Speech, language, and hearing function in twins with Alport syndrome: A seven-year retrospective case report

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Abstract

Alport syndrome is an X-linked syndrome that results in nephritis, renal failure, sensorineural hearing loss, and eye deficits. As a result of sensorineural hearing loss, these individuals are likely to experience difficulties in the area of speech and language. While studies in the past have examined the speech and language characteristics of children with syndromic sensorineural hearing loss, to our knowledge there are no previous studies to have documented the speech and language characteristics of these children on a long-term basis. The current study addresses this limitation by reporting speech, language, hearing, and function of twin brothers with X-linked Alport syndrome across a seven-year period. Information was collected by examining the medical records of the participants as well as through a verbal interview with the participants' guardian. Results revealed that the participants' hearing abilities gradually deteriorated over the seven-year period which affected their speech and language development as well. The kidney function tests revealed significant presence of hematuria (blood in the urine) as well as proteinuria (protein in the urine) suggesting chronic kidney dysfunction. This longitudinal study demonstrates the functional relationship between the kidneys and the cochlea, although they appear to be independent of one another. As individuals with Alport syndrome exhibit systemic complications, interdisciplinary collaboration is essential among health care providers including audiologists, speech-language pathologists, nephrologists, and ophthalmologist to promote evidence-based practice.

1. Introduction

Hearing loss is the most common birth defect in developed countries and affects about 6—8% of the population (Hilgert et al., 2009; Schrijver, 2004). Hearing loss is commonly categorized as either conductive, sensorineural, or mixed types (Schrijver, 2004). Sensorineural (SN) hearing loss is typically characterized by damage to the inner ear and is often irreversible. The incidence of SN hearing loss at birth is about 1—2 per 1000 births (Berlin and Keats, 2000). Approximately 50%

of cases of SN hearing loss are caused by genetic factors (Schrijver, 2004). Out of this 50%, about 70% of the cases of SN hearing loss are associated with non-syndromic conditions and the remaining 30% are associated with syndromic conditions. Hearing loss that is associated with a syndromic condition is referred to as syndromic hearing loss (Berlin and Keats, 2000). A syndrome is defined as a disease or disorder that has significant and unique characteristics and symptoms. They can be either hereditary or appear with no family history. Many well-known syndromes present with hearing loss as one of the associated characteristics (Berlin and Keats, 2000). Syndromic hearing loss is typically categorized based on the mode of inheritance and includes autosomal dominant, autosomal recessive, and X-linked types. Autosomal dominant syndromes that present with hearing loss as a symptom include Waardenburg

syndrome, branchiootorenal syndrome, stickler syndrome, and neurofibromatosis-2. Autosomal recessive syndromes that are associated with hearing loss include Usher syndrome, Jervell and Lange-Nielsen syndrome, Biotinidase deficiency, and Refsum disease. X-linked syndromes that present with hearing loss include Mohr−Tranebjaerg syndrome and Alport syndrome (Smith et al., 2014). Syndromic hearing loss is commonly accompanied by delays in speech and language development in addition to other problems such as cognitive impairment, learning disability and physical malformation. Although there is well-documented information on the phenotypic features of children with the above-mentioned syndromes, very little is known about speech and language development in children with syndromic hearing loss. The limited studies that have investigated speech and language in children with syndromic hearing loss have focused on how hearing and speech intelligibility improved post-amplification. For example, Daneshi, Hassanzadeh and Farhadi (2005) studied the effects of cochlear implantation in six children with Waardenburg syndrome. The post-implantation results revealed that speech intelligibility of these six children significantly improved and they were placed in regular education settings. Similar results were also seen in studies that investigated the effect of cochlear implantation in children with Usher syndrome and Mohr−Tranebjaerg syndrome (Loundon et al., 2003; Aguirre et al., 2006). Although these studies help us to understand the speech and language characteristics of children with different syndromic hearing loss, the long-term trajectory of speech and language development in children with syndromic hearing loss remains to be studied. It is essential to pursue this line of research not only to understand the impact of a syndrome on speech and language, but also to implement a successful treatment protocol for treating speech and language deficits in this population. To address this shortcoming, we present a retrospective case report of twins born with a rare syndrome called Alport syndrome (AS). Specifically, we provide background information on Alport syndrome and report developmental history, medical history, hearing function, and most importantly the development of speech and language of twins born with this syndrome.

