Children with 7q11.23 Duplication Syndrome:

Speech, Language, Cognitive, and Behavioral Characteristics and their Implications for Intervention

Shelley L. Velleman, Ph.D., CCC-SLP
Department of Communication Sciences and Disorders
402 Pomeroy, 489 Main Street
University of Vermont
Burlington VT 05405
shelley.velleman@uvm.edu
802-656-3868

Carolyn B., Mervis, Ph.D.
Department of Psychological and Brain Sciences
317 Life Sciences Building
University of Louisville
Louisville, KY 40292
cbmervis@louisville.edu
502-852-3604

Preparation of this manuscript was supported by grants # R01 NS35102 from the National Institute of Neurological Disorders and Stroke and R37 HD29957 from the National Institute of Child Health and Human Development (C. B. Mervis, PI).
Abstract

7q11.23 duplication syndrome is a recently-documented genetic disorder associated with severe speech delay, language delay, a characteristic facies, hypotonia, developmental delay, and social anxiety. Developmentally appropriate nonverbal pragmatic abilities are demonstrated in socially comfortable situations. Motor speech disorder (Childhood Apraxia of Speech and/or dysarthria), oral apraxia, and/or phonological disorder or symptoms of these disorders are common as are characteristics consistent with expressive language disorder. Intensive speech/language therapy is critical for maximizing long-term outcomes.
7q11.23 duplication syndrome (Dup7) is caused by a duplication (extra copy) of the ~26 genes that are deleted in Williams syndrome (WS). (Dup7 is sometimes referred to as “duplication of the Williams syndrome region;” this terminology is particularly likely to be used in reports describing the results of genetic testing.) From the time the genetic basis for WS was discovered (Ewart et al., 1993) it was assumed that there also would be a syndrome caused by a duplication of the same region (same set of genes). However, researchers had no idea what the phenotype (characteristics) associated with this syndrome would be, other than that it would be different from that for WS (see Mervis & Velleman, this issue). Thus, it is not surprising that the first documented case of Dup7 (Somerville et al., 2005) was found by chance; this child, who had a severe speech delay and was being tested for velocardiofacial syndrome, was instead found to have Dup7. It is important to note, however, that although this child was the first confirmed case of Dup7, many children with undiagnosed Dup7 have been and will continue to be on SLP caseloads. In fact, an adult participant in our research who was diagnosed with Dup7 following her son’s diagnosis is pictured as a child client in Hodson and Paden’s 1991 book, *Targeting Intelligible Speech* (Hodson, personal communication, November 19, 2008).

The prevalence of Dup7 is unknown. However, it may be estimated based on the prevalence of WS (1 in 7500 live births) and known genetic mechanisms causing deletions and/or duplications. Based on this information, the *de novo* prevalence of Dup7 is estimated to be 1 in 12,000. As illustrated by Hodson’s former child client, however, many individuals with Dup7 have children of their own. Dup7 is autosomal dominant, meaning that if the mother or father has Dup7, there is a 50% chance with every pregnancy that the child will have Dup7. Once these children are factored in, the prevalence of Dup7 is estimated to be 1 in 7500 live births (Osborne & Morris, personal communication). So far, approximately 50 cases have been described in the scientific literature (e.g., Berg et al., 2007; Osborne & Mervis, 2007; Somerville et al., 2005; van der Aa et al., 2009) and we, in collaboration with Colleen Morris, M.D., have studied about 30 additional children with Dup7.
Given the relatively small number of children with Dup7 who have been studied, it is not surprising that the phenotype is not yet well defined. Although the authors of the first case series to be published (Berg et al., 2007) concluded that there was not a recognizable facies (facial configuration) associated with Dup7, more recent research has indicated that Dup7 is indeed associated with a characteristic facies, as illustrated in Figure 1. Common facial features include a broad forehead, a short philtrum, and a thin upper lip (Merla et al., 2010; Morris, personal communication; van der Aa et al., 2009). Facial asymmetry is very common and macrocephaly has been reported (Berg et al., 2007; Morris, personal communication; Somerville et al., 2005). Hypotonia is very common (Berg et al., 2007; Morris, personal communication; van der Aa et al., 2009). Most young children with Dup7 have developmental delay; the intellectual abilities of preschool and school-age children with Dup7 range from moderate intellectual disability to average for the general population (Berg et al., 2007; Osborne & Mervis, 2007; van der Aa et al., 2009). One of the most prominent phenotypic characteristics, mentioned in all journal articles presenting case reports of individuals with Dup7, is severe speech delay. As described below, characteristic cognitive/language and personality/behavior profiles are beginning to be fleshed out.

