Expanding the speech and language phenotype in Koolen-de Vries syndrome: late onset and periodic stuttering a novel feature

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Abstract

Speech and language impairment is core in Koolen-de Vries syndrome (KdVS), yet only one study has examined this empirically. Here we define speech, language, and functional/adaptive behaviour in KdVS; while deeply characterising the medical/neurodevelopmental phenotype in the largest cohort to date. Speech, language, literacy, and social skills were assessed using standardised measures, alongside an in-depth health and medical questionnaire. 81 individuals with KdVS were recruited (35 female, mean age 9 y 10mo), 56 of whom harboured the typical 500–650 kb 17q21.31 deletion. The core medical phenotype was intellectual disability (largely moderate), eye anomalies/vision disturbances, dental problems, sleep disturbance, musculo-skeletal abnormalities, and cardiac defects. Most were verbal (62/81, 76.5%), while minimally-verbal communicators used alternative and augmentative communication (AAC) successfully in spite of speech production delays. Speech was characterised by apraxia (39/61, 63.9%) and dysarthria (28/61, 45.9%) in verbal participants. Stuttering was described in 36/47 (76.6%) verbal participants and followed a unique trajectory of late onset and fluctuating presence. Receptive and expressive language abilities were commensurate, but literacy skills remained a relative weakness. Social competence, successful behavioural/emotional control, and coping skills were areas of relative strength, while communication difficulties impacted daily living skills as an area of comparative difficulty. Notably, KdVS individuals make communication gains beyond childhood and should continue to access targeted therapies throughout development, including early AAC implementation, motor speech therapy, language/literacy intervention, as well as strategies implemented to successfully navigate activities of daily living that rely on effective communication.

Introduction

Koolen-de Vries syndrome (KdVS) is a chromatin-related disorder caused by haploinsufficiency of the *KANSL1* gene. It is caused by either a variant in *KANSL1* or by a deletion of chromosome 17q21.31 that encompasses *KANSL1* [1–4]. The prevalence of a 17q21.31 deletion is estimated at 1 in 55,000 individuals, while limited cases with pathogenic *KANSL1* variants have been identified yet, the actual overall prevalence of KdVS might be 1 in 30,000 individuals [5].

Core features of KdVS are developmental delay and intellectual disability (largely within the mild to moderate range), early childhood hypotonia, characteristic facial dysmorphism, and behavioural characteristics, including a friendly and amicable disposition [2]. Other recurrent features are congenital heart defects, structural brain anomalies, kidney and urogenital concerns, vision issues, and epilepsy [2].

A striking speech and language profile is a key component the KdVS phenotype. A study of speech and language in 29 individuals with KdVS documented markedly delayed speech, with first words not achieved until 2–7 years of age. Speech acquisition is slow and effortful, with a core early diagnosis of childhood apraxia of speech (CAS), alongside oromotor hypotonia. Once CAS resolves, dysarthric features become more prominent with poor intelligibility (ability to be understood) extending into the

teenage and adult years [6]. Stuttering was noted in 3/18 participants by Morgan et al. [6] but was not systematically explored.

Morgan et al. [6] attempted to systematically investigate language, showing that receptive and expressive language abilities are typically commensurate. Whilst linguistic development is slow, such skills do continue to develop, and most verbal children can form sentences by the middle school years. Literacy impairment was also noted in 6 individuals, but most (n = 22) could not be assessed with standardised tools (i.e. too young, no access to assessment tools). Further, most of the cohort were under 5 years of age and were unable to be assessed [6], and as such, early reading and writing abilities remain relatively unexplored.

Social skills have been noted as a relative strength in KdVS, yet have only been empirically examined in n = 3 individuals using standardised measures [7]. Given the critical involvement of speech and language within the KdVS phenotype, here we conduct a comprehensive study of speech, language, literacy and social skills using standardised tools, in a large cohort of individuals with KdVS. Considering the complex medical and neurodevelopmental features that are often present in KdVS, we explore these features, and how they interact with and impact the speech and language profile of the condition. In addition, we utilise adaptive functioning and behaviour measures to provide an understanding of how the communicative abilities in KdVS affect activities of daily living.

Materials & Methods

Participants

Participants were recruited via study flyers posted on Koolen-de Vries Syndrome Foundation social media pages (i.e., website, Facebook, newsletter), study advertising at the Koolen-de Vries Syndrome Patient Advocacy Summit, and via the Australian Association of Clinical Geneticists. Inclusion criteria were (a) confirmed genetic diagnosis of KdVS (either a causative variant in *KANSL1* or 17q21.31 deletion inclusive of the *KANSL1* gene) and (b) aged 6 months or older. Exclusion criteria were the presence of any other confirmed genetic variant or syndrome likely to impact the clinical phenotype.

