Prader-Willi Syndrome (PWS)

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Introduction

Prader-Willi Syndrome (PWS) is an abnormality within the paternal chromosome 15; deletion of the paternal 15 chromosome is the most common resulting in 70% of the cases, UPD (maternal disomy in which there are two maternal chromosome 15s, and no paternal chromosome 15) is 25%, and imprinting defect of the paternal 15 chromosome is 5% (PWSA, 2004). PWS creates life-threatening obesity in children, along with other medical and developmental issues (Kundert, 2008; PWSA, 2010). Issues related to PWS are short-stature (without growth hormone treatment), underdeveloped muscle tone, incomplete sexual development, learning and behavioral disorders, low IQ (average IQ is 70), as well as the most common and life threatening issue of satiety coupled by decrease metabolism (PWSA, 2010). Infants often fail to thrive because of the lack of muscle tone (hypotonia) needed to suck for feeding, followed by the onset of hyperphagia (insatiable drive of hunger) around two to five years of age (Kundert, 2008; PWSA, 2010). Kundert (2008) reviewed various studies related to PWS and determined that it is a "multisystem disorder with genetic, developmental, and behavioral features" requiring multidisciplinary approaches for developmental/cognitive disabilities and maladaptive behaviors.

Brain Function and Involvement

Food related issues and motivation

Brain function and neurological abnormalities within those with PWS creates issues dealing with hunger and eating problems. Hinton, Holland, Gellatly, Soni, and Owen (2006) found that PWS participants will indicate a food preference on the questionnaire, yet their behavior was not consistent with the preference and incentives; the input from the incentive reward pathways in the brain are over powered by the dysfunction of the neural satiety system. They found within their study that images of highly valued food of the control group stimulated activity in the amygdala and left medial orbitofrontal cortex region; while PWS did not have this activity associated with food categorized as highly valued.

Although studies may differ on specific values of food to those with PWS, they confer abnormality in brain function is involved. Contrary to Hinton et al. (2006) findings, Holsen et al. (2009) showed PWS participants did not rate certain foods more valuable than the control, yet there is greater activity in the disinhibition of behavior and lack of self-control regions of the brain. Nevertheless, these findings support the divergent pattern of neural activity of both studies in response to food. Holsen et al. further differentiated the brain activity between UPD and deletion groups of PWS. Within their study they determined those with deletion showed greater and more widespread brain activity before and after eating compared to UPD (especially within the motivation and reward regions). UPD however showed stronger brain activity within the decision-making regions for cognitive judgment determining the lack of health benefits related to the reward of eating food. Holsen et al. suggested that this may be linked to the higher verbal IQ observed in the UPD group, along with greater memory function in reward value and potential outcomes.

There have been similarities between the brains of those with PWS and Early-onset Morbid Obesity (EMO), as compared to control populations. Miller et al. (2009) found that

cerebral volume and cerebral/cerebellar volume ratio are smaller compared to sibling control groups. Since there was no distinct genetic disorder linked to EMO group, it was hypothesized in this study that the excess adipose tissue affected brain development during childhood. These findings of the size of cerebral and cerebral/cerebellar ratio of PWS, and some EMO, were linked to other developmental delays and behavior.

Cognition

These regions of the brain, cerebral and cerebellar, which are associated with PWS influences working memory, behavior, and speech; as well as previously discussed issues with food. Differences in the cerebral and cerebral/cerebellar volume ratio were linked to speech delays in both PWS and EMO groups, and working memory of PWS (Miller et al, 2009). Various studies have shown that IQ scores for PWS are significantly lower than autistic and standard populations, averaging around 40-90 (Bertella, Girelli, Grugni, Marchi, Molinari, Semenza, 2005; Dimitropoulos, Ho, Klaiman, Koeing, & Schultz, 2009; Höybye, Thorén & Böhm, 2005; Walley &Donaldson, 2005). Milner et al. (2005) found that IQ differed within the verbal and nonverbal sections for the PWS population depending on the form of PWS; T II deletions had higher verbal IQ scores over TI deletions, and higher non-verbal scores over UPD. Bertella et al. (2005) found that PWS scores on temporal orientation, street test, and verbal fluency were normal, yet the rest of the tests scores were 2-4 standard deviations below normal. List learning was well below the normal mean related to working memory. Rey Auditory Verbal Learning Test (RAVLT) indicated that performance of PWS improved with practice until they reached normal population; two participants obtained maximum score described for savants (Jauregi et al., 2007). Motor responses within PWS group have large errors and deficits that are found within several studies (Bertella et al., 2007; Höybye et al., 2005; Jauregi et al., 2007). Jauregi et al. (2007) suggested the deficit in motor response indicated attention deficit possibilities.