1.1. Alport syndrome

AS is a heterogenous disease that is known primarily for progressive kidney dysfunction leading to end-stage renal disease (ESRD) and sensorineural deafness. It is the most common form of glomerulonephropathy, an umbrella term for kidney diseases (Mochizuki et al., 1994). Alport syndrome is associated with mutations in type IV collagen (COL_4) that is typically located in the glomerular (kidney-filtering) and cochlear basement membranes. There are six isoforms of COL_4 [$\alpha1(IV)−\alpha6(IV)$] encoded by six genes, COL4A1−COL4A6, that are variably expressed in basement membranes. Mutations in the $\alpha3$, $\alpha4$, or $\alpha5$ COL_4 chains result in disruption of the $\alpha3−\alpha4−\alpha5(IV)$ network, which eventually leads to basement membrane dysfunction in kidneys as well as the cochlea (Mochizuki et al., 1994).

Prevalence for AS has been known to range from every 1 in 10,000 individuals to every 1 in 50,000 individuals (Mohammad et al., 2014). Individuals with AS are known to present with several systemic complications. The most frequent complications are nephritis and progressive renal failure (Wang et al., 2014). Progressive bilateral high-frequency SN hearing loss is also common among individuals with AS. This syndrome accounts for at least 1% of congenital hearing loss occurrences (Gorlin et al., 1995). Hearing loss typically presents itself during school age for those diagnosed with AS (Flinter et al., 1988). Other prominent features of AS include hematuria (presence of blood in the urine), proteinuria (excessive levels of protein in urine), and various eye complications (Jais et al., 2000). The eye complications that occur as a result of Alport syndrome are bilateral anterior lenticonus (a cone-shaped appearance on the anterior lens), perimacular flecks (yellow flecks that may or may not affect visual acuity), retinopathy, and retinal thinning (Gorlin et al., 1995; Kanski and Bowling, 2011). An individual with Alport syndrome may experience all, some, or none of the eye complications mentioned above.

1.2. Inheritance of Alport syndrome

AS can be inherited through three different genetic routes that include X-linked, autosomal recessive, and autosomal dominant types of inheritance. About 80% of AS is inherited through X-linked type (XLAS) due to mutations in COL4A5 located on the X chromosome (Miner, 2014). Almost all the males diagnosed with XLAS will develop ESRD. On the other hand affected heterozygous females exhibit a wide variability in disease severity ranging from living symptom-free to having significant kidney complications (Mochizuki et al., 1994). The autosomal recessive manner of inheritance accounts for about 15% of individuals with AS. In this case it is caused due to mutations in both the alleles of either COL4A3 or COL4A4. The autosomal dominant type of inheritance is the least common type and accounts for just 5% of individuals with AS and is caused by heterozygous mutations in either COL4A3 or COL4A4 (Mochizuki et al., 1994).

2. Method

2.1. Participants

Jacob and Tyler (names changed), are fraternal twins who were diagnosed with X-linked Alport syndrome in 2009. They served as participants for the current study and were recruited based on a convenience non-probability sampling. They were 15 years old at the time of recruitment. They have a female half-sister, aged 12 years, who was also diagnosed with Alport syndrome in 2009. She was not recruited as a participant due to her typical hearing abilities as well as typical speech and language development. The Institutional Review Board at the authors' University approved the current study (approval number: AS1595). The participants were living with their