Measures

Caregivers/participants completed assessments, either via online (REDCap-administered) survey and/or videoconference interview, and/or in-person (when possible) as detailed below using our previously validated approach. Caregivers began by completing an in-depth health and medical survey [8–9] and provided relevant clinical reports for medical or developmental diagnoses previously received to confirm survey responses (i.e., intellectual disability, autism). Participants completed a verbal or minimally-verbal assessment protocol according to their abilities.

Language, literacy, and adaptive behaviour

The Vineland Adaptive Behaviour Scales Parent/Caregiver Rating Form – Third Edition [10] provided standard scores for Communication, Daily Living Skills, Socialization, and Motor abilities, as well as an overall Adaptive Behaviour Composite (an average of Communication, Daily Living Skills and Socialisation). Scaled scores were calculated for the subdomains: expressive, receptive, and written (denoting Communication); personal, domestic, and community (denoting Daily Living Skills); interpersonal relationships, play and leisure, and coping (denoting Socialisation); and gross and fine motor (denoting Motor). Normative data for Motor subtests are only available up to age 9y 11m (as all motor skills are expected to be achieved by this point), and so chronologically older individuals were compared against the oldest age data available to estimate the level of motor delay. The Children's Communication Checklist-2 (CCC-2) was used to assess more specific communication domains in verbal participants aged between 4–16 years [11]. Individuals who were chronologically older than the assessment age-range (n = 12), but with linguistic abilities seen in younger persons were compared against the oldest age data available to estimate the level of language delay. The Communication and Symbolic Behaviour Scales Developmental Profile was used to assess early language and social development in those younger than 4 years of age [12].

Speech

Speech was assessed for verbal communicators, including a differential diagnosis across speech conditions (articulation disorder, phonological disorder, dysarthria, childhood apraxia of speech and stuttering). All speech assessments were video- and/or audio-recorded. For non-English speaking families, clinical reports were collected to confirm speech diagnoses.

Articulation (i.e., motor act of producing sounds) and phonological (i.e., understanding the sound contrasts in a given language) abilities were assessed with the Diagnostic Evaluation of Articulation and Phonology (DEAP, [13]). This is a single word test with stimuli designed to assess all the phonemes of English. The presence of dysarthria was determined from rating a five-minute conversational speech sample using the Mayo Clinic dysarthria classification system [14–16]. Childhood apraxia of speech (CAS) was diagnosed by examining connected speech samples, DEAP scores, and production of multisyllabic words (when indicated, using the Single Word Test of Polysyllables, [17]) [16]. Individuals were considered to meet criteria for a CAS diagnosis if they met the three main diagnostic criteria: (1) inconsistent errors, (2) lengthened and disrupted coarticulation between sounds and syllables, and (3) inappropriate prosody [18]. The presence of stuttering was assessed via an in-depth fluency questionnaire, regarding onset, progression and triggers surrounding stuttering (See Appendix). Once identified and rated by a parent, the presence and severity of stuttering was then rated utilising connected speech samples obtained. Stuttering was rated using a 10-point stuttering severity rating scale [19].

Statistical Analyses

One-way ANOVA was used to compare the mean scores across Vineland domains to determine the relative impact on communication, as well as to compare across individual subdomains.

Ethical Considerations

Ethical approval

was obtained through the Royal Children's Hospital, Melbourne, Human Research Ethics Committee (HREC #37353). Written informed consent was obtained from the participant or their parents/legal guardian in the case of minors or adults with intellectual disability.

Results

Medical and neurodevelopmental characteristics

Eighty-one individuals (35 female, 46 male) were recruited. Participants were aged between 1 year 6 months and 40 years 2 months (mean = 9y 10mo, SD = 7y 0mo). Most participants and their families were English-speaking (n = 73, 90.1%), with smaller proportions of Dutch (n = 4, 4.9%), German (n = 2, 2.5%), French (n = 1, 1.2%) and Portuguese speakers (n = 1, 1.2%), Table 1. Most individuals presented with the typical 500- to 650-kb deletion of 17q21.31 encompassing five genes (*CRHR1, IMP5, MAPT, STH, KANSL1*) (n = 56, 69.1%), while n = 4 had larger deletions of 17q21.31 with additional genes deleted (see Table 2). 19 individuals had genetic variants that affected only the *KANSL1* gene (n = 11 truncating variants; n = 7 splice site variants; n = 1 intragenic deletion, exons 5–7). For summary and analysis, intragenic deletions of *KANSL1* were classified within the category of "*KANSL1* variants". A further two individuals had small deletions (54kB and 51kB), not large enough to equate to a "typical deletion" but affecting more than *KANSL1* alone.

