Review Article

J Mucopolysacch Rare Dis 2021;5(1):29-33
https://doi.org/10.19125/jmrd.2021.5.1.29
pISSN 2465-8936 · eISSN 2465-9452

JMRD
Journal of Mucopolysaccharidosis and Rare Diseases

Behavioral Problems in Patients with Prader-Willi Syndrome

Sung Won Park

Division of Pediatrics Endocrinology, Department of Pediatrics, Gangseo MizMedi Hospital, Seoul, Korea

Prader-Willi Syndrome (PWS) is a neurodevelopmental genomic imprinting disorder involving a lack of gene expression from the paternal chromosome 15q11-q13 region. This is typically due to paternal 15q11-q13 deletions (in approximately 60% of cases), maternal uniparental disomy 15, or when both 15s are from the mother (about 35% of cases). An imprinting center controls the expression of imprinted genes in the chromosome 15q11-q13 region. PWS is a neurodevelopmental disorder characterized by mental retardation and distinct physical, behavioral, and psychiatric features. Characteristic behavioral disturbances in PWS include excessive interest in food, skin picking, difficulty with a change in routine, temper tantrums, obsessive and compulsive behaviors, and mood fluctuations. Individuals with PWS typically have intellectual disabilities (borderline to mild/moderate mental retardation) and exhibit a higher overall level of behavior disturbances compared to individuals with similar intellectual disabilities. This condition severely limits social adaptations and quality of life. Different factors have been linked to the intensity and form of these behavioral disturbances, but there is no consensus regarding the cause. Consequently, there is still controversy surrounding management strategies and there is a need for new data. PWS is a multisystem disorder. Family members, caregivers, physicians, dieticians, and speech-language pathologists all play an important role in the management and treatment of symptoms in an individual with PWS. Here we analyze behavioral problems in children and adults with PWS by age and review appropriate management and treatment strategies for these symptoms.

Keywords: Behavior disturbances, Prader-Willi syndrome

Introduction

Prader-Willi Syndrome (PWS) is a rare, complex, multisystem genetic disorder recognized as the most commonly known genetic cause of life-threatening obesity in humans[1]. PWS is a neurodevelopmental genomic imprinting disorder involving a lack of expression of genes inherited from the paternal chromosome 15q11-q13 region. This is usually due to paternal 15q11-q13 deletions (~60%), maternal uniparental disomy 15, or in cases of both 15s from the mother (~35%). An imprinting center controls the expression of imprinted genes in the chromosome 15q11-q13 region[2].

Individuals with PWS typically have intellectual disabilities (borderline to mild/moderate mental retardation) and exhibit a higher overall level of behavior disturbances compared to individuals with similar intellectual disabilities[3]. This condition severely limits social adaptation and the patient's quality of life. Different factors have been linked with the intensity and form of these behavioral disturbances, but there is no consensus regarding the cause. Consequently, there is still controversy regarding management strategies, and new data is needed[4].

PWS is a multisystem disorder. Family members, caregivers, physicians, dieticians, and speech-language pathologists all play an important role in the management and treatment of symptoms in an individual with PWS[5].

The objective of this review is to analyze behavioral problems in children and adults with PWS by age and review appropriate management and treatment of these symptoms.

Received May 20, 2021; **Revised** May 31, 2021; **Accepted** June 8, 2021
Correspondence to: Sung Won Park
Division of Pediatrics Endocrinology, Department of Pediatrics, Gangseo MizMedi Hospital, 295 Gangseo-ro, Gangseo-gu, Seoul 07639, Korea
Tel: +82-2-2007-1923, Fax: +82-2-2007-1249, E-mail: swped@naver.com

Typical Behavioral Disturbances in PWS

A behavior pattern typical of PWS begins in early childhood in 70–90% of affected individuals. It is typified by temper tantrums, stubbornness, controlling and manipulative behavior, compulsive behaviors (repeated organizing, writing, collecting, the need to finish one thing before moving to the next), and difficulty with changes in routine[6-10].