Deficiency in executive function was also found by measure of Wisconsin Cart Sorting Test (WCST), verbal fluency, and Trail Making Test (TMT) for mental flexibility, attention, motor function, and visual search speed (Jauregi et al., 2007). Jauregi et al. (2007) found that deficiency in processing speed may have resulted in the observation of TMT-A scores, while poorer performance in TMT-B than TMT-A reflected deficits in visual search, working memory, or attention. Poor working memory may also be a source of the poor performance on WCST, rather than executive function. However, the study also indicated the Rey-Osterrieth Complex Figure (ROCF) showed executive function deficit with the PWS redrawing complex geometric shapes from memory; especially in the ability to organize and plan information.

Although there is not an agreement on what process may attribute to the lower IQ on verbal, attention, and memory sections of assessment, studies all indicate that the dysfunction of the brain of PWS attributes to various issues and aspects involved in development and behavior of PWS.

Some of the various cognitive deficits which occur with PWS population include math, language, processing and sequencing. IQ scores were significantly lower along with neuropsychological measures and visuoperceptual organization found within PWS study conducted by Jauregi et al. (2007). The deficit within these processes affects several areas of memory and cognition. Memory scores for visual sequential processing were low, yet simultaneous processing of figural memory remained the same as the standard population within the study (Jauregi et al, 2007). Short-term memory deficits were a major contributor to PWS

errors in math, with the lowest scores on arithmetic subtest and digit span of IQ tests (Bertella et al., 2005; Walley & Donaldson, 2005). It was determined that there was not a system to their errors that would indicate flawed strategies within PWS group when performing mathematical operations; it is a complete lack of memory and understanding of number comprehension (Bertella et al., 2005). PWS performed lower on dot counting, while regular counting was normal until asked to count backward by two or three (Bertella et al., 2005). Alteration in phonological loop may result in the deficit of verbal sequencing, while there was also deficit in visual sequencing (Jauregi et al., 2007). Error in digit span may be attributed to dysfunction in the phonological loop located in the left parietal lobe, rather than executive function as a result of better self-order pointing tasks given visually than those given verbally (Walley & Donaldson, 2005).

Along with speech and memory deficits, PWS have other behavioral related issues beyond what was found with EMO groups. PWS group behavior was unique with temper outbursts, self-injury (skin-picking, scratching, hair pulling/ trichotillamania, and nail biting), compulsivity, and hyperphagia related to the smaller cerebral and cerebellar brain regions; only a few EMO were found to have these behaviors, and were considered to be PWS-like (Miller et al., 2009). Behavior of PWS is hard to control when responding to the refusal of food due to the source of the behavior being a hypothalamic dysfunction; reinforcement strategies for behavior modification are not typically successful (Einfeld, 2005).

Maladaptive Behavior and Emotional Disturbances

There is some variability within the maladaptive behavior, yet behavioral and emotional disturbances are found within PWS; some deceptive behavior (such as lying and stealing) are related to the attempted obtainment of food (Dimitropoulos et al., 2009). Skin-picking and self-injury are very common behaviors among PWS, which can begin around five years of age, with the prevalence increasing with age; 78-86% of PWS show this behavior (Didden, Korzilius, & Curfs, 2007; Wigren & Hansen, 2003; Wigren & Hansen, 2005). Severity of skin-picking and other SIB (Self Injury Behavior such as nail biting, trichotillamania, and scratching) were found to be related to intellectual ability (Didden et al, 2007). Skin-picking is associated with OCD (Obsessive Compulsive Disorder) which is categorized as an anxiety disorder, yet the scores on the anxiety scale did not indicate anxiety in Wigren and Hansen study (2005); while other studies have indicated anxiety (Descheemaeker et al, 2002; Walley & Donaldson, 2005).

