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Multidisciplinary Approach in Prader Willi Syndrome: A Case Report of 3 Years Follow Up and Review of the Literature

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The aim of this study was to present the 3 years follow up of a subject with Prader Willi Syndrome (PWS). The subject was a 3.5 years old girl (height of 92 cm and weight 13.5 kg). Characteristic facial appearance, severe general hypotonus, mental and motor retardation were presented in the subject at eight months of age. At the age of 15 months she was diagnosed as PWS by means of chromosome analysis. She was then referred to physiotherapy and rehabilitation program and follow ups were conducted by a team consisting of a paediatric neurologist, a paediatric endocrinologist and a physiotherapist. Sitting, crawling, standing and walking abilities were achieved at 12, 24, 30 and 38 months, respectively. Her first meaningful word noted was at the age of 2,5 years and when this study was completed she had been using 6 words with no sentence formation. This case report is one of the first that presents a relatively long period follow up of a subject with PWS. Highlighting the necessity of a multidisciplinary approach to PWS.

Key Words: *Prader Willi Syndrome, physiotherapy, neurodevelopment, hypotonia, comparative study.*

Prader Willi Sendromunda Multidisipliner Çalışma: Bir Olgunun Üç Yıllık İzlemi ve Literatürle Gözden Geçirilmesi

Bu çalışmanın amacı, Prader Willi Sendromu (PWS) tanısı konmuş bir olgunun 3 yıllık sonuçlarını literatür eşliğinde irdelemektir. Olgu 92 cm boy, 13,5 kg ağırlığında, 3,5 yaşında bir kız çocuğu olup, 8 aylıkken karakteristik yüz şekli, şiddetli genel hipotonisi, mental ve motor gelişim geriliği ile PWS düşünülmüş ve kromozom analizi ile tanısı konmuştur. O dönemde fizyoterapi ve rehabilitasyon programına yönlendirilmiş, düzenli olarak pediatrik nörolog, pediatrik endokrinolog ve pediatrik fizyoterapist tarafından takip edilmiştir. Oturma, emekleme, ayakta durma ve yürüme basamaklarını sırasıyla 12, 24, 30, 38. aylarda tamamlamıştır. İlk kelimesini 2,5 yaşında söylemiş olup kelime hazinesi halen 6 kelime ile sınırlıdır: henüz cümle kuramamaktadır. Bu çalışma, uzun süre takip edilen PWS'li ilk olgu özelliğini taşımaktadır. PWS'li olgularda multidisipliner yaklaşımların gerekli olacağını düşünüyoruz.

Anahtar Kelimeler: *Prader-Willi Sendromu, rehabilitation, nörogelişim, hipotoni, karşılaştırmalı çalışma.*

Introduction

Prader Willi syndrome (PWS) is a rare genetic disease (prevalence: 1/15000-1/30000) described by Prader, Labhart and Willi in 1956; and, is characterized by dismorphological features with major neurological, cognitive, structural, behavioral and psychological disorders (1-4). Hypotonia, hypogonadism, obesity and short stature are the main characteristics of PWS (5). Additionally, coxa/genu valga, scoliosis, small hands and feet, decrease in physical activity level and metabolic energy consumption, sleep related breathing disorders may be observed (3, 4, 6). In PWS children, cognition is impaired and patients have learning difficulties with mild to moderate mental retardation in addition to developmental motor retardation (1, 3, 6).

It clinically consists of two phases. First phase is characterized by a variable degree of hypotonia, weak cries, hypothermia, and weakness of sucking reflex in perinatal and neonatal periods. Severe motor retardation and insufficient nutrition may be observed. Second phase expresses itself with physical and motor retardation between the ages of 1-2 years. The typical impairment in nutritional behavior is hyperphagia that is the reason for later obesity observed between the ages 2-5 years. Between the ages of 2-4 years motor retardation decreases, leaving its place to speech pathologies and learning difficulties (1, 7-9).