biological mother prior to 2007, and in 2009 they were legally adopted by an adult female. All of the participants' information related to birth history (post-natal), developmental history, medical and treatment history from 2009 to 2015 were collected through two sources: (1) verbal interview with the participants' legal guardian and (2) inspection of their medical records. Information about participants prior to 2009 was obtained through inspection of the medical records that were available at the time of their recruitment as their biological mother was unavailable for a verbal interview. The current legal guardian of the participants provided written consent to participate in this study. She signed a Health Insurance Portability and Accountability Act (HIPAA) waiver for the authors to inspect the participants' medical records. Utmost care was taken so that there was no coercion and the participants' guardian was made aware that participation in this study was completely voluntary and was free to withdraw at any stage of this study. Based on the information collected from all of the above-mentioned sources, information about developmental, medical, and treatment history for each of the two participants are presented below in a chronological order. Information regarding the participants' renal function, speech, language, and hearing problems during their course of development are specifically highlighted as individuals with Alport syndrome commonly present with renal dysfunction, delayed speech and language development, and hearing loss.

3. Results

3.1. Birth and developmental history

The participants' biological mother had a history of chronic hematuria and proteinuria, the maternal grandmother had heart and kidney problems throughout her life, and the maternal grandfather died of kidney failure as a result of lupus. There was no information on the participants' paternal history. Both the participants were born premature and at low birth weights in March of 2001. Information regarding the participants' gestational age was unavailable. Jacob was born weighing 3 lb., 7 oz., and spent initial few months in the hospital's neonatal intensive care unit due to neonatal jaundice and other health complications. He was also born with an incomplete unilateral cleft lip and an incomplete cleft palate which caused difficulties with breathing and feeding. Jacob received multiple corrective surgeries during his stay in the neonatal intensive care unit to fix his unilateral cleft lip. Since then, Jacob has had a number of primary as well as secondary surgeries to repair his primary palate as well as to correct his speech production prior to as well as after his adoption. However, the exact nature of surgeries was not mentioned in the medical records. During his first year of life, Jacob suffered from chronic middle-ear infections due to his cleft palate. He received pressure equalization tubes during his second year. He was diagnosed with hearing loss and received hearing aids at age 3, but lost them after a few weeks. After that, he did not receive new hearing aids until age 7. Jacob was also noted to present with delayed speech and language development during

his childhood. Tyler was born with a birth weight of 3 lb., 4 oz. His stay in the hospital's neonatal intensive care unit was brief, and he did not have any other associated medical conditions. He also experienced no significant hearing impairments prior to his eighth year, in 2009. Tyler's development was typical as he did not experience any speech or language delays until after the onset of his hearing loss.

Both the participants went from living with their biological mother to their now-legal guardian in 2009. In the same year, the participants were referred to a nephrologist when hematuria and proteinuria were noted during a routine medical check-up with their primary care physician. The two participants and their sibling were diagnosed with Alport syndrome in 2009. Additionally, both the participants were diagnosed with ADHD prior to 2009. Tyler's diagnosis was more severe than Jacob's, as he had difficulty focusing and remaining calm. They were also diagnosed with Asperger's syndrome (DSM-IV), or mild Autism Spectrum Disorder (DSM-V), in 2013.

3.2. Hearing function

Both the participants received a comprehensive audiological evaluation on a regular basis (at least once every year). The audiological evaluation included pure-tone audiometry (PTA), speech recognition testing (SRT), word recognition testing, and tympanometry. The results of these evaluations for Jacob and Tyler are presented in Tables 1 and 2, respectively. As seen from Table 1, Jacob's hearing loss severity was moderately-severe in his right ear and ranged from moderately-severe-to-severe in his left ear across the seven-year period. Additionally, from 2009 to 2012, he experienced a mild conductive hearing loss in his left ear on an intermittent basis due to middle ear infections. His aided speech reception threshold (SRT) ranged from 50 to 62.5 dB HL. From 2009 to 2012, Jacob was provided with bilateral behind-the-ear hearing aids, which he used them on a

Table 1
Jacob's audiological assessment results from 2009 to 2016.