Figure 1. Three children who have 7q11.23 duplication syndrome, aged 2 years, 7 years, and 9 years.
Intellectual Abilities

During the toddler and early preschool period (ages 1 – 4 years), most children with Dup7 evidence developmental delay. As most of the publications on Dup7 are case series, very few standardized assessment scores are available. Our research group has evaluated 13 children in this age range using the Mullen Scales of Early Learning (Mullen, 1995). Children’s overall Early Learning Composites [ELC; similar to Developmental Quotient (DQ)] ranged from the moderate developmental delay range to average for the general population [49 [(lowest possible) – 102] with the median DQ in the borderline range. Performance was best on the Visual Reception (nonverbal reasoning) and Receptive Language scales, with median performance in the low average to average range. Consistent with the hypotonia associated with Dup7, median performance on the Fine Motor scale was in the borderline to mild delay range. As expected given the severe speech delay associated with Dup7, median performance on the Expressive Language scale was in the mild delay range, with 6 of 13 children earning the lowest possible standard score (SS), even though signed responses and verbal approximations were accepted as correct. One child scored in the average range.

We also have evaluated 25 children aged 4 – 15 years using the Differential Ability Scales-II (DAS-II; Elliott, 2007), a full-scale measure of intellectual abilities. Mean General Conceptual Ability (GCA; similar to IQ) was in the low average range, with GCAs ranging from the moderate disability to high average range (45 – 118). Mean SSs were in the low average range on the Verbal, Nonverbal Reasoning, and Spatial clusters, with performance on the Spatial cluster improving considerably with age. Mean SSs were in the borderline range for the Working Memory and Processing Speed clusters.

Behavioral Profile

The personalities of children with Dup7 (who have three copies of a set of 26 genes on chromosome 7q11.23) are very different from those of children with WS (who have one copy of these genes). The most striking difference is in shyness/social approach. Whereas children with WS are highly
gregarious, often evidencing socially inappropriate approach, children with Dup7 are typically quite shy, often appearing withdrawn when around strangers. As part of our research, children aged 4 – 16 years are evaluated for internalizing and disruptive disorders. More than 75% of the children met DSM-IV criteria for at least one anxiety disorder, with more than 50% diagnosed with Specific Phobia and/or Social Anxiety, more than 25% with Separation Anxiety, and several with Selective Mutism. In addition, ~50% met DSM-IV criteria for Attention Deficit Hyperactivity Disorder (ADHD) and ~20% were diagnosed with Oppositional Defiant Disorder (ODD). Most of the children evidenced repetitive behaviors as assessed by the Repetitive Behavior Scales (Bodfish et al., 2000) and most were classified on the Short Sensory Profile (Dunn, 1999) as demonstrating definite sensory modulation difficulties.

The combination of extreme shyness around strangers, social anxiety, selective mutism, repetitive behaviors, sensory modulation difficulties, and significant (often severe) speech and/or speech/language disorder has resulted in many children with Dup7 being considered for an autism spectrum disorder (ASD) diagnosis and some children receiving the diagnosis (e.g., Berg et al., 2007; van der Aa et al., 2009). In fact, the authors of two recent genetics articles (Levy et al., 2011; Sanders et al., 2011) have argued that Dup7 is strongly associated with autism. However, children with Dup7 also evidence important characteristics that are not consistent with ASD. For example, in play sessions with their parents, the participants in our study reliably demonstrated social communication strengths such as appropriate eye contact during communicative acts, clear pleasure in interacting with their parent, shared enjoyment, and creative and imaginative play. As the children became more comfortable in the research setting, these types of appropriate interactive behaviors increased considerably during interactions with the researchers. Thus, in most cases the reluctance of children with Dup7 to engage with people they do not know well is likely secondary to their severe speech and/or anxiety problems, rather than to ASD.