Lying, stealing, and aggressive behavior are common in PWS. True psychosis is evident in young adulthood in approximately 5–10% of patients[11]. Behavioral and psychiatric problems interfere the most with the quality of life in adulthood.

Many of these behavioral characteristics are suggestive of autism spectrum disorder, which has been diagnosed in up to 25% of individuals with PWS[12]. Attention-deficit/hyperactivity symptoms and insistence on sameness are common of early-onset[13]. The severity of behavioral problems increases with age and body mass index[14] and then diminishes in older adults[15]. Psychosis is evident by young adulthood in at least 5–10% of individuals[16,17].

The Role of Age

Behavioral disturbances in PWS patients differ by age. In infancy, there are more physical than behavioral concerns, including hypotonia, feeding difficulties, failure to thrive, hypogonadism, lethargy, and decreased interest in eating[18] In early childhood, externalizing behaviors increase, such as tantrums, aggression, and stealing, and internalizing behaviors, such as anxiety, depression, and skin picking increase[15]. Intellectual disabilities or social difficulties become more apparent as the patients go to school.

Although some PWS patients have a high IQ, most have mild or moderate intellectual impairment, which can often cause difficulties in learning or socializing. Therefore, patients prefer to be with an older or younger group than their peers and independent activities, such as word searches and puzzle matching games[19-21].

In early and late adulthood, serious mental illnesses such as depression and affective psychosis can occur. Older adults may experience a reduction in hyperphagia, a significant diminishment of both maladaptive and compulsive behaviors, an increase in self-absorbed behaviors, daytime sleepiness, and episodes of psychopathology.

In summary, hyperphagic eating issues and food compulsions may persist in those 2–15 years old. Many patients develop extreme appetite behaviors, such as food-seeking and temper tantrums. Nonfood compulsive symptoms also increase with increasing age from 5 to 47 years old[22].

Patients in their twenties are also emotionally unstable and demonstrate severe maladaptive behaviors, social problems, and compulsive symptoms due to stress in new environments, such as school. In previous studies, PWS patients aged 20–29 years have exhibited significantly more aggressive behavior than those aged 12–19 or 30–45 years[23]. As patients become over 30 years of age, maladaptive and compulsive behaviors are significantly reduced.

A study published in Japan in 2007 based on parent questionnaires examined the prevalence of behavioral and psychiatric disorders of 165 persons with PWS aged 2–31 years. The data compared four different age groups of people with PWS: group 1: 2–5 years (n=34); group 2: 6–11 years (n=57); group 3: 12–17 years (n=45); and group 4: 18–31 years (n=29). Their results showed that repetitive speech and stubbornness were prominent from early childhood and other behavioral problems, such as hyperphagia, stealing food, temper tantrums, lying, and emotional lability, tended to be more frequent with age. Moreover, young adults with PWS have significantly higher rates of behavioral and psychiatric disorders than those with non-PWS intellectual diseases, such as stubbornness, hyperphagia, temper tantrums, self-injurious behavior (skin picking), hypersomnia, inactivity, and delusions[24].

Because symptoms appear and increase or decrease according to age, age is the largest predictor of behavioral problems in PWS, and older children tend to have more behavioral problems than younger children[25].

The Role of Genetic Subtypes

During early and late adulthood, severe psychiatric illnesses, such as depression and affective psychosis, may develop, especially in those with UPD[16,17,26,27]. Maladaptive and compulsive behaviors that began in childhood, such as overeating, hoarding, and tantrums, may occur in middle adulthood, but typically diminish in older adults[15,28]. While physical, cognitive, and behavioral concerns are almost universally reported in PWS, there is some evidence that the manifestation of these concerns differs by subtype. Compared to individuals with UPD, individuals with the deletion subtype demonstrate more compulsive behaviors[23,29-31], which is associated with both social and academic challenges.

Within the deletion subtypes, some have reported no significant difference in behavior between the TI and TII deletions[28,32]. Studies reporting a difference between the two differ in their account of which deletion subtype exhibits more severe compulsive behaviors[29,33].

