but with individual variations. Motivation for physical activity is usually low but beginning and maintaining a "family culture" of activity early can help create healthy habits.
- Hypotonia and decreased muscle mass cause decreased energy utilisation (body fat>lean muscle mass) and impair function of skeletal muscles, cardiac muscles and smooth muscles.
- In general, the energy need of a child/adolescent with PWS is only 60-80% of the typical caloric needs/cm height (or about 8-10 kcal/cm/day) due to small lean body mass and low motor activity. Weekly weight measurement, daily physical activity (at least 1 hour per day), and an individualised plan for meals are recommended.

Hormone Deficiencies and Hormone Replacement:

- Growth hormone (GH) deficiency is nearly universal in persons with PWS and should be treated from infancy throughout the developmental period to improve skeletal growth, body composition, strength, and quality of life. Regionally depending, most adolescents with PWS will have been receiving GH for many years and have experienced normalisation of the typical facial and body dysmorphisms associated with PWS. There is growing evidence that GH treatment should continue in adulthood, but the GH dose should be reduced to achieve adult levels when final height has been reached. In many countries re-testing for growth hormone deficiency is required. However, some countries permit continuing low dose GH in adults with PWS.
- Hypothyroidism is diagnosed in about 15%. Adrenal insufficiency is rare. For the few adolescents treated with cortisone for adrenal insufficiency, it is important to increase the cortisone dose during illness.
- Hypogonadism is very frequent and often apparent in early adolescence when the onset of puberty is delayed. Puberty involves two biological components, *adrenarche*, and *gonadarche*. Adrenarche, which typically begins between ages 6 and 9, during which the levels of adrenal androgens (e.g., dehydroepiandrosterone and its sulfate) begin to increase resulting in axillary and pubic hair, whereas gonadarche typically begins in early adolescence, at approximately ages 9 to 11, when the levels of LH-FSH and gonadal sex hormones (e.g., testosterone and oestrogens) begin to increase resulting in genital and in girls breast development. Individual evaluation is needed, and slow

gradual titration of sex hormone replacement is recommended, monitoring mood and behavioural adjustment. Sex hormones are important for growth, general well-being, and to slow the loss of bone density.

- Guidance is needed for surrounding issues of sexuality, particularly where they pertain to risk of sexual exploitation in exchange for food or other favourite items, exposure to sexually transmitted diseases, and gender specific issues of fertility. Pregnancy has been reported in 12 women with PWS worldwide. Genetically, if the mother has the deletion genotype, the baby has a 50% chance of having Angelman syndrome or of being unaffected. If the mother has the UPD genotype, she will pass on a normally imprinted maternal chromosome 15 and will have the same chance as a non-PWS woman of having a non-PWS baby. In the few reports of completed pregnancies in PWS, the mothers were unable to breast feed or properly care for their infants. The use of contraception in adolescent girls is recommended. Males with PWS are presumed to be infertile, and there are no reports of one fathering a child.
- Premature adrenarche is common but should not be confused with precocious puberty, which is rare but may occur in PWS.

Oral, Gastrointestinal and Bladder Issues:

- Dental caries is common due to reduced salivation and poor self-care. Gastric reflux can erode tooth enamel, and bruxism can abrade the tooth surface.
- Swallowing problems due to oesophageal dysmotility often lead to aspiration which can be misattributed to reflux and rumination, as those conditions also occur frequently in PWS. The "Pace and Chase" feeding protocol is recommended to aid safe oesophageal transit.
- Many suffer from constipation ascribed to motility problems throughout the gastrointestinal system (for further information see Bristol Stool Chart).
- Delayed gastric emptying predisposes to gastric distention, occurring most alarmingly in instances of overeating, but also associated with constipation, dietary change, infections, or anaesthesia. Symptoms may deceptively be few, a change in behaviour and abdominal distention are early signs. Vomiting is a late sign of gastroparesis and may signal critical circumstances. Medical evaluation should include a careful history and physical with a low threshold to proceed with an abdominal radiograph, computerised tomography (CT scan), and prompt intervention. Decompressing the stomach with a nasogastric tube can be lifesaving, as gastric overdistension can lead to gastric necrosis, followed by a catastrophic gastric rupture.
- Enuresis can be caused by low bladder tone, inability to feel fullness, and inability to empty the bladder completely.

Bone Health:

- Spinal deformities of scoliosis, kyphosis and kyphoscoliosis have a prevalence of nearly 25% by 4 years of age, increasing to 60-70% by the end of adolescence. Yearly clinical spine examinations and radiographs of the back should be performed until 4 years of age, followed by yearly clinical examinations, obtaining radiographs for any observed spinal asymmetry.
- People with PWS characteristically have low bone mineral density for age (Z-score), worsening during adolescence. Heightened pain threshold and decreased ability to identify the anatomical source of discomfort are characteristics of PWS, putting them at risk for unappreciated injury. Findings of limping, swollen extremities or vague complaints of pain should be evaluated with a radiograph to check for traumatic or stress fractures.