**Speech-Language Profile**
From the first report of a child with Dup7, significant speech-language delays/disorders have been listed as among the syndrome’s primary characteristics (e.g., Berg et al., 2007; Merla et al., 2010; Osborne & Mervis, 2007; Somerville et al., 2005; van der Aa et al., 2009). Only a few reports (e.g., Osborne & Mervis, 2007; Somerville et al., 2005) have detailed the nature of these communication disorders, however.

**Speech Sound Production Skills**

Oral motor and speech sound delays and disorders are the most common and severe characteristics of Dup7. Of 42 adults and children (aged 18 months to 61 years) with classic Dup7 whom we have assessed, all but one had some detectable ongoing oral motor or speech sound symptoms. (The child who had no current speech symptoms had received speech/language therapy previously.) These symptoms were divided into four categories: oral apraxia, verbal apraxia [Childhood Apraxia of Speech (CAS)], phonological disorder, and dysarthria. Oral apraxia included non-speech planning symptoms such as groping while trying to protrude the tongue and difficulty producing sequences of oral postures (e.g., stick out your tongue then smile). Verbal apraxia included speech planning symptoms such as effortful, choppy speech; difficulty sequencing speech (e.g., “say a-i-u”, diadochokinesis); reduced variety of syllable or word shapes (e.g., restriction to CV syllables, lack of clusters at ages at which they would be expected); vowel deviations; and groping during speech. Phonological disorder included patterned speech errors with no evident motoric basis (e.g., stopping, fronting). Dysarthria included non-speech and speech symptoms indicating weakness, low or high muscle tone, voice differences, movement asymmetries, or poor coordination of the muscles themselves.

Most participants demonstrated mixed motor speech disorders, with symptoms in more than one area. Most of the toddlers produced very limited speech and few identifiable meaningful words. Typically, their syllable and word shapes were very simple; they often relied upon CV syllables with frequent reduplication or harmony and few or no final consonants or clusters. Observations of their
feeding skills and elicited oral imitations typically identified symptoms of both apraxia and dysarthria, although these children were too young for a full diagnosis of these disorders.

Among the 25 children with Dup7 aged 4 – 15 years whom we have studied, >75% either met full criteria for a diagnosis of CAS or showed symptoms of CAS and >75% exhibited either dysarthria or symptoms of dysarthria. More than 50% demonstrated phonological disorder or phonological symptoms and >50% had oral apraxia or oral apraxia symptoms. Phonotactic deficits also were present. That is, word and syllable shapes were simpler than expected for the children’s ages and speech sound error patterns frequently included cluster reduction and weak syllable deletion. Vowel deviations, such as are typically seen in children with CAS, were also frequent. Many children demonstrated effortful, choppy speech typically resulting in inappropriate word stress patterns.

We have also assessed the speech of eight adults with Dup7 (aged 28 – 61 years, all diagnosed following the diagnosis of a child or grandchild). Most had learned to compensate well for their difficulties; the errors they made were primarily in challenging multisyllabic words (e.g., “aluminum”) or tongue twisters. None of the adults demonstrated enough symptoms that were severe to be diagnosed with a speech disorder although the majority evidenced some symptoms of CAS, phonological disorder (residual error patterns such as gliding or deaffrication), and/or dysarthria and some also evidenced features of oral apraxia.