Table 1
Medical and Neurodevelopmental Characteristics

Characteristic	**n (%)**
Age, years (mean, SD)	9y10m (7y0m)
Sex	
Male	45 (55.6%)
Female	36 (44.4%)
Primary Language	
English	73/81 (90.1%)
Dutch	4/81 (4.9%)
German	2/81 (2.5%)
French	1/81 (1.2%)
Portuguese	1/81 (1.2)
Developmental delay	78/81 (96.3%)
Intellectual Disability	49/56 (87.5%)
Mild	9/56 (16.1%)
Moderate	29/56 (51.8%)
Severe	11/56 (19.6%)
Too young/not assessed	25/81 (30.9%)
Eye anomalies/vision disturbance	48/81 (59.3%)
Dental problems	36/72 (50.0%)
Sleep disturbance	33/81 (40.7%)
Musculo-skeletal abnormalities	32/81 (39.5%)
Cardiac malformations	32/81 (39.5%)
Epilepsy/seizures	29/81 (35.8%)
Allergies	29/81 (35.8%)
Skin conditions	26/81 (32.1%)
Renal/Urogenital complications	25/81 (30.9%)
Gastrointestinal concerns	24/81 (29.6%)
Hearing impairment	24/81 (29.6%)

Characteristic	n (%)
SNHL	6/81 (7.4%)
Conductive	13/81 (16.0%)
Mixed	5/81 (6.2%)
Mild	11/81 (13.6%)
Moderate	12/81 (14.8%)
Severe	1/81 (1.2%)
Profound	0/81 (0.0%)
Mental health problems (i.e. anxiety, depression)	23/81 (28.4%)
Asthma	16/81 (19.8%)
Behavioural concerns	15/81 (18.5%)
Endocrine disorders	14/81 (17.3%)
Blood/immune disorders	9/81 (11.1%)
Sensory Processing Disorder	9/81 (11.1%)
Developmental Coordination Disorder	8/81 (9.9%)
ADHD	8/81 (9.9%)
Movement disorders	6/81 (7.4%)
Autism	5/81 (6.2%)
Tremor	4/81 (4.9%)
Cerebral palsy	2/81 (2.5%)
Chronic pain	2/81 (2.5%)
Cancer	1/81 (1.2%)
Arthritis	1/81 (1.2%)

Table 2
Genetic Data

ID/s	Genetic anomaly	Variant details incl. minimum deletion, est. breakpoints	Genes affected
20	17q21.31 deletion	1114kB; 43,685,925 – 44,800,046	*CRHR1, IMP5, MAPT, STH, KANSL1, LRRC37A, LRRC37A2, NSF*
56	17q21.31 deletion	1019kB;43,706,895 – 44,725,843	*CRHR1, IMP5, MAPT, STH, KANSL1, LRRC37A, LRRC37A2, NSF*
49	17q21.31 deletion	699kB; 43,513,643 – 44,212,416	*PLEKHM1, CRHR1, IMP5, MAPT, STH, KANSL1*
1	17q21.31 deletion	638kB; 43,574,907 – 44,212,416	*PLEKHM1, CRHR1, IMP5, MAPT, STH, KANSL1*
2, 3, 4, 5, 8, 10, 12, 13, 14, 15, 16, 17, 18, 19, 21, 22, 23, 24, 25, 27, 28, 29, 30, 31, 32, 33, 34, 35, 37, 40, 41, 43, 45, 48, 50, 51, 53, 55, 57, 58, 59,65, 68, 69, 70, 71, 72, 73, 74, 75, 76, 77, 78, 79, 80, 81	17q21.31 deletion	Typical KdVS deletion, 500-650kB; 43,700,000– 44,250,000 range	*CRHR1, IMP5, MAPT, STH, KANSL1*
64	17q21.31 deletion	72kB; 44,047,215 – 44,119,098	*KANSL1, MAPT, STH*
26	17q21.31 deletion	51kB; 44,094,241 – 44,145,588	*MAPT, KANSL1*
61	Truncating variant	c.2066G > A, p.Trp689*	*KANSL1*

