Speech and Language Issues in Children with Prader-Willi Syndrome

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Abstract: Background: Prader-Willi syndrome (PWS) is a genetic disorder caused by the lack of the paternal contribution of Chromosome 15q11.2-q13.2 region. It is associated with global developmental delays, including speech and language delay. There is no information regarding the prevalence of apraxia of speech in this syndrome, despite the fact that it is often recognized clinically. In this study, we sought to investigate the prevalence of apraxia in children with PWS and speech and language delay.

Methods: Thirty children with genetically confirmed PWS, ages 22 months to 9 years of age, were evaluated by a certified speech-language pathologist due to physician concerns about speech and language development. Children were assessed by a variety of tests based on their age.

Results: Sixteen children had receptive language deficits and 18 had expressive language deficits. Fourteen of the thirty children (47%) had results on evaluation that were consistent with apraxia, of which 57% were male, and 71% ($p<0.001$) had deletion-type PWS.

Conclusion: As expected, children with PWS who are referred for concerns about speech and language development are commonly found to have receptive and expressive language deficits. However, there was a high prevalence of apraxia in our patients, which has not previously been reported in this population. We recommend that children with PWS be evaluated for apraxia by a speech-language pathologist once their expressive language skills are developed enough for speech assessment. The diagnosis of apraxia will necessitate specific speech therapy techniques which may not otherwise be used for individuals with this syndrome, thus resulting in more severe and prolonged speech delays.

Keywords: Prader-Willi syndrome, apraxia, speech delay.

INTRODUCTION

Prader-Willi syndrome (PWS) is a complex genetic disorder which is caused by the absence of normally active paternally expressed genes from the chromosome 15q11-q13 region. PWS is an imprinted condition with approximately 70% of the cases due to a *de novo* deletion in the paternally inherited chromosome 15 q11-q13 region, 25% from a maternal uniparental disomy of chromosome 15 (UPD), and the remaining 5% from either microdeletions or epimutations of the imprinting center in the 15q11-q13 region (i.e. imprinting defects; ID) [1,2]. The deleted region in PWS is flanked proximally by either breakpoint 1 (BP1) or breakpoint 2 (BP2) and distally by the BP3 breakpoint. The larger Type I deletions are flanked by BP1 and BP3 [1,2]. Those with this deletion are reported to have a more severe phenotype than individuals with either Type II deletions (BP2-BP3) or uniparental disomy 15 [3,4]. The BP1-BP2 region spans approximately 500 kb and contains four non-imprinted, evolutionarily conserved genes.

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Features of PWS include poor feeding in infancy often associated with failure to thrive, with obesity beginning around age 2, hyperphagia, hypotonia, developmental and cognitive delay, speech and language delay, behavioral problems, sleep abnormalities, and neuroendocrine abnormalities [1,5]. The speech and language delays may contribute to some of the behavioral problems, especially in young children with this syndrome [6].

The speech and language delays have classically been attributed to hypotonia and characteristic issues with the mouth, tongue, and larynx [7]. Individuals with PWS often have hypernasal speech, thought to be due to velopharyngeal insufficiency (VPI), as well as articulation and phonologic difficulties [8]. However, recent studies have suggested that the speech and language issues may actually be due to the underlying neurodevelopmental abnormalities in PWS or due to the genetic defect itself.

Structural brain scans have demonstrated normal leftward asymmetry of the planum temporale in individuals with PWS due to paternal deletion, but not in those with maternal UPD [9]. Because the planum temporale is necessary for auditory language processing and speech generation, it would be thought

that those with maternal UPD type of PWS would therefore be the most susceptible to speech and language deficits given the structural abnormalities on brain scans, but studies have indicated that speech and articulation defects are more common in those with deletion than UPD type of PWS [10]. Additionally, brain scans have revealed sylvian fissure polymicrogyria in up to 60% of individuals with PWS. Sylvian fissure polymicrogyria has been shown to be associated with compromised verbal production and gestural communication in other individuals [11].