Although PWS scores are low on attention to dirt and cleanliness, lacking the typical behaviors as OCD, such as hand washing, other assessment tools separate from the standard psychiatric assessments for OCD may need to be used to identify OCD markers in PWS (Wigren & Hansen, 2003). Intensity of compulsive behaviors and symptoms may be related to executive dysfunction and intellectual disability (Didden et al., 2007; Wigren & Hansen, 2005). Severity of compulsive behavior did not differ among age or UPD and deletion PWS groups, with the average age of onset around six years (Milner et al., 2005; Wigren & Hansen, 2003). Compulsive behaviors are just one of the several maladaptive behaviors observed in PWS; other behaviors include temper outbursts, irritability, insistence on sameness, and repetitive behaviors.

Tantrums are frequent behavioral issue among PWS, with occurrence of at least once a month or more, with frequency decreasing with age (Didden et al, 2007; Wigren & Hansen, 2005). Oliver, Woocock, and Humphreys (2009) observed the progression of behavior in a group of 4 females with paternal deletion, which showed questioning would proceed more challenging behavior such as arguing, followed by crying or ignoring. UPD group indicated more behavioral

problems than deletion group, indicating that it is more than a result of executive function (Walley & Donaldson, 2005). Teacher rating of behavior correlated negatively with cerebral/cerebellar ratio, indicating an increase in ratio observed fewer behavioral issues; while cerebral/cerebellar ratio as previously discussed showed unique behaviors such as temper tantrums (Miller et al., 2009).

PWS tends to have increased irritability and agitation during early years, then decreasing with age, while lethargy and withdrawal increases with age (Walley & Donaldson, 2005; Wigren & Hansen, 2005). The difference of behavior between UPD and deletion groups is autistic behavior and not adaptive social behavior, with UPD daily living scores lower than deletion group, and higher on autistic like behavior of socialization domains; indicating a genetic risk factor for autistic phenotype (Milner et al., 2005). Walley and Donaldson (2005) found that PWS scored higher on aberrant behavior, stereotypical behavior, and inappropriate speech than those with anxiety disorders.

Insistence on sameness, repetitive behavior, and hoarding tends to decrease with normal childhood development, yet remains the high with PWS (Wigren & Hansen, 2003). PWS rarely showed a preference for food, and the lack of rightness with food is an indicator of the hyperphagia; yet insistence on sameness for all other areas scored extremely high (Wigren & Hansen, 2003; Wigren & Hansen, 2005). Few parents observed the typical child behavior of post-poning bedtime, reflecting the excessive daytime sleepiness and sleep disturbance (Wigren & Hansen, 2003). Wigren and Hansen (2003; 2005) suggested the importance of maintaining routine for coping mechanism of PWS.

Behavioral and psychiatric through development

Typical behavioral disorders observed within PWS can be placed into two distinct groups: active-extrovert, and passive-introvert. Each has their own developmental behavioral processes that are observed.

Toddler period of development. The first group (active-extrovert) during toddler development will have poor social skills with little interaction with peers; when interaction with peers does occur, dominance and control of the game is inevitable. They can be found exploring their environment, with poor distinction between fantasy and reality. Observed behavior tends to be demanding, attention seeking, obstinate, easily frustrated, and frequent tantrums. These behaviors are in response to the need of maintaining ritual and routines. Speech problems are observed which may include self-directed speech (Descheemaeker et al., 2002)

Passive-introverts are typically socially withdrawn and not seen participating in peer activities and games. They like to be mothered by peers and are reserved with adult social interaction. Unlike the first group, they prefer quiet games and less activity, such as reading, with less frequent tantrums that are easily controlled. (Descheemaeker et al., 2002)