Year	Ear	Audiological assessment			
		PTA	SRT	WRS	Tympanometry
2009	Left	62 dB HL	57.5 dB HL	72% at 80 dB HL	As
	Right	59 dB HL	55 dB HL	90% at 80 dB HL	A
2010	Left	70 dB HL	60 dB HL	76% at 95 dB HL	As
	Right	62 dB HL	50 dB HL	92% at 95 dB HL	A
2011	Left	71 dB HL	60 dB HL	79% at 93 dB HL	A
	Right	62 dB HL	55 dB HL	83% at 87 dB HL	A
2012	Left	74 dB HL	62.5 dB HL	76% at 95 dB HL	As
	Right	67 dB HL	55 dB HL	92% at 90 dB HL	A
2013	Left	72 dB HL	62.5 dB HL	88% at 95 dB HL	A
	Right	64 dB HL	57.5 dB HL	96% at 90 dB HL	A
2014	Left	70 dB HL	65 dB HL	40% at 95 dB HL	A
	Right	61 dB HL	65 dB HL	80% at 95 dB HL	A
2015	Left	68 dB HL	65 dB HL	40% at 95 dB HL	A
	Right	58 dB HL	55 dB HL	68% at 90 dB HL	A
2016	Left	68 dB HL	65 dB HL	48% at 95 dB HL	A
	Right	57 dB HL	50 dB HL	80% at 90 dB HL	A

Table 2
Tyler's audiological assessment results from 2009 to 2016.

Year	Ear	Audiological assessment			
		PTA	SRT	WRS	Tympanometry
2009	Left	18 dB HL	25 dB HL	96% at 55 dB HL	A
	Right	33 dB HL	35 dB HL	96% at 70 dB HL	A
2010	Left	38 dB HL	30 dB HL	97% at 67 dB HL	C
	Right	41 dB HL	35 dB HL	92% at 73 dB HL	C
2011	Left	45 dB HL	33 dB HL	99% at 70 dB HL	A
	Right	44 dB HL	37 dB HL	93% at 70 dB HL	A
2012	Left	51 dB HL	40 dB HL	100% at 70 dB HL	A
	Right	48 dB HL	40 dB HL	100% at 70 dB HL	A
2013	Left	49 dB HL	48 dB HL	88% at 72 dB HL	A
	Right	47 dB HL	43 dB HL	93% at 72 dB HL	A
2014	Left	54 dB HL	45 dB HL	82% at 78 dB HL	A
	Right	52 dB HL	43 dB HL	78% at 78 dB HL	A
2015	Left	55 dB HL	45 dB HL	82% at 78 dB HL	A
	Right	52 dB HL	45 dB HL	78% at 78 dB HL	A
2016	Left	55 dB HL	50 dB HL	88% at 80 dB HL	A
	Right	52 dB HL	50 dB HL	88% at 80 dB HL	A

PTA = Pure Tone Audiometry; SRT = Speech Reception Threshold; WRS = Word Recognition Testing.

consistent basis. In 2012, Jacob's hearing loss worsened and he was provided with another set of hearing aids to receive appropriate amplification. The gain of hearing aids was evaluated whenever he visited his audiologist (at least on an annual basis). If the hearing loss had increased during a specific year, the gain of the hearing aids was adjusted based on the severity of the hearing loss. The results of his unaided SRT revealed that he could perceive the presented words at 57.5 dB HL in 2009 and over the years, his unaided SRT gradually worsened. Binaural aided sound field testing revealed that he could hear sounds in the normal to mild loss range. This gave Jacob the ability to hear others without with slightly less reliance on visual support, such as lip-reading.