There is some data that suggest that speech disorders have a genetic etiology. A study linked speech sound disorder to a locus on Chromosome 15q14 [12]. Additional studies have found that deletions or duplications of chromosome 15q11.2 between BP1 and BP2 are associated with speech and motor delays, as well as behavioral problems and autism [13, 14]. Individuals with tetrasomy 15q also have profound language impairments, with expressive language often absent and intention to communicate and verbal comprehension both very limited, thus further supporting the hypothesis that this area of chromosome 15 is critical in speech and language development [15]. Therefore, we sought to investigate the types of speech and language problems in children with PWS.

METHODS

Thirty children with genetically confirmed PWS were evaluated by a certified speech-language pathologist due to physician concerns about speech and language development. These children ranged from 22 months to 9 years of age and consisted of 19 males and 11 females, of whom 17 had PWS due to paternal deletion of the chromosome 15 q11-q13 region and 13 had maternal uniparental disomy. All of the children were being treated with growth hormone therapy at the time of evaluation. Many of the children with deletions were further tested using Methylation-Specific Multiplex Ligation-dependent Probe Amplification (MS-MLPA) to determine the size of the deletion, but not all had had this testing completed. MS-MLPA was done using a commercial MS-MLPA kit for Prader-Willi/Angelman syndrome (MRC-Holland, Amsterdam, The Netherlands) which contains 25 probes specific for sequence in 15q11-q13 [16]. All guardians provided written informed consent for this evaluation.

Children over the age of 6 were administered the Test of Nonverbal Intelligence-3 (TONI-3) when possible. Those less than 36 months of age were evaluated using the Birth to Three Comprehensive Test of Developmental Abilities 2nd Edition (BTCTDA-2). For those 3 to 6 years old the Goldman Fristoe Test of Articulation 2nd edition (GFTA-2), the Preschool Language Scale 4th edition (PLS-4), and the Test of Auditory Comprehension of Language 3rd edition (TACL-3) were used as appropriate. General Intellectual Ability (GIA) was determined using the Woodcock-Johnson test of Cognitive Abilities, 3rd edition (WJ-III) when possible and behavioral assessment was done using the Behavioral Assessment Scale for Children, 2nd edition (BASC-2).

We defined apraxia using the American Speech-Language-Hearing Association (ASHA) description of several behavioral diagnostic markers, including the "presence of vowel errors, inconsistent errors in speech production over repeated trials, difficulty with smoothness toward specific articulatory configurations, and prosodic abnormalities, especially those with lexical or phrasal stress" [17]. Additionally, we used the definition by Crary: "Developmental Apraxias of Speech are a group of phonological disorders resulting from disruption of central sensorimotor processes that interfere with motor learning for speech" [18]. Crary distinguishes apraxia from dysarthria, which is another motor speech disorder by stating: "Paralysis or weakness may be present, but is not sufficient to account for the nature and severity of the observed speech disorder".

RESULTS

The characteristics of the children evaluated are described in Table **1**. Two children were nonverbal at the time of testing, but demonstrated evidence of both receptive and expressive language delays. Because they were nonverbal, formal evaluation for apraxia was unable to be performed.

Overall, 50% of the children evaluated had both receptive and expressive language deficits. Fourteen of the thirty children evaluated had evidence of apraxia (47%). Eight of those children with apraxia were male (57%). Of those with evidence of apraxia, 10 had PWS due to deletion (71%; $p<0.001$) and only 4 had UPD. Within the deletion sub-type, seven of the children with apraxia (50%) had type 1 deletions (between BP1 and BP3) while only one had a type 2 deletion (between BP2-BP3; $p=0.045$) and the remainder had not yet had their deletion subtyped. Six of the children with apraxia had a significant receptive/expressive language gap of

Table 1: Characteristics of Participants

Genetic Subtype	N	Sex	Age (months) [mean]	Unintelligible Speech	Expressive speech/language delay	Receptive speech/ language delay	Non- verbal
UPD	14	57% male	18 -72 [29 months]	29%	57%*	0%	14%
Deletion (non-specific)	7	86% male	18– 48 [31 months]	57%	43%	0%	0%
Type 1 Deletion	7	29% male	22 -36 [26 months]	71%*	29%	0%	0%
Type 2 Deletion	2	50% male	36-108 [72 months]	0%	50%	50%	0%