Primary school period of development. Active-extroverts were often diagnosed as autistic-spectrum disorder with social interaction impaired by poor eye contact and facial expressions. Difficulty determining the difference between reality and fantasy continues with this stage of development. The need to have a controlled environment is observed through rituals, many times evolving to obsessive-compulsive behavior followed by anxiety, tantrums, and panic attacks if not maintained. Observed alteration of periods consisting of high activity followed by underactivity and tiredness were seen throughout this stage of development. Obsession and fixation on things are observed to the intensity that sleep will be disrupted with periods of

talking, writing, or drawing about the object of obsession. Continued speech issues are evident with word finding problems and speech disfluency. (Descheemaeker et al., 2002)

The passive-introvert group progressed to internalizing emotions and behavior problems resulting in anxiety and depressive symptoms with mood swings. Interaction with peers is initially searched out, but is impaired with seclusion and bullying; yet social interaction with familiar adult is good. Outward behavioral problems such as tantrums, obsessive-compulsiveness, and the need to control are less intense than active-extrovert group. Speech and language impairment are less obvious than the other group as well. (Descheemaeker et al., 2002)

Puberty period of development. Manifested psychiatric problems during this stage of development fluctuate making the identification of the antecedents difficult. Behaviors associated with eating and emotions were observed to be cyclic with periods of good control and happiness followed by lack of control and psychiatric symptoms. Psychotic disorders were different between the groups ranging from acute polymorphic psychotic disorders (periods of self-neglect and lethargy) to delusions and hallucinations, coupled with anxiety. The passive-introvert group had bipolar affective disorder with sudden mood swings, emotional instability, obsessive behavior, SIB, as well as sleep and eating disturbances. (Descheemaeker et al., 2002)

The myriad of symptoms and issues related to PWS creates difficulty with treating the disorder as a whole. Treatments have been focused at treating independent issues.

Treatment

Patients suffering from PWS experience multifaceted symptoms which need to all be approached during treatment. The most obvious and focused attention for treatment is the control of hyperphagia, yet other issued are just as vital to treat. Dykens and Hodapp (1997) addressed various aspects of PWS that should be included in treatment. Although some self-monitoring food behaviors have been successful with a few individuals, the hypothalamic anomalies associated with hyperphagia require continued external supervision. This article also addressed the need to provide treatment for non-food related obsessive-compulsive behavior through family therapy providing strategies to alleviate tantrums, along with serotonin uptake inhibitors. The need to treat the lack of social skills was also addressed with recreational activities, and improved self-esteem.

Growth Hormone

Impaired growth hormone (GH) secretion affects the body composition, motor performance, energy expenditure and respiratory function as indicated by a study done in 2004 by Allen and Carrel (Bertella et al., 2007). Growth hormone treatment can benefit PWS in multiple aspects of life including muscle development, psychological development, and well-being. Parents in Bertella et al. (2007) study noticed an increase in self-control of their child during GH treatment; yet aggressiveness and frequency of tantrums increased when treatment was discontinued (Höybye et al., 2005). PWS self-report and parental report indicated an increase in well-being during GH treatment, including mental speed and flexibility; along with increasing in coding test score of IQ and cognitive tests (Bertella et al., 2007; Höybye et al., 2005). Growth hormone treatment also improved motor skill and speed, mental speed and flexibility, as well as body composition and physical performance (Bertella et al., 2007; Höybye et al., 2005). However, Höybye et al. (2005) did not showed patient self-evaluation indicating a change in their mental, emotional, or social situations during GH treatment.

Medication and other treatments

Since many of the symptoms of PWS stem from activity within the prefrontal lobe, treatments focused on this area of the brain may alleviate many of the symptoms. Boggio, de Macedo, Schwartzman, Brunoni, Teixeira, and Fregni (2009) suggested transcranial direct current stimulation which will inhibit excessive activity in the amygdala. As previously mentioned, the amygdala was found to be involved in food motivation (Hinton et al., 2006). This approach seems to go to the source of the problems associated with the brain with PWS, yet it has not been attempted yet. Until treatments which reverse the disorder at the source are established, individual treatments will need to be utilized to address various aspects, including sleep disturbance.