Tyler began receiving regular hearing evaluations from 2009 not because of his hearing concerns but due to his diagnosis of Alport syndrome. As all three siblings were diagnosed with Alport syndrome, it was recommended for all the three siblings to receive hearing evaluations at least on an annual basis. As seen from Table 2, Tyler had normal hearing in left ear and mild hearing loss in right ear in 2009. But his hearing deteriorated over the years and in 2016 he was diagnosed with bilateral moderate hearing loss. Similarly his SRT worsened from 25 dB HL in 2009 to 50 dB HL in 2016. Due to the mild hearing loss in Tyler's right ear, he was recommended by his audiologist to wear behind-the-ear hearing aid only in his right ear. As his hearing started deteriorating bilaterally, he was recommended to use binaural hearing aids as well as a FM system from 2010. However, in 2013, Tyler refused to wear the hearing aids due to stigma associated with using hearing aids. As an alternative, he started using in-the-canal hearing aids, but they did not provide him with sufficient amplification, so he again started using the behind-the-ear hearing aids thereafter. The gain of hearing aids was evaluated whenever he visited his audiologist (at least on an annual basis). If the hearing loss had increased during a specific year, the gain of the hearing aids was adjusted to meet the severity of the

hearing loss. Binaural sound field testing in 2016 revealed that, with his hearing aids, he could hear sounds in the normal to mild hearing loss range.

3.3. Speech and language function

Jacob as well as Tyler received speech and language evaluations on an annual basis from a certified speech-language pathologist. The speech and language evaluations included administration of formal tests such as the Clinical Evaluation of Language Fundamentals (CELF — 4th and 5th editions) and Goldman—Fristoe Test of Articulation (GFTA — 2nd edition) as well as information assessment measures. CELF evaluates language function of individuals in the age range of 5—21 years. GFTA-2 is an articulation test that assesses the sound production abilities of individuals within the age range 2—21 years at word, phrase, and sentence levels. Informal measures included assessing skills such as maintenance of monologue topics, mean length of utterance (MLU), conversational skills, recognition of the Ling's 6 sounds (/m/, /ɑ/, /i:/, /u/, /ʃ/, /s/), and vocabulary. Jacob's performance on each subsection of CELF as well as on GFTA-2 is shown in Figs. 1 and 2, respectively. The baseline CELF evaluation revealed that Jacob was below the 10th percentile in each subtest. Prominent language deficits included difficulties in use of irregular plurals as well as past tense markers. With regard to GFTA, the baseline scores revealed that he was at the 19th percentile. Specific articulation errors included substitution of /ʃ/ in place of /s/ (e.g. saying "ship" instead of "sip") and substituting /b/ for /v/ (e.g. saying "bat" instead "vat"). Jacob received auditory-verbal therapy two times per week from a certified auditory-verbal therapist from 2010 to 2016. As indicated by the GFTA-2 standard scores in Fig. 5, his misarticulations were not severe enough to impede his speech intelligibility. So, the speech-language pathologist predominantly focused on improving his language and auditory perception skills. The therapy goals for Jacob as well as the progress attained for each goal over the seven-year period are shown in Appendix 1.