Sleep Issues:

- Sleep problems with sleep/wake disturbances (difficulty staying asleep at night, excessive daytime sleepiness) are frequent. Pulse oximetry and sleep studies may reveal sleep apnoea (obstructive and/or central). Continuous positive airway pressure (CPAP) may be required, especially for obstructive sleep apnoea that is exacerbated by overweight/obesity. Bi-level positive airway pressure (BiPAP) may be required for central sleep apnoea and hypoventilation. A multiple sleep latency test (MSLT) is required for a diagnosis of narcolepsy; cataplexy (episodic sudden loss of muscle tone while awake) may also occur.

Mental Health and Behavioural Challenges:

- Common phenotypic behaviours are disruptive behaviour, excessive/repetitive behaviours, cognitive rigidity, perseverance, difficulty with transitions, social skills problems. Those behaviours increase with stress. Skills to increase coping strategies can be taught to adolescents and their caregivers and should be practiced together, so that they can be implemented on cue.
- Skin picking is a common characteristic of PWS, which can be related to stress but can also be a habit. It can result in serious infections, in particular protection of surgical scars is crucial. Rectal picking may be caused or worsened by constipation and result in rectal bleeding or even a rectal ulcer, causing chronic anaemia; colonoscopy may misdiagnose this for other bowel disease e.g. ulcerative colitis. Bleeding from vaginal picking can be misinterpreted as menses. Management is difficult but may include behavioural modification. For some N-acetyl cysteine might have an effect.

- Cognition and learning are delayed with great variations. Short term memory is usually more impaired than longer time memory. Many have a much better visual memory than memory of what is only heard. Processing speed can be delayed and misinterpreted as oppositional behaviour. Social communication and understanding the nonverbal communication of gestures and facial expressions can be impaired and interfere with social interaction with peers. Executive function is impaired and rarely equal to intellectual ability. Emotional development is very immature and can be the cause of behavioural problems. Autonomic nervous system-related dysfunction includes temperature dysregulation, decreased pain perception, gastrointestinal dysfunction, reduced heart rate variability and decreased elevation of pulse and blood pressure during exercise.
- Psychosis and/or bipolar disorders can arise unexpectedly or gradually with stress. Hallmarks may include a change in mood, muscular rigidity or waxy flexibility, hallucinations, delusions or confusion, failure to eat or sleep, and loss of ability to perform grooming or dressing activities. Prompt medical and psychiatric evaluation is required. A sudden change in behaviour can deceptively be also caused by physical illness, with a lack of clinical symptoms, and requires a thorough evaluation prior to exclusion.

Additional Issues:

- Central temperature regulation might be faulty in those with PWS because of hypothalamic dysfunction, resulting in either hyperthermia (fever of unknown origin), or a lack of febrile response or even hypothermia despite severe infections. Because of deficient peripheral sensors for body temperature, they may bathe or shower in too hot or cold water or may wear too little clothing in the cold weather and too much clothing when it is warm. Behavioural rigidity to change impairs seasonal adjustment of clothing.
- Many adolescents with PWS have a desire for romantic relationships, but the associated interpersonal conflict may be too stressful for them. Most such relationships are pregenital with kissing, hand holding, and role identification as “boyfriend” or “girlfriend”. Both males and females with PWS have voiced fantasies of marriage and expressed the desire to have a baby. A strategy to help mitigate disappointment and channel the emotions is substitution, such as playing with dolls, working with animals, and spending time with children in their family. Some adolescents become fixated on a love object (real or imagined) who does not reciprocate their affection. The emotional turmoil may require psychological or psychiatric evaluation and treatment. Because adolescents have more freedom with exposure to the community and the internet, this can create difficult desires and behaviour that demands more attention and support.

Evaluating a new adolescent patient with PWS requires a comprehensive medical history and complete physical examination, with emphasis on the following:

- Make sure the diagnosis of PWS was confirmed by appropriate genetic testing as recommended by a medical geneticist. If not, a referral to a medical geneticist is appropriate, for confirmatory testing and subsequent family genetic counselling about recurrence risk.
- Obtain height and weight, and calculate the body mass index (BMI, kg/m^2) and track using gender and ethnic BMI chart. All measurements should be plotted on the appropriate growth curves for adolescents with or without growth hormone.
- Obtain standard vital signs: blood pressure and heart rate, and make a careful clinical examination of heart, lungs and abdomen.
- Observe the quality of interpersonal interaction, such as alertness, capacity to engage and sustain eye contact, and ability to establish rapport.
- Listen to the quality of speech, such as hypernasality and articulation, and the quality of communication ability and intelligibility, the capacity to express wants and needs.
- Inspect the teeth for signs of bruxism and decay; erosion of enamel may indicate issues with gastric reflux.
- Inspect the back while standing for kyphosis, and with forward bending for asymmetries that could indicate scoliosis.
- Watch the patient walking barefoot to assess gait fluidity and the severity of their pes planus. Severe pes planus inhibits efficient walking and may require corrective orthotics.
- Lower extremity
    - Assess joint range of motion for mobility problems
    - Examine for signs of leg oedema, pitting may indicate heart failure, non-pitting may indicate lymphedema. Ulcers may develop from skin picking or infection
- Integument – examine skin, intertriginous folds, perianal areas for scars, active picks, open sores, ulcers, infections, acanthosis nigricans.
- Genitals – assess pubertal status; Tanner staging (rarely progresses beyond stage III)
- Rectum – inspect for fissures, rectal bleeding, evidence of rectal picking.