The severity of the social, cognitive and functional disabilities of an individual with PWS varies according to the medical treatment received, presence of secondary obesity, diabetes, hypertension and respiratory impairments (6, 10-12). PWS cannot be treated with a single approach; rather, follow-ups are necessary with the contribution of many fields related to and involving medical treatment, nutritional counseling, behavioral control, special education, neurodevelopment approaches and hormone replacement treatment (1, 6). In physiotherapy and rehabilitation of an individuals with PWS, severity

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of the disability, level of motor skills and participation in social activities are the most important parameters evaluated (1). Physiotherapy applications mainly focus on increasing muscle strength, level of mobility, functional level, and improving aerobic endurance and postural control (1, 6). Prevention of obesity is crucial to decrease risk factors related to cardiovascular capacity and osteoporosis (3, 5, 7, 13).

The aim of this case study was to discuss the results of 3 years of multidisciplinary and to present the efficacy of Bobath Neurodevelopmental Therapy approach in a subject with PWS.

Case Report

Subject and Settings

The patient, a Caucasian female born at $36^{6/7}$ weeks of gestation (2.215 g, 45 cm) via ceserean section after the first pregnancy of a 28 year- old mother, was diagnosed with PWS at 15 months of age.

The study included a $3^{6/12}$ –year-old female subject with a height of 92 cm and a weight of 13,5 kg. Amniosynthesis was done with the suspicion of Down syndrome in 6th week of the gestation. In addition, the rate of increase in abdominal circumference was found to be below normal range. During the first 2 months after birth, above-normal sleeping hours and weak head control had raised an attention. At 6 months, her parents was referred to a pediatric neurology clinic with complaints of abnormally low level of reactions and activity. Pre-diagnostic was thought to be PWS which was later confirmed by FISH test. At 8 months the subject was referred to Hacettepe University Faculty of Health Sciences Department of Physiotherapy and Rehabilitation because of hypotonia. Both parents are graduates of high-level education program and were thoroughly informed about PWS at the beginning.

Observational parameters related to physiotherapy and rehabilitation consisted of investigation of social, emotional, cognitive, motor and sensorial characteristics. Furthermore, developmental reflexes was noted and for detailed analysis of motor development Gross Motor Functional Measurement (GMFM) was used (14). GMFM is a standardized observational test designed to evaluate the changes over time in motor development in children with developmental disabilities like cerebral palsy and Down syndrome. It consists of 88 items and 5 subscales (supine-prone, crawling, sitting, kneeling, standing-walking and running) parallel to normal developmental milestones.

Parental informed consent was obtained after detailed information was provided about the ongoing case study.

Baseline Assessment

Initial Evaluation at 8 months

The subject was fed with the help of a baby bottle because of weak sucking. Starting at 5 months, liquid foods (ie. yoghurt, fruit juices) were included in feeding. Frequent fevers were present.

Body Composition: At 7 months body weight was measured as 7.5 kg and head circumference was 42.5 cm (evaluated as normal).

Motor Development: Severe hypotonia was present. Motor activities including head control were absent. “Floppy infant” appearance was present. GMFM score for the first evaluation was “0”.

Cognitive Status: No reactions were present in response to audible and visual stimuli and the subject was not interested in toys or objects. No recognition of father, mother or any other person.

Social Development: No social behaviors were present.

Emotional Development: High-pitched crying was present. No sign of smiling or any other facial expressions.

Sensorial Status: Visual and auditory systems were intact with marked internal strabismus. However, subject was unable to produce meaningful sounds.

Physical Appearance: Compared to body size, feet and hands were small in appearance. Almond shaped eyes and well-rounded cheeks were marked features of the subject.

Reflex Development: Asymmetrical tonic neck reflex, amphibian reaction, symmetric tonic neck reflex, corrective and protective reflexes were absent.

Neurodevelopmental Treatment Approaches

Following initial evaluation, a physiotherapy and rehabilitation program based on Bobath Neurodevelopmental Treatment Approach was initiated for 2 days/week (15). The program consisted of tonus regulation, positioning, facilitation of head control, balance and protective reactions, sensory-motor and cognitive training, and techniques aiming to enhance postural stability and proprioception. In parallel to the increase in age, activities focusing on muscle strengthening and aerobic endurance were included in the rehabilitation program.

Parental training was provided to ensure that home based therapy was sufficient enough.

Observational Findings

Neurological Development: At 10 months activities of independent sitting and passing objects from one hand to another were gained. At 12 months some spelling and mimicking speech voices were obtained. At 12 months the subject was observed normal in the aspects of fine motor and speech skills, however gross motor evaluation was concordant with 9 months of normal development.