Over the years, his speech and language skills gradually improved as indicated by his performance on formal as well as informal measures. Findings from his most current evaluation, in 2015, revealed that Jacob's CELF subtest scores ranged from the 16th percentile to the 92nd percentile in CELF and he was above the 21st percentile in GFTA. Similarly, informal measures revealed his speech and language skills had improved over the seven-year period. For example, in 2009 Jacob demonstrated expressive language delay as well as considerable difficulty in maintaining a topic as well as comprehending open-ended interrogative sentences. In 2015, although he did not achieve age-appropriate speech and language skills, his vocabulary was expanding by at least three words per week and his conversational skills were at an appropriate level, with only mild difficulties with topic maintenance and perspective taking, which was primarily due to his autism spectrum disorder. By 2015, he was able to identify and discriminate all the six Ling's sounds in the
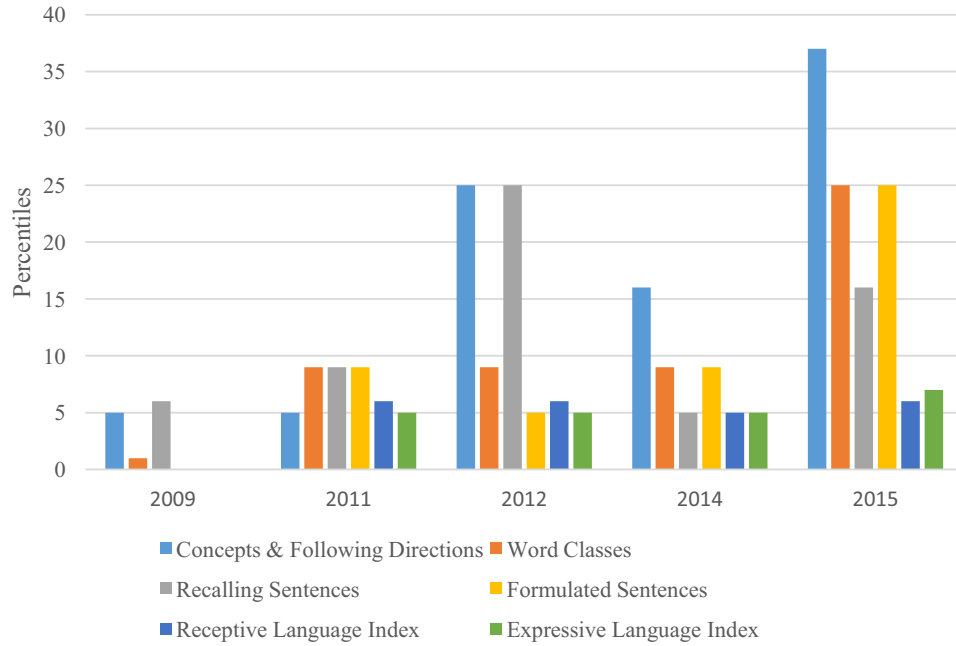
Fig. 1. Jacob's Clinical Evaluation of Language Fundamentals (CELF) percentile scores from 2009 to 2015.
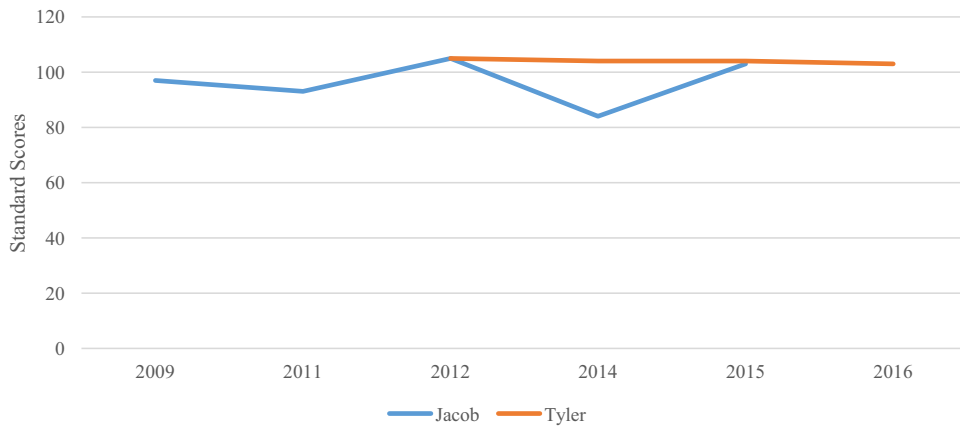

Fig. 2. Jacob's and Tyler's Goldman−Fristoe Test of Articulation (GFTA − 2nd edition) standard scores from 2009 to 2015.

absence of background noise. However, in 2013, Jacob started demonstrating lack of reciprocal eye gaze during conversation and some stereotypical behaviors. Further examination revealed that he had Asperger's syndrome. So his speech and language therapy goals started focusing on improving verbal and non-verbal pragmatic skills.