*p<0.001.

greater than 12 months. Five children could not be tested for expressive language age equivalency scores because of lack of cooperation with the examiner, and the remaining 3 children were equally delayed in both receptive and expressive language. Those children with apraxia who were tested using the GFTA-2 or PLS-4 (n=13) had age equivalency scores that were 2 or more years delayed compared to their chronologic age.

Four of the males with apraxia had severe behavioral problems, one of which necessitated inpatient placement for management of psychiatric medications. Subsequent to this analysis, two of the females with apraxia developed significant behavioral issues, suggesting a possible correlation between the presence of apraxia and the development of behavioral problems in PWS.

DISCUSSION

Speech and language delays are extremely common in children with PWS making evaluation by a speech pathologist imperative in this population. In this study, we confirmed a high frequency of both expressive and receptive language delays within this population of children. Therefore, early evaluation by a speech-language pathologist is essential for children with PWS, as studies have shown that early and frequent treatment of speech delays can improve clinical outcomes.

ASHA has proposed that the term “childhood apraxia of speech” (CAS) be used when apraxia occurs due to a known neurological condition; as part of a known or unknown genetic or metabolic neurobehavioral condition; or when the cause is unknown and not part of a more complex condition [17]. As PWS is a known genetic syndrome with associated neurological issues, our study suggests that CAS is highly prevalent in these children. Treatment for CAS should be instituted as early as possible and studies suggest that optimizing motor learning is an essential part of the treatment [19]. Many of the children in our study had been unsuccessfully treated using oral motor strengthening exercises [20] prior to evaluation by our program due to the fact that historically the speech abnormalities in PWS have been attributed to hypotonia. However, studies have shown that these types of exercises, while they do improve the strength of oral movements, do not carry over and actually improve speech in children with CAS [19]. In this study we confirmed that this treatment

Table 2: Characteristics of Children with PWS/Apraxia

Genetic Subtype		Sex	Receptive Delay	Expressive Delay	Receptive/ Expressive Language Gap
UPD	4	75% male	0%	100%	100%
Deletion - nonspecific	2	75% male	67%	100%	67%
Type 1 Deletion	7*	67% male	50%	33%	33%
Type 2 Deletion	1	0% male	Yes	Yes	None

*p<0.05.

approach was universally unsuccessful in children with PWS diagnosed with CAS.

There are three classical approaches to treatment of CAS, including tactile/gestural approaches, prosodic or melodic approaches, and articulatory approaches [19]. Tactile and gestural approaches to treatment of CAS use touch and gesture to cue children regarding articulatory placement and movement. These approaches use tactile and kinesthetic feedback from placing the child's hand or fingers on their face, arm, or chest to cue place and manner of articulation [21]. These methods incorporate the tactile, as well as simultaneous auditory and visual cues to assist with speech production. There is controversy as to whether using non-speech techniques is effective for treatment goals of improved speech production [19]. However, the individuals with PWS and apraxia in this study all responded well to tactile cueing techniques, with improved speech production, increased smoothness of articulation, and fewer verbal errors.

It is interesting to note that seven children with apraxia had type 1 deletions, considering reports that deletions or duplications of chromosome 15q11.2 between BP1 and BP2 are associated with speech and motor delays [22, 14]. Since type 1 deletions include the area between BP1 and BP2, this study provides additional evidence that the four genes between BP1 and BP2 likely play an important role in speech and language development.

CONCLUSIONS

In conclusion, we confirmed that there is a high prevalence of speech and language delay in children with PWS, but also discovered that CAS may be the cause of some of these delays, and therefore children with PWS need to be evaluated, diagnosed, and treated for CAS as soon as possible. Tactile cueing techniques work well in this population of children and should be considered by speech-language pathologists working with children with PWS and apraxia.

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