**Language Skills**

Very young children with Dup7 consistently demonstrate language delay, with expressive delay typically in the moderate to severe range. Receptive language ability ranges from average for the child’s age to moderately delayed. For school-age children, there is considerable discrepancy in vocabulary and grammatical abilities between those who have had consistent speech/language therapy from the late infant or early toddler period and those who have not. For children who have had consistent speech/language therapy, mean level of performance is in the average range for receptive vocabulary...
[as measured by the Peabody Picture Vocabulary Test-4 (PPVT-4; Dunn & Dunn, 2007)], expressive vocabulary [as measured by the Expressive Vocabulary Test-2 (Williams, 2007)], and receptive grammar [as measured by the Test for Reception of Grammar-2 (TROG-2; Bishop, 2003) although a broad range of levels—from moderate disability to above average has been found. Expressive grammar [as measured by the Clinical Evaluation of Language Fundamentals-4 (Semel et al., 2003) and language samples] typically is considerably more delayed.

When consistent speech/language therapy has not been provided, school-age children with Dup7 do not fare nearly as well. Their receptive vocabulary abilities tend to be in the low average range and are considerably better than their expressive vocabulary abilities, which typically are at the severe disability level (Osborne & Mervis, 2007; Somerville et al., 2005). Both receptive and expressive grammar also are typically at the severe disability level.

**Literacy Skills**

We have assessed the literacy skills of 12 school-age children with Dup7 aged 7 – 15 years. The primary method of reading instruction was phonics for nine children and sight/whole word for three. The children taught to read using phonics earned median SSs on the Wechsler Individual Achievement Test-III (WIAT-III; Wechsler, 2009) in the average range for Word Reading, Pseudoword Decoding, Reading Comprehension, and Oral Reading Fluency (with SSs ranging from low average to above average on all subtests), although performance on Word Reading was stronger than on Oral Reading Fluency. The children taught primarily with sight-word methods had considerably more difficulty, with SSs in the mild disability to low average range across subtests.

**Social-Pragmatic Skills**

As described above, individuals with Dup7 typically demonstrate a relative strength in pragmatics if they are interacting with people with whom they are comfortable. The toddlers who have participated in our research evidence good nonverbal communication skills, using eye gaze combined
with communicative gestures such as pointing to make their message clear to the recipient. Once the children are able to talk, they incorporate words or word approximations into these communications. Older children who continue to have difficulty communicating verbally (often because they have had very limited speech therapy) typically compensate nonverbally, using gesturing or mime combined with drawing or writing to make their intended meaning clear. Children with Dup7 who have been exposed to sign language have typically successfully adopted it as a supplemental communication strategy. In some cases, augmentative and alternative communication (AAC) devices also have been used successfully. Children with Dup7 usually enjoy engaging in imaginative play and often evidence an excellent sense of humor. These strong pragmatic skills may be hidden in unfamiliar or uncomfortable contexts or with new conversational partners. Lack of eye contact, minimal responsivity or resistance to interaction, use of others as interpreters, and even selective mutism may be observed under these circumstances.

**Clinical and Educational Implications**

It is vital for speech-language pathologists (as well as psychologists and physicians) to be aware of this recently identified syndrome and consider it as a possible diagnosis when evaluating someone with the associated speech-language and social-behavioral profiles and the characteristic facies. The relevant speech/language characteristics include mixed oral-motor and motor speech symptoms; severe speech delay; and expressive language delay. Commonly associated behavioral difficulties include social anxiety sometimes accompanied by selective mutism, ADHD, ODD, and sensory processing differences. Importantly, the consequences of social anxiety, selective mutism, sensory processing differences, and expressive speech and language delay should be carefully distinguished from ASD.

Appropriate speech-language goals for children with Dup7 include age-appropriate non-speech oral motor functions (e.g., feeding); communicative competence in the nonverbal (e.g., gestures, eye contact, joint attention) modality; and intelligible, grammatical, and effective oral communication, as appropriate to the child’s age, developmental level, and severity of involvement. All of these areas of
competence should be evaluated and addressed as appropriate. In cases of moderate to severe oral communication delay, goals addressing non-oral (e.g., sign language, PECs, AAC devices) communicative modalities should be included as well.