NB: RefSeq: NM_001193466, Genome assembly GRCh37/hg19

ID/s	Genetic anomaly	Variant details incl. minimum deletion, est. breakpoints	Genes affected
44	Truncating frameshift variant	c.2659_2660insGA, p.Thr887Argfs*13	*KANSL1*
66	Truncating frameshift variant	c.540delA, p.Lys180Asnfs*22	*KANSL1*
46	Splice site variant	c.1652 + 1G > A	*KANSL1*
52	Splice site variant	c.2830_2837 + 13del21	*KANSL1*
67	Truncating variant	c.1532delT, p.Leu511*	*KANSL1*
9	Splice site variant	c.2837 + 1G > A	*KANSL1*
42	Truncating frameshift variant	c.930delC, p.Lys311Serfs*19	*KANSL1*
47	Truncating variant	c.1816C > T, p.Arg606*	*KANSL1*
11	Splice site variant	c.1289 + 1 G > A	*KANSL1*
54	Truncating variant	c.1042C > T, p.Arg348*	*KANSL1*
39	Deletion exons 5–7	18kB; 44,127,593 – 44,145,131	*KANSL1*
60	Truncating frameshift variant	c.808_809delCT, p.L270Vfs*11	*KANSL1*
38	Splice site variant	c.2837 + 2T > A	*KANSL1*
62	Splice site variant	c.2837 + 4 A > G	*KANSL1*
7	Truncating variant	c.647del, p.Asp216*	*KANSL1*
63	Truncating variant	c.2470 C > T, p.Arg824*	*KANSL1*

NB: RefSeq: NM_001193466, Genome assembly GRCh37/hg19

ID/s	Genetic anomaly	Variant details incl. minimum deletion, est. breakpoints	Genes affected
36	Truncating frameshift variant	c.611dupG, p.Met205Tyrfs*9	*KANSL1*
6	Splice site variant	c.1652 + 5 G > C IVS5 + 5 G > C	*KANSL1*
NB: RefSeq: NM_001193466, Genome assembly GRCh37/hg19			

Dysmorphic facial features were noted in 73/81 participants (90.1%), including pear shaped nose with bulbous nose tip (48/81, 59.3%), ear anomalies (32/81, 39.5%), hypertelorism (25/81, 30.9%), lip/tongue tie (11/81, 13.6%), macroglossia (11/81, 13.6%), narrow mouth/thin lips (7/81, 8.6%), high-arched palate (7/81, 8.6%), underbite (6/81, 7.4%). Two individuals had submucous cleft palates. Medical and neurodevelopmental features are summarised in Table 1, Fig. 1. In those who were assessed for intellectual ability (n = 56), 87.5% had a diagnosis of ID, and most were moderately impaired (29/56, 51.8%). 9/56 (19.6%) had severe ID. 30.9% (25/81) were too young to be assessed or had never been assessed for ID. A diagnosis of developmental delay (DD) by a paediatrician was taken as a comparable measure of ID and was present in 78/81 (96.3%) of individuals. There was a high incidence of eye anomalies and vision disturbances (48/81, 59.3%), most commonly strabismus and hyperopia, dental problems (36/72, 50.0%) including too few teeth and complex orthodontics, sleep disturbances (33/81, 40.7%) often frequent and early waking, musculo-skeletal problems (32/81, 39.5%) including scoliosis and joint laxity, cardiac defects (32/81, 39.5%) most commonly atrial septal defects, and epilepsy and seizures (29/81, 35.8%). To a lesser extent but still highly prevalent were the presence of skin conditions (26/81, 32.1%) i.e., eczema, renal/urogenital complications (25/81, 30.9%), including hydronephrosis and vesicoureteral reflux, gastrointestinal concerns (24/81, 29.6%), often constipation, and mental health problems (23/81, 28.4%) often anxiety. 21/46 (45.7%) males had cryptorchidism (i.e., undescended testicles). 29.6% (24/81) had hearing loss (HL), which was most often moderate (i.e., 40–69 dB HL) and conductive in nature. A complete and detailed list of individual patient comorbidities can be found in Supplemental Table 1.