One symptom of PWS is sleep disruption and sleep apnea; sleep apnea has been linked to lowered neurocognitive performance, including executive function, verbal and IQ performance, memory, and attention in several studies discussed by Camfferman, Lushington, O'Donoghue, and McEvoy (2006). Reduced REM sleep is associated with intellectual disability and treatment of GH along with other forms of treatment for sleep apnea would be very beneficial; GH secretion level have been linked and related to slow-wave sleep (Bruni et al., 2010). The abnormality within Chromosome 15 influences the activity of various chemicals such as GH, serotonin, dopamine, and GABA activity, influencing physiological functions.

GABA receptor activity that is associated with chromosome 15 has created possible alteration in the postsynaptic GABA receptor, decreasing the ability to bind GABA, consequently increasing the levels present. The complex alteration in GABA receptor function throughout the brain has shown to result in physiological and behavioral consequences in the regulation of eating, satiety, aggressive behavior, motor function and seizures. GABA levels of PWS were two to three times higher than obese and mentally retarded control groups, and some were fourfold higher than the control mean. Treatments and medication controlling the level and secretion of GABA would be very beneficial in the control of symptoms of PWS (Ebert, Schmidt, Thompson, & Butler, 1997)

Several medications have been successful in the treatment of the symptoms of PWS. Antiepileptic topiramate was successful in the treatment of SIB, and improve measures on impulsive behavior; participants even reported decreased urges to pick (Shapira, Lessig, Murphy, Driscoll, & Goodman, 2002). This study also discussed other antiepileptic drugs, such as carbamazapine and lamotrigine, have previously been shown to improve SIB. Since some of the behaviors are associated with autism, medications that have proven to benefit those suffering from autism, such as risperidone which manages dopamine and serotonin dysfunction, have shown to benefit PWS patients (Durst, Rubin-Jabotinsky, Raskin, Katz, & Zislin, 2000). Within this study, they also found that communication improved, patients became less aggressive, less impulsive, and experienced fewer outburst; along with the management of food seeking behaviors. Didden et al. (2007) referred to two studies done by Hellings and Warnock (1994), and Akefeldt (1998) which showed that skin-picking was reduced with the use of antidepressants to reduce the turnover of serotonin.

Behavioral approach

Two case studies indicated improvement of hyperphagia behaviors through behavioral strategies. These two studies were limited to a case study of one individual, and cannot be generalized to the rest of PWS population easily. Most of my previous discussion indicated that

behavioral approaches are not very successful because of the motivation being hypothalamic. However, I thought these two studies were note worthy in their success. One case study was concerning a 14 year old girl who was harshly reprimanded when she ate from containers of off-limit foods (Maglieri, DeLeon, Rodriguez-Catter, & Sevin, 2000). This study indicated that the child could be conditioned to avoid foods that have a picture label indicating an off-limit container. The other was a case study of a 17 year old boy whose parents wanted to established behavior that would help him be successful while living on his own (Singh et al, 2008). This boy was taught self-control strategies through mindfulness-based health wellness program, exercise, visualization exercises labeling hunger, and refocusing of attention on his feet to control tantrums. This study was successful in establishing these self-monitoring behaviors, and he even began to lose weight.

Conclusion

The symptoms and treatment of PWS is complex and multifaceted as a result of abnormality in paternal chromosome 15. Every gene that is responsible for physical, mental, and social development on this chromosome is affected. Various aspects that were discussed is the change in brain function and structure, which the cause is unknown, that influences intellectual, motivational, emotional, and chemical functions. The dysfunction within the brain, hypothalamic system, and chemical balance creates a myriad of symptoms and disorders which can alter and change throughout development. Treatment of PWS is difficult because of the complex interactions of gene expression and brain function. Ideal treatment would focus on the source with gene therapy or brain stimulation, yet more study and research needs to be done to make these treatment options available. Currently treatment options focus on the individual symptoms with greater success on GH treatment and medication for psychosis.

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