For the majority of children with Dup7 who demonstrate at least some symptoms consistent with CAS, strategies developed to remediate motor speech programming and planning deficits are most appropriate. For children who have little or no useful oral communication, the initial goal is automaticity – to facilitate the development of a core set of highly functional, phonetically simple vocalizations, such as “no”, “more”, and “mine”. These should be selected through consultation with all relevant stakeholders – family, school, therapists, etc. Because sound effects (“pow”, “baa”, etc.) and emotional words (“uh-oh”, “whee”, “wow”, “ooh”, etc.) are typically both phonetically simple and easier for children with motor planning/programming disorders to produce, these are often good choices.

The use of verbal routines – such as songs, predictable books, and greeting or bedtime rituals – is also very helpful for young children. These involve low communication pressure, especially when produced in unison (e.g., singing or reciting in the classroom), because they are predictable. Verbal routines selected through consultation with relevant adults can be carried through in all contexts, thereby maximizing their automaticity and functionality for the child.

However, it is important to note that facilitating automaticity for a set of words and phrases does not address the core problem associated with motor programming/planning disorders. The most powerful feature of human communication is its flexibility. Once the child has a core set of communicative vocalizations and a clear understanding of the functions and benefits of oral communication, other strategies must be used to develop his or her ability to program and plan intelligible novel utterances at will.

Appropriate motor speech programming/planning strategies for this purpose include multi-modal input, including tactile cues such as those used within Prompts for Restructuring Oral Motor
Children with 7q11.23 Duplication Syndrome 12

Phonetic Targets (PROMPT; Hayden, 2004). A recent study by Dalton (2011) suggests that children with suspected CAS may benefit more from tactile cues than from auditory + visual cues (i.e., visual imitation on command). Participants in our study have benefited from PROMPT therapy. Other types of multimodal input include rhythmic cues (e.g., singing), gestural cues, and speaking in unison (Strand & Skinder, 1999). However, modeled rhythms should always be speech-like. Otherwise, robotic "excess equal stress" speech (Shriberg, Aram, & Kwiatkowski, 1997), which calls negative attention to the speaker, may result. Also, the SLP can use puppets, finger plays, gestures, sign, or augmentative communication devices to draw the child’s focus away from the mouth, a tactic that is especially helpful for children with selective mutism. Such non-speech forms of communication (and AAC of any kind) are not intended to replace oral communication, but rather to supplement and facilitate it by reducing communication pressure associated with speech. Gestures, picture cues – such as those provided in the Fokes Sentence Builder (Fokes, 1976) – or written words for those who are old enough, can be used to help the child to structure longer utterances, such as those including multiple words.

Other relevant principles of motor learning include repetitive practice; many trials are necessary. However, excessive repetitions of the same stimuli are not appropriate, as they yield automaticity but not flexibility. Motor learning studies demonstrate that motor patterns are learned and generalized more effectively when a variety of exemplars is practiced and when practice of different patterns is alternated. For example, when working on production of final consonants, a variety of consonants (that are already in the child’s repertoire) should be targeted in that position. In addition, one other goal should be included in the same session, in alternating fashion if possible. Finally, feedback frequency should be gradually decreased so that the child will begin to self-monitor instead of relying on external feedback alone.

As indicated above, phonotactics – production of more complex word and syllable shapes – is an area of particular weakness for many children with Dup7 (as it is for children with CAS). Therefore, it is
often appropriate for phonotactic goals – such as production of final consonants, consonant clusters, and weak syllables – to be prioritized. Note that articulatory accuracy is not the target of such goals. For example, if the objective is that the child will produce final consonants in CVC words, the production of any final consonant meets that goal. The correct final consonant should always be modeled, but articulatorily inaccurate responses should be accepted as long as the coda position is filled (i.e., some final consonant is produced).