Language, literacy, and adaptive behaviour

Adaptive functioning was impaired across all participants (mean = 71.6, SD = 10.2) on the VABS, compared to a population mean = 100, SD = 15, and no participant performed within the average range across all subdomains assessed. Four participants (ID23, ID29, ID26, ID51) scored within the average range on the Adaptive Behaviour Composite (an average of Communication, Daily Living Skills and Socialisation); however, even these four individuals scored below average on at least one subdomain. Daily Living Skills were most severely affected (mean = 67.4, SD = 12.4), followed by Communication (mean = 70.2, SD = 15.2), see Table 3. Socialisation was a relative strength (mean = 79.1, SD = 14.3) across the group. Motor skills were also impaired (mean = 72.8, SD = 11.0). One-way ANOVA found a

significant between group difference across Communication, Daily Living Skills and Socialisation Scores (p = 0.0003). Post hoc analyses with a Bonferroni-corrected value of 0.017 revealed that Socialisation scores were better than Daily Living Skills (p = 0.0006) and Communication (p = 0.008). Communication and Daily Living Skills did not differ from one another (p = 0.69).

Table 3
Adaptive Behaviour Scores

	All		***Larger deletions***		***Typical deletions***		***KANSL1 variants***	
Adaptive behaviour domain/subdomain	*Mean*	*SD*	*Mean*	*SD*	*Mean*	*SD*	*Mean*	*SD*
COMM	**70.2**	**15.2**	**73.5**	**10.1**	**69.6**	**16.2**	**70.3**	**9.9**
rec	*10.4*	*3.5*	*11.0*	*1.8*	*10.4*	*3.6*	*10.4*	*3.1*
exp	*10.4*	*3.7*	*9.3*	*1.7*	*10.4*	*4.1*	*10.5*	*2.9*
wrn	*8.3*	*3.5*	*9.0*	*4.4*	*8.2*	*3.6*	*8.3*	*2.6*
DLS	**67.4**	**12.4**	**73.5**	**4.5**	**65.7**	**12.5**	**67.1**	**8.2**
per	*9.0*	*3.1*	*9.3*	*1.5*	*8.7*	*3.2*	*9*	*2.7*
dom	*9.8*	*2.3*	*10*	*1.0*	*9.7*	*2.4*	*9.8*	*1.7*
cmm	*8.6*	*2.5*	*10*	*1.0*	*8.4*	*2.4*	*8.6*	*1.7*
SOC	**79.1**	**14.3**	**81.3**	**5.0**	**79**	**14.8**	**79.2**	**10.2**
ipr	*11.5*	*2.9*	*12.0*	*1.6*	*11.5*	*3*	*11.5*	*2.4*
pla	*11.1*	*3.3*	*11.0*	*0.8*	*11.3*	*3.3*	*11.1*	*3.0*
cop	*11.3*	*2.7*	*11.0*	*1.0*	*11.3*	*2.7*	*11.4*	*2.2*
ABC	**71.6**	**10.2**	**74.5**	**3.4**	**71.0**	**10.7**	**71.6**	**6.3**
MOT	**72.8**	**11.0**	**72.5**	**3.7**	**71.7**	**9.6**	**71.7**	**7.7**
gmo	*10.7*	*2.5*	*9.8*	*1.0*	*10.5*	*2.3*	*10.6*	*2.3*
fmo	*9.1*	*2.7*	*9.3*	*1.5*	*8.9*	*2.8*	*8.9*	*2.1*

COMM, Communication; rec, receptive; exp, expressive; wrn, written; DLS, Daily Living Skills; per, personal, dom, domestic; cmm, community; SOC, Socialisation; ipr, interpersonal relationships; pla, play and leisure; cop, coping; ABC, Adaptive Behaviour Composite, MOT, Motor; gmo, gross motor; fmo, fine motor

Individuals with KdVS were impacted across all subdomains of the VABS, see Table 3. The most affected domains were in the 'Written' subdomain, i.e., reading and writing skills (mean = 8.3, SD = 3.5), and the 'Community' subdomain, i.e., functioning in the world outside the home, including safety and using

money (mean = 8.6, SD = 2.5). Individuals showed relative strength across all Socialisation subdomains, including 'Interpersonal Relationships' i.e. responding and relating to others (mean = 11.5, 2.9), 'Play and Leisure' i.e. engaging in play and activities with others (mean = 11.1, SD = 3.3), and 'Coping' i.e., behaviour and emotional control across situations (mean = 11.3, SD = 2.7).

In regard to subdomain differences, one-way ANOVA found a significant between group difference across the 11 subdomains (*p = 0.00*). Post hoc analyses with a Bonferroni-corrected value of 0.006 revealed that average 'Receptive' language scores were better than 'Written' language scores (p = 0.0006), while 'Community' skills were poorer than 'Domestic' skills (p = 0.008) (i.e., completing household tasks such as cleaning up and cooking). Overall, the subdomains of 'Interpersonal Relationships', 'Play and Leisure' and 'Coping' were not commensurate with a number of other areas, indicating relative strengths in the Socialisation domain.