At 18 months, standing with the help of a holding, spelling of unmeaningful words (dada) and demonstration of body parts were observed. At 24 months the subject’s status in fine motor activities and

speech was in concordance with 12-15 months of normal development, whereas gross motor development matched with 11-12 months of normal development. At 24 months there found to be an increase in the number of words used by the subject. Head circumference was 45cm at 12 months and 46 cm at 24 months.

Endocrinologic Development

Pediatric endocrine visits were initiated at 23 months of age in parallel with development of oral motor functions and solid feeding. It was noted that her weight was at 50th percentile in between 6 to 12 months and decreased to below 25th percentile after 12 months. Her height had been increasing around 25th percentile until 18th month, however demonstrated a decline to 10th percentile after that age (Figure 1). Laboratory tests revealed subclinical hypothyroidism as evidenced by her normal T4 and FT4 with slightly elevated TSH. All other biochemical tests were in normal range including serum IGF-I. Therefore, her decreased growth rate was explained by subclinical hypothyroidism and Levothyroxine replacement treatment was initiated. Nutritional recommendations were provided for the parents on adequate and balanced feeding.

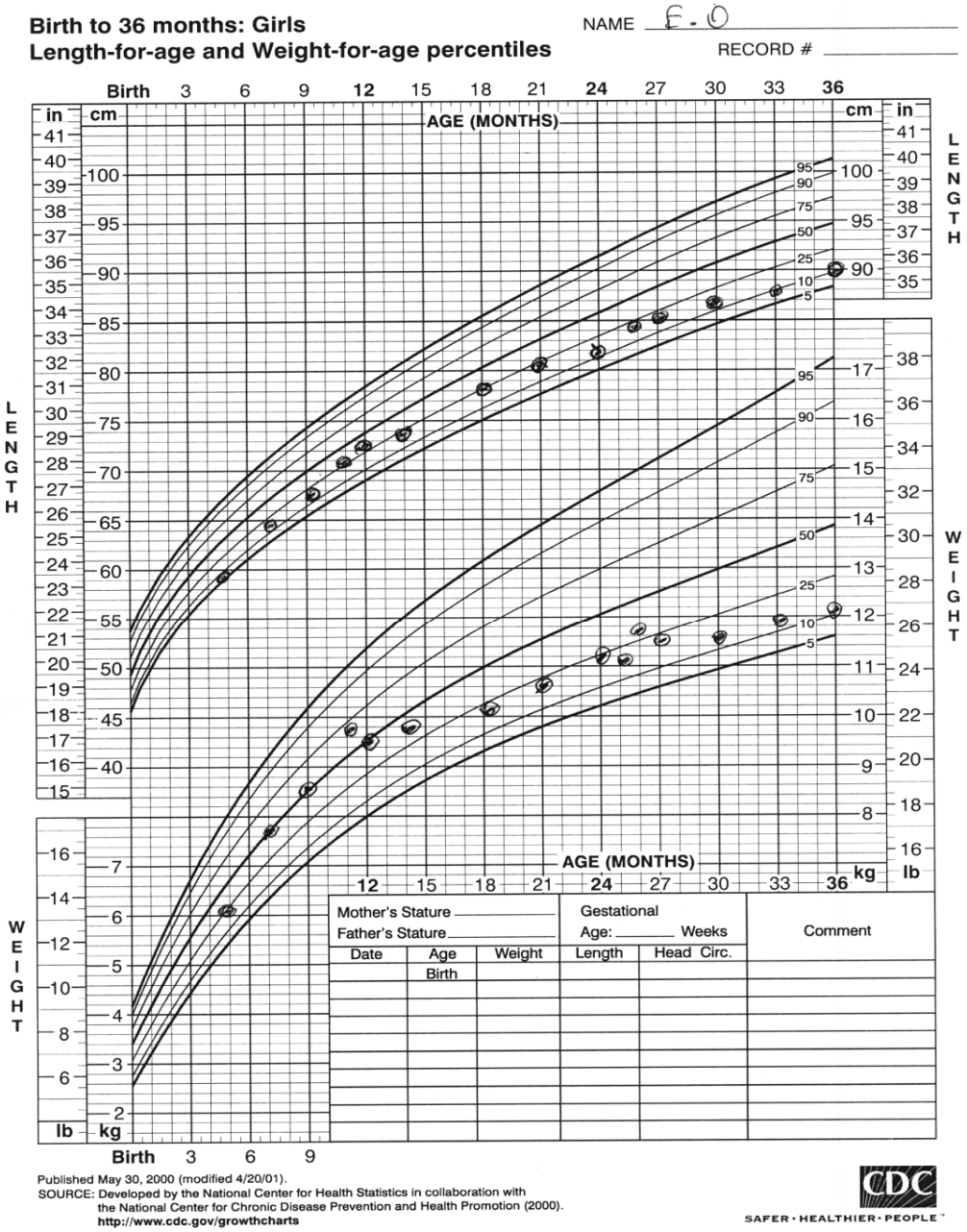

Figure 1. Growth curve of the subject.

Findings of 3 years of follow-up

Neurological: At the age of 3 independent walking and speaking up to 5-6 words were accomplished. Hypotonia was persistent throughout the period.

Head circumference was measured as 48cm at 36 months.

Physiotherapy and Rehabilitation

Neck correction reflex, amphibian reaction and sitting balance were evaluated as normal, however, kneeling, standing and walking balance were insufficient.

The change in observational parameters after 3 years of physiotherapy and rehabilitation are provided in Table 1. Table 2 presents the overall change in motor development and in Table 3 the change in GMFM is provided.

Table 1. The changes in characteristics of PWS.

	8 months	3,5 years
Social	No social response	Minor social interaction indoors and outdoors. No regular speaking but tendency to talk.
Emotional	No smiles and mimics. Responds with sharp cries to painful stimulants.	Happy and extrovert. Obsessive in activities of play and feeding.
Cognitive	Inert	Mild cognitive problems. 2-3 words of speaking.
Motor	No motor activities including head control	Independent standing and walking. Dependent in stair climbing and running.
Sensorial	Internal strabismus	Persistent internal strabismus. Eyeglass usage. Characteristic facial expression.