Because progress tends to be gradual, objectives should target small, systematic, achievable steps. For example, for a child with many vowel deviations, it is more appropriate to start with an objective such as, “Sherry will produce high vowels as such 90% of the time” – i.e., when attempting to produce a word with a high vowel (such as [i, u, ɪ, ʊ]), she will produce any high vowel, but not a mid or low vowel – rather than “Sherry will produce vowels with 90% accuracy,” a vague and overwhelming goal. As noted above, the correct model should always be provided even if an approximation will be accepted in the response.

When remediating morphological deficits, it is important to take phonetic factors as well as grammatical factors into account. Although this is not the typical order of acquisition, it is easier for children with significant motor speech disorders (or other speech sound disorders) to produce whole-syllable morphemes (such as “ing” and the plural “es” in “horses”, the third person singular “es” in “catches”, or the past tense “ed” in “patted”) than those that require the production of a cluster (such as the [nz] of “pans” or the [kt] of “kicked”). As long as some portion of the syllable is present, the meaning of the morpheme is communicated (e.g., if the child says [hoʔiʔ] for “horses”, the listener will recognize the plural even though the final [z] is not produced). As noted above, gestural, pictorial (e.g., Fokes Sentence Builder), or written cues can help the child to learn to formulate new sentence structures.
Children with speech sound disorders and/or language disorders are at increased risk for phonological awareness and literacy deficits. Research has demonstrated that intervention that addresses speech production and phonological awareness/literacy in tandem yields stronger results in both domains (Moriarty & Gillon, 2006). Materials such as Lindamood LiPS (Lindamood & Lindamood, 1998) that take such an approach, including phonics training, can facilitate this work.

For adolescents with Dup7 who have persistent speech-language issues, the focus of intervention may shift to self-monitoring/self-teaching strategies, listener awareness, repair strategies, and self-advocacy. For example, older students might be taught skills for determining and practicing the pronunciation of unfamiliar multisyllabic words encountered in academic contexts. Another role for the SLP could be in helping the student to prepare for oral presentations, including a voice in the determination of the assigned grades for such projects.

Findings from a pair of case studies (Currier, Velleman & Mervis, 2010) that we have carried out and another child who made quite striking progress have reinforced the hypothesis that appropriate, intensive speech-language therapy, when combined with behavioral intervention and appropriate academic supports, makes a large positive difference in the outcomes of children with Dup7. It is very important to note that behavioral challenges, especially ODD, may interfere with the children’s ability to benefit from intervention if they are not assertively addressed both at school and at home. Thus, strong family and academic supports that address social-behavioral skills as well as speech-language and academic skills are critical for children with Dup7. Duplication Cares (www.duplicationcares.org), a support group created by families of children with Dup7 for other such families, provides very helpful information as well as the opportunity for families to share challenges and triumphs.

Intense one-on-one speech-language therapy provided by a licensed, certified speech-language pathologist with experience in motor speech disorders is almost always required for young children with Dup7 to introduce new skills and address areas of greatest challenge. In addition, small group therapy
(e.g., 3 children total, including the child with Dup7) or therapy provided by an SLPA or a less experienced SLP may supplement primary therapy for carryover of skills emerging from more intense therapy sessions. Session durations will vary depending on the child’s attention span and related factors, but in our experience at least two or three hours of therapy per week with a licensed, certified SLP are typically necessary. As the child’s intelligibility, sentence formulation, and literacy skills approach age expectations, the frequency of therapy may be reduced.

Participation in class is a challenge for most children with Dup7, due to both their significant speech-language difficulties and their social anxiety. This challenge will be compounded, in some cases, by ADHD, ODD, and/or selective mutism. These problems will be best addressed if teachers, SLPs, psychologists, and other individuals involved in the children’s education and care work together with their families.

Conclusion

Children with Dup7 and their families face many speech-language and social-behavioral challenges that may mask the children’s strong potential for progress in communication, cognitive, and academic arenas. SLPs can play a crucial role, through advocacy and support as well as intensive specialized intervention, in maximizing the long-term outcomes for individuals with this syndrome.
References


Osborne, L. R., & Morris, C. A. (2011, August 30). Personal communication.