Scores were compared for those with larger deletions versus the typical 500- to 650-kb 17q21.31 deletion versus those with *KANSL1* variants (Table 3). No group differences were observed across scores and no statistical differences were found across these genetic groups across any domain or subdomain assessed (Fig. 2.). Considering deletion breakpoints are not always precisely defined, we also performed the same group comparisons comparing all deletions (larger *and* typical*)* with *KANSL1* variants to ensure no subtle differences were missed. No group differences were observed with this dichotomous split.

Across the 42 verbal patients who completed the CCC-2, the average General Communication Composite (GCC) scores were low (mean = 31.2, SD = 16.2). See Table 4. Average scaled scores across all subdomains were markedly low, in particular for 'Speech' (mean = 2.0), 'Syntax' (mean = 4.0) and 'Use of Context' (mean = 3.2). Individuals had relative strengths in 'Interests' (mean = 5.7), 'Social relations' (mean = 5.5) and 'Nonverbal communication (mean = 5.1). Scaled scores 6 and above (I.e. greater than 15th percentile) indicate skills within normal limits. The average was not above 6 for any subdomain. Again, no group differences were observed across scores when comparing deletions with *KANSL1* variants.

Table 4
Children's Communication Checklist (CCC-2) Scores

	All		*Larger deletions*		*Typical deletions*		*KANSL1 variants*	
Communication domain	*Mean*	*SD*	*Mean*	*SD*	*Mean*	*SD*	*Mean*	*SD*
a. speech	2.0	2.6	0.0	0.0	2.2	2.5	2.2	3.1
b. syntax	4.0	3.8	1.7	2.1	4.3	3.7	4.7	4.2
c. semantics	3.7	2.8	4.3	4.0	3.9	2.8	3.6	2.8
d. coherence	4.0	2.4	3.7	2.1	4.1	2.4	4.2	2.3
e. inappropriate initiation	4.3	2.8	5.3	3.1	4.1	3.1	4.3	0.8
f. stereotyped language	5.0	2.6	4.0	2.6	4.9	2.7	5.5	2.2
g. use of context	3.2	2.9	3.7	4.0	3.1	2.9	3.1	3.0
h. nonverbal communication	5.1	3.0	4.3	5.1	4.9	2.7	6.1	3.1
i. social relations	5.5	2.5	3.3	4.2	5.8	2.6	5.4	1.3
j. interests	5.7	2.3	4.7	2.1	5.9	2.4	5.5	1.9
GCC	**31.2**	**16.2**	**27.0**	**19.2**	**31.4**	**16.3**	**33.7**	**16.0**

GCC, General Communication Composite

Speech disorder profile

CAS and dysarthria

19/81 individuals (23.5%) were classified as non-verbal or minimally-verbal at the time of assessment, however n = 2 of these were younger than 2 years of age. The remainder of the non-verbal or minimally-verbal individuals were aged between 2 years 1 month and 6 years 9 months. All individuals classified as minimally-verbal utilised alternative and augmentative communication (AAC) options or multimodal strategies to communicate, including non-verbal gestures and sign language, low tech options such as picture communication systems, or high tech options such as iPads with dedicated communication applications and speech generating devices. Verbal speech was assessed, for the remainder of the participants (62/81, 76.5%). Differential diagnoses revealed the CAS and dysarthria profiles were most prominent, while sometimes co-occurring with more mild articulation and phonological features. 39/62 (62.9%) had CAS, many alongside more mild features of articulation errors (e.g., interdental lisp) (20/39; 51.3%) and phonological impairment (10/39; 25.6%). 27/62 (43.5%) had clinical features of dysarthria. 68/80 (85.0%) individuals had delayed communication milestones, and 63/80 (78.8%) reported the use of multimodal/AAC options prior to their child's verbal speech development, and as a facilitator to this development. Most utilised multiple AAC forms and systems to support communication, with 39/80

(48.8%) using sign language, 32/80 (40.0%) using low technology visual communication systems like communication boards, and 24/80 (30.0%) using high technology visual communication systems (e.g., Proloquo2Go on an iPad).

Stuttering

The speech fluency questionnaire was completed by 47 families. Individuals who did not complete this questionnaire were either non-English speaking, non-verbal at the time of assessment, or did not finish all questionnaires in entirety.