There are also differences in behavioral problems according to

genetic subtypes. UPD patients have better expressive language development than deletion subtype patients, whereas deletion subtype patients have a better visual memory and puzzle-solving skills.

The repetitive behavior pattern in individuals with PWS is similar to that of individuals with an autism spectrum disorder (ASD). About 25% of patients with PWS are diagnosed with ASD, which is more than in UPD patients, and psychiatric and sleep disorders are also more frequently reported in these patients[12,16]. On the other hand, skin-picking, distress, mood lability, compulsive behaviors, food stealing, withdrawal, sulking, nail-biting, hoarding, overeating, and attention-deficit hyperactivity disorder (ADHD) symptoms are more frequent in patients with the deletion subtype[30].

The Role of Gender

There are not many studies on the behavioral patterns of patients with PWS according to gender. A study by Marie et al. in 2020 found that boys show differences in socialization and helpfulness at home and school and exhibit higher social competence when comfortable, such as at home. In addition, compulsive behaviors, such as hiding and stacking food, or food-related obsessive behaviors were more common in girls[25].

Skin picking is a behavioral problem seen in almost all age groups but is most commonly reported in female children and adolescents[15]. Further research on the classification of behavioral phenotypes by sex in PWS patients is warranted.

Clinical Management of PWS Behaviors

The various behavioral disorders in children with PWS are classified in different ways. Management of PWS should be age-dependent, multidisciplinary, and utilize a problem-based approach. The symptoms of PWS patients increase with age, so management should be proactive through early diagnosis.

Since age, growth, and food-related obsessions can be the basis of behavioral and emotional disorders, food-related issues must be managed before non-food-related issues. Reduced fat and modified carbohydrate meals and growth hormone therapy may be helpful.

Skin picking, which occurs in 95% of PWS patients aged 4–19, may be treated by habit-reversal training[34]. This is helpful when combined with behavioral treatments, such as acceptance and commitment therapy, but research is insufficient[35]. In the short term, applying an ointment and attaching a band-aid may help.

Rectal picking seen in 15% of PWS patients in adolescence and adulthood can lead to complications such as blood loss, anal sphincter damage, and perirectal abscess[36]. Behavioral modifications are suggested as a treatment.

Carrel and colleagues[37] found that treatment for growth hormone (GH) deficiency in PWS shows a dose-dependent effect on height, body composition, and resting energy expenditure[38]. A combination of reduced-fat and modified-carbohydrate meals along with GH treatment may result in increased height and a normalized BMI. This is the first long-term study with a follow-up period to report on the effectiveness of early dietary intervention in children with PWS.

Long-term GH therapy increases height velocity, final adult height potential, lean body mass, muscle strength, and activity levels and decreases fat mass. While growth hormone treatment improves poor memory problems, social withdrawal, and depression in patients suffering from growth hormone deficiency due to other diseases, the behavioral and cognitive implications of growth hormone in PWS patients are unclear. However, it has been reported that infant patients show behavioral changes, such as improved cognition and increased alertness and enjoyment of physical activity[39-41]. However, other studies have noted an increase in ADHD patterns in PWS patients receiving growth hormone therapy[39,42].

Studies are underway on treating hyperphagia behaviors through the ghrelin pathway. Acylated ghrelin is believed to be associated with hyperphagia and obesity and unacylated grehlin, acting through a different pathway, opposes these orexigenic effects[43]. Ongoing studies are examining if diazoxide choline controlled-release may reduce appetite-related behaviors and fat mass in PWS patients[44].

Clinical studies on oxytocin, a known food-suppressing hormone, are ongoing. Efforts to resolve the behavioral problems of high-grade patients are continuing through these new treatments[45].

Due to the range of behavioral symptom across individuals with PWS, management of this condition is age-dependent, multidisciplinary, and utilizes a problem-based approach for each individual. While there is no cure for PWS, individuals with PWS can live a full and meaningful life with early diagnosis and a proactive treatment approach. Continuous research and cooperative treatment across various fields will help to resolve the behavioral problems of PWS patients.

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