Muscle Tone	Extensive, severe and central hypotonus	Slight hypotonus
Speech and language	No meaningful sounds except sharp crying	First word at 1.5 years of age. Present speech pathology with 6-7 words usage. No sentence formation.

Table 2. Motor Development

Motor Development	Age (Months)
Head Control	10 Months
Creeping	19 Months
Sitting	12 Months
Crawling	24 Months
Kneeling	28 Months
Standing	30 Months
Walking	38 Months (first step at 34 months)

Table 3. GMFM score prior to and after physiotherapy and rehabilitation program

GMFM	8 Months	3,5 Years
Supine-prone	0	51
Crawling	0	81.9
Sitting	0	83.3
Kneeling	0	56.4
Standing\walking\running	0	38.8
Total score	0	62.28

GMFM: Gross Motor Function Measure

Endocrinological

Anthropometric measurements for the first 3 years are provided in Table 4. As it is shown in the Figure 1, growth of the subject was observed to be in between 10-20th percentile after initiating thyroid hormone replacement treatment. The subject was followed at intervals of 3 months to keep her TSH in 1/4 lower limits of normal range and with nutritional recommendations.

The subject`s body mass index did not increase over 85th percentile so far and dyslipidemia, cholestasis, gastro-oesophageal reflux, non-alcholic liver diseases and hypertension often seen in PWS patients were not observed in our subject.

The subject was consulted both by a paediatric neurologist and a paediatric endocrinologist. In addition, the level of education of her parents who often followed the current developments in the related literature and collaborate accordingly with the interdisciplinary team, further facilitated the rehabilitation process.

Table 4. Anthropometrical characteristics of the subject

Age (Months)	6/12	12	18 ay	23 ay	2 $^{6/12}$ y	3 y	3 $^{4/12}$ y
Height (cm)	62	72,5	78	81,8	86	90	92.3
Weight (kg)	7.145	9.530	10.070	11.130	11.500	12.050	13.570
BMI (kg/m^2)	-	-	-	-	15.55	14.88	15.93
BMI SDS	-	-	-	-	-0.39	-0.74	+0.31

BMI: Body Mass Index
BMI SDS: Body Mass Index Standart Deviation Sscore

Discussion

This study was designed to present the interdisciplinary approach to a subject with PWS and to discuss the results of neurodevelopmental treatment in PWS with the relevant literature. Although there are several studies related with PWS, most of them are case studies and they usually investigate the effects of medical treatment and growth hormone on mental and motor development (2, 3, 16, 17). While planning this study, we especially aimed to present data about the change in growth and developmental parameters of a subject who did not undergo a growth hormone treatment and to introduce early rehabilitation results with a relatively long follow-up period.