Stuttering was observed in n = 36 individuals, pertaining to 76.6% of those assessed. Individuals had an average stuttering rating of 4.36 across the 10-point severity rating scale. (Fig. 3a.) Stuttering behaviours were varied, with the most common stuttering behaviours being sound repetitions (n = 17, 47.2%), whole word repetitions (n = 17, 47.2%), syllable repetitions (n = 16, 44.4%), and phrase repetitions (n = 16, 44.4%), see Fig. 3b.

16 of 36 did not display accompanying physical behaviours alongside their stutter (44.4%), although for those who did, the most common physical signs were facial grimaces (including groping) (n = 18, 50.0%), head movements (n = 8, 22.2%), and trunk or limb movements (n = 7, 19.4%). See Supp Fig. 1.

Stuttering onset occurred most often during the ages of 5–6 years (n = 13, 36.1%) and < 4 years (n = 11, 30.6%), however stuttering onset was also reported into the adolescent years for others (participants 69, 63, 71, 77) (Fig. 3c.). For most individuals in this group (n = 22, 61.1%) stuttering had not resolved at the time of assessment and remained a current and significant challenge. For others (n = 10, 27.8%), parents reported that their child's stuttering "comes and goes" significantly over time. At the point of assessment, only n = 4 (11.1%) reported that the stuttering had resolved; this occurring at the ages of 5 years, 7 years, 12 years and 14 years respectively. (Supp Fig. 1)

9/36 individuals (25.0%) reported that their stuttering is brought on by specific situations (under pressure, nervous, or tired), however the majority (27/36, 75.0%) did not report any such triggers. Most parents reported that their children were aware of their own stutter (28/36, 77.8%) and in turn, the majority reported some degree of anxiety due to their stuttering (25/36, 69.4%) (Supp Fig. 1). Of these, parents report that "specific situations" caused the most anxiety (13/27, 48.1.3%) (Supp Fig. 1).

Although n = 36 individuals reported a history of stuttering, only n = 24 (66.7%) had sought speech pathology services, and only n = 16 (44.4%) had received a diagnosis of "stuttering" or "stammering" from a trained speech-language professional. 12/36 (33.3%) individuals had received some form of therapy or intervention, yet only n = 4 (11.1%) had undergone a formal, evidence-based stuttering intervention. One individual completed the Lidcombe Program in a one-to-one setting [19] and had also trialled a smooth speech intervention. Three others had completed a smooth speech intervention alone. All others did not follow any set therapy program but had speech-language pathologists using their own "techniques". Almost always the specific therapeutic techniques for addressing stuttering were not made explicit or shared with parents.

Analysis of factors potentially associated with stuttering development

Several phenotypic and genotypic factors were analysed to identify any associations with the presence of stuttering. Statistically and qualitatively, we saw no association between stuttering and the following factors: history of seizures or epilepsy, medication taken for a neurological condition (i.e. ADHD, epilepsy), or in those with 17q deletions (as opposed to smaller *KANSL1* variants).

Discussion

Here we provide the most comprehensive study of speech, language, and adaptive functioning in individuals with KdVS. Novel features of the study include a detailed analysis of stuttering in the context of the broader medical and neurodevelopmental profile, a characterisation of literacy development and a direct comparison of social skills relative to other domains of functional communication and daily living skills.

A consistent observation [i.e., 6–7] that has not been comprehensively quantified within a cohort, are the strong social skills of those with KdVS. Only one study has examined this systematically in n = 3 [7]. Our data confirmed that social skills are a relative strength for individuals with KdVS. Although standard scores for social skills do sit below the population average, those with KdVS show relative strengths in their development of play skills and ability to form interpersonal relationships with others, in comparison to their overall communication skills and daily living skills. In addition, their higher scores in the 'Coping' subdomain, confirm previous reports of resilience and high frustration tolerance [7]. Such relative strength in coping is perhaps a positive predictive factor for why individuals with KdVS persist with therapies (speech and physical) so successfully; a key in their continued functional gains over many years.

Although communication impairment is key to the KdVS profile, daily living skills were most impaired across the group, with almost all individuals presenting with relative weakness here. Considering the heavy reliance on communication ability (such as reading and talking) in activities of daily living, it is unsurprising that individuals with KdVS have particular struggles around personal care tasks (e.g., dispensing medication correctly), domestic jobs (e.g., reading a recipe) or community activities (e.g., reading street signs or using words to ask for directions). These findings emphasise that, although traditional motor speech therapies and receptive/expressive language work (e.g., vocabulary, syntax) are fundamental in KdVS, it is of equal importance that speech-language pathologists (and other professionals, i.e., occupational therapists, psychologists, educators) pay close attention to how such communication difficulties are affecting the wider activities of daily living at school and in the community, and provide strategies to successfully navigate the world, particularly into adolescence.