Blood tests (yearly):

- Measurements of haemoglobin, haematocrit, white blood cell and platelet count, sodium, potassium, BUN, creatinine, liver function, 25-hydroxyvitamin D, calcium, Glycosylated haemoglobin (haemoglobin A1C), fasting blood glucose and blood lipids. An oral glucose

tolerance test (OGTT) is more sensitive for detecting insulin resistance. Measurement of insulin can be considered.

- Hyponatremia may suggest excessive fluid intake or syndrome of inappropriate anti-diuretic hormone secretion (SIADH), a recognised side effect from psychotropic medications and/or mood stabilising anticonvulsants. Symptoms range from mild nausea and headache to confusion, seizures, and coma in severe cases.
- Thyroid stimulating hormone (TSH), free thyroxine (FT_4)
- Insulin-like growth factor (IGF-1) for those treated with growth hormone, confirming dose and compliance.
- Males – serum testosterone, luteinising hormone (LH), follicular stimulating hormone (FSH). Assessments are typically started between 8 and 13 years of age.
- Females – serum oestradiol, luteinising hormone (LH), follicular stimulating hormone (FSH). Assessments are typically started between 9 and 13 years of age.
- In both, male and female receiving no sex hormone replacement, serum Inhibin B level, correlates positively with fertility, in particular women with higher level (>20 ng/L). Low Inhibin B levels in conjunction with high FSH levels in women suggest diminished ovarian function.

Recommended Clinical Diagnostic Tests

- Radiograph (X-ray) of back either standing or sitting, both anteroposterior and lateral, for scoliosis/kyphosis at initial evaluation; yearly until the patient has reached skeletal maturity, as per closed epiphyses and whenever there are clinical signs of a spinal asymmetry. After skeletal maturity, radiographs every 1-4 years as an adult, if the scoliosis curve is over 35°. If the curve is found to progress over 50° in adulthood, the patient should be referred to an orthopaedic surgeon for consultation. Ask the radiologist to comment on the amount of stool in the abdomen.
- Bone age (determined by a radiograph of the left hand) is compared to chronological age to determine how fast the skeleton is growing, usually in association with growth hormone treatment until near adult height is achieved (bone age 16-16.5 years or growth less than 2 cm per year).
- Dual energy X-ray absorptiometry (DEXA) after skeletal maturity, then every 4-5 years if bone density within 2 SD of the mean.
- Bio-impedance every year to assess body composition.
- Polysomnography to rule out sleep apnoea and obesity-hypoventilation syndrome, especially with recent weight gain; multiple sleep latency test (MSLT) for excessive daytime sleepiness to rule out narcolepsy; or re-evaluation by sleep medicine for adjustment of

settings on continuous positive airway pressure (CPAP) or bi-level positive airway pressure (BiPAP).

Recommended Clinical Consultations and/or Counselling

- Bi-annual vision evaluation; referral to ophthalmology for suspected refractive error.
- Hearing evaluation, if not done before.
- Evaluation by an endocrinologist to discuss sex hormone therapy.
- Discuss need for gynaecological care for girls, family values regarding sex, risk of pregnancy, and sexually transmitted diseases (STD's).
- Consultation including parents/carers with a dietician (or equal) every 4-6 months, assuring knowledge of PWS requirements for nutrition and weight management.
- Physiotherapy assessment of joints, muscles and recommendations for motor activities and suitable exercise for energy expenditure.
- Occupational therapy consultation for developmentally appropriate sensory motor stimulation (sensory diet).
- Consider appropriateness of school placement with respect to curriculum, vocational programming and future supportive employment.
- Consider referral to psychology or psychiatry for evaluation and treatment of behaviour or mood problems.

Future Planning:

Emotionally and socially, adolescence can be a difficult time, with the anticipation of the end of school. The future for work and living must be carefully planned. Hyperphagia and behaviour problems do not lessen with age, and personal support will always be needed.

- Discuss need for establishing legal guardianship once the child has reached the legally defined age of adulthood.
- Discuss future residential care options with the parents.
- Discuss future financial status and administrative guidance for obtaining government funding and subsidies.

Medication:

- Adolescents with PWS may be receiving a variety of psychotropic medications and over the counter supplements. They may have an increased sensitivity to drugs; therefore, a low starting dose is suggested, especially for antihistamines and psychotropic drugs.

More information can be found on the International Prader-Willi Syndrome Organisation (IPWSO) website that includes information about family support organisations in over 100 countries: http://www.ipwso.org

Advice in acute situations: for health professionals and families: https://ipwso.org/information-for-medical-professionals/important-medical-facts/

A source of detailed information about PWS on the internet is in GeneReviews: https://www.ncbi.nlm.nih.gov/books/NBK1330/