The beneficial effects of exercise programs on growth, development, aerobic capacity and body composition in children and adults with PWS were presented in previous studies (18, 19). The treatment in our study consisted of a program aiming to enhance normal development, to introduce normal movement patterns and to build up balance, corrective and protective reactions. In addition, specific exercise programs to increase aerobic capacity and muscle strength were added to the baseline program, considering the performance and the age of the subject. The muscle tonus and movement patterns were significantly improved as a result of regular physiotherapy program which also supported normal motor and mental development.

In the literature it is reported that children with PWS were able to sit at 12 months, walk at 24 months and speak at the age of two (1, 7). One of the cases McEntegart et al. (20) presented was a boy with generalized hypotonus, bilateral hip dislocations and nutritional difficulties. It is reported that he was able to sit at 7 months, walk at 20 months and his first attempt to speak was at the age of two years. They also noted physical characteristics like almond shaped eyes, underdeveloped genital organs and narrow forehead with a rapid gain of weight at the age of three. The second subject of their case report was a girl with generalized hypotonia at neonatal period and nutritional problems (ie. the need for nutritional catheter used in the first two weeks of her life). She was reported to be able to sit at 8 months, walk at 18 months and speak at the age of 1 and a half years. They also emphasized that she had a moderate level of cognitive problems and was in need of special education.

Similar to the cases described above, our subject was able to sit at 12 months but walked at 38 months. Body mass index was kept at a normal level by modifying nutritional program as she got older. She had a mild hypotonia, moderate cognitive problems and was able to speak her first word at the age 1.5 years. It is a remarkable point that her functional cognitive parameters like speech and fine motor abilities were close to the normal children in the first year of her life while, after the age of 1, the difference got clear with her peers. We think the main reasons that our subject who had a late gross motor development at all ages and walked later than all the cases described above were her unwillingness for walking due to some cognitive and/or psychological problem. This may be the cause of a long period of ambulation in sitting or crawling positions.

Belt et al. (1) reported that differing from the normal children, children with PWS tend to mimic a position resembling Gower`s sign similar to those of with Duchenne Muscular Dystrophy. The same was observed with our subject. The balance of our subject in kneeling position was insufficient and was not able to accomplish half kneeling position independently which is used as a transitional activity to standing. In addition, when her hands were supported she was able to stand from the position of half kneeling, though not without help.

Another interesting point was that the mental and motor development was at their peak when the subject was socialized with outdoor activities, especially summer holidays at a seaside. However, the subject was residing at the 3rd story of a 5 story building and because of flu, fever and body temperature problems; she rarely participated in outdoor activities in winter. Thus, most of the time she was occupied with her toys in her room. Although her parents were well educated, they experienced some psychological problems due to the question asked by their social environment concerning whether their child was crippled and/or disabled. As a result they had rejected to let her participate in community life until she reached a functional level of supported walking. Especially her mother, despite the warnings and persistent attitude of the physiotherapist delayed this process explaining that she felt very uncomfortable when people asked why her child did not walk. As a result, her parents were asked at least the rehabilitation program was to be conducted by other family members like grandmother/father and uncle. From the age of 2.5 years the subject was often let to play at common playgrounds. As a result of this a remarkable progress in her cognitive skills and balance reactions was observed.

In the literature there are numerous studies indicating that the growth hormone utilization supports the mental, physical and neurodevelopmental status of the children with PWS (2, 3, 8, 16, 21). However, there are also studies stating that this treatment had no effect on speech while facilitating motor development (17). In our case growth hormone was not used but, after initiating thyroid hormone replacement treatment, the improvements in muscle tonus and cognitive functions were noticed by her parents.

We think this study conducted by a multidisciplinary team is important as it highlights a path to future studies in PWS and to health care providers working in pediatric rehabilitation clinics.

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