Previous research suggested receptive language skills were more intact in comparison to expressive language [5], yet these were commensurate across our group. Reading and writing subdomains were, however, more severely impacted in comparison to receptive language. Considering strikingly delayed

early speech milestones in KdVS, and the known impact of such delays on later literacy, this is unsurprising, but warrants emphasis, as literacy skills should remain a focus in therapy. It is important to note that the literacy subdomain used within our measures includes reading and writing as one score, however it was noted, descriptively, that poor fine motor skills were a significant factor in lowering the literacy scores overall. This is important to note, as individuals should be provided with other means of developing written communication skills that do not rely so heavily on precise fine motor control (e.g., using a keyboard rather than pen and paper).

Previous work described the speech and language profile of KdVS as distinct and largely homogeneous [6], which is emphasised here. Of specific importance is the finding that communication and functional behaviour outcomes do not appear at all influenced by the specific genetic anomaly (i.e., regardless of whether an individual with KdVS has a 17q deletion or a smaller *KANSL1* variant. Our differential diagnosis of speech disorders confirms previous reports of an early apraxic profile; many being diagnosed with CAS alongside delayed speech milestones and early hypotonia. In addition, those in the later childhood and adolescent years often displayed a dysarthric profile, significantly impacting the clarity and intelligibility of speech for both familiar and unfamiliar listeners. Such data emphasises once again, the continued need for motor speech therapies in these individuals, even when the initial development of phonemic repertoire is slow and as CAS begins to resolve.

Previous reports indicate around 17% of individuals with KdVS present with stuttering [5], however the prevalence appears to be higher than originally reported, such that it is one of the key and distinctive speech features of KdVS, in comparison to other neurodevelopmental disorders. Half of the sample from Morgan et al. [6] were under 5 years of age, and so it is not surprising that the true prevalence has not been previously captured, as we saw many individuals develop persistent dysfluency from 5–6 years of age. Past research has indicated that stuttering prevalence in individuals with ID and stuttering in typically developing individuals is 5% and 1% respectively [20, 21], and so a prevalence of 76.6% in our sample is striking. Stuttering in KdVS is distinct, not only in onset but in presentation. While stuttering in the wider population typically begins at 2 to 3 years, stuttering in KdVS appears to emerge later (often between 5–8 years, but also into the teenage years in some). Stuttering onset is thought to coincide with preschool linguistic development, i.e., when children begin to combine words and speak in longer sentences. Considering the delayed speech milestones in KdVS, it is unsurprising that the onset of stuttering would also be delayed; however, this does not explain such high a prevalence of dysfluency. Further work regarding functional brain imaging may assist in understanding the neural networks that may be impacted in KdVS to help better pinpoint the underlying neurobiological mechanisms of the condition to guide more targeted therapies. Only a handful of children had received an evidenced-based stuttering intervention program, and amongst these, none saw a complete resolution of their stutter.

Conclusion

In summary, those with KdVS present with a relatively homogenous profile of speech development with slowed communication milestones, childhood apraxia of speech, and dysarthria, impacting heavily on

intelligibility in the early years. Early multimodal communication options are key during these stages of early development, yet we emphasise that the vast majority begin to rely more on verbal speech by early childhood (6–7 years). In addition to the features above, stuttering is a core feature in KdVS, following a unique onset pattern compared to idiopathic stuttering seen in the general population. Evidence for stuttering management in complex genetic disorders is lacking (let alone in KdVS specifically). Speech therapists should utilise the best evidenced-based stuttering therapies applicable in the typical population (i.e., Lidcombe program, Demands and Capacities Model) and modify these according to age and cognitive ability [19, 22–24]. Well-developed social skills, as well as behaviour and emotional control across situations (i.e., a strong ability to cope) are a relative strength in KdVS, as shown here with standardised measures, and such social competence and resilience should be utilised in therapy plans. Literacy (reading, spelling) and writing are challenging for those with KdVS, however written communication is often complicated by poor fine motor development and as such, alternative options should be used to develop such skills. Individuals with KdVS should continue to access speech therapy throughout development, as the therapeutic focus shifts from motor speech control and language understanding, to successful literacy acquisition, and the development of more complex communication skills required for life beyond school and into the community.

Declarations

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Conflict of Interest Statement

The authors declare no conflict of interest.

Data Availability Statement

The data that support the findings of this study are available from the corresponding author upon reasonable request.

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