Compared to Jacob, Tyler received speech and language evaluations and intervention on an intermittent basis from 2010. As his legal-guardian's traveled constantly on her job, he accompanied her to all the places she went and this prevented him from attending speech and language therapy sessions on a regular basis. Tyler received intermittent auditory-verbal therapy once per week from a certified auditory-verbal therapist from 2012 to 2016. Tyler's performance on each subsection of CELF as well as on GFTA-2 is shown in Figs. 3 and 2, respectively. His speech and language evaluation in 2012 revealed that he was below the 10th percentile in each

expressive language subtest and in the 25th percentile of each receptive language subtest of CELF, and he was above the 30th percentile in GFTA-2. Specifically, he had difficulty following conversations and his expressive speech output was characterized by predominant syntactic errors. In 2013, similar to Jacob, Tyler was also diagnosed with Asperger's syndrome, so the speech-language pathologist focused on improving his social/pragmatic skills. Over the next couple of years, Tyler's speech and language gradually improved as indicated by his performance on formal as well as informal assessment measures. Results from his most current evaluation, in 2014, revealed that his CELF subtest scores ranged from below the 10th percentile to the 50th percentile and he was above the 24th percentile in GFTA. Informal assessment measures also suggested that he showed moderate improvement in his speech and language from 2012 through 2015 in mean length of utterance and topic initiation skills. During these years, he was
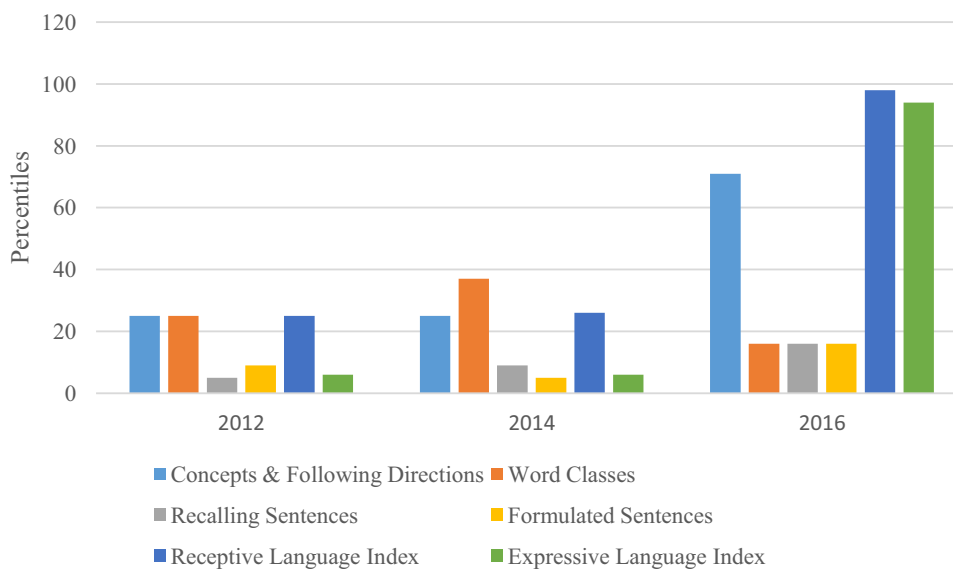
Fig. 3. Tyler's CELF percentile scores from 2012 to 2015.

3.4. Renal function

As individuals with Alport syndrome are at risk for chronic kidney dysfunction, both the participants' kidney function was assessed every year to monitor hematuria and proteinuria. The biochemical investigations included examination of serum creatinine, serum albumin, protein to creatinine ratio (Pr:Cr), and red blood corpuscle (RBC) count. Creatinine is a chemical used to supply energy to the muscle and high levels of creatinine indicate that the kidneys are not adequately filtering waste products in the body (Sobh, 2000). Normal creatinine levels range from 0.6 to 1.2 milligrams per deciliter (mg/dL) in healthy adults. The creatinine levels are slightly higher in males than in females and also higher in individuals with more muscle mass (Sobh, 2000). Albumin is a protein created in the liver and the normal albumin levels range from 3.5 to 5.5 grams per deciliter (g/dL) (Peters and About Albumin, 1995). The Pr:Cr is a measure taken from the urine sample. The urine sample can either be a spot urine sample or a 24 h urine collection sample (normally less than 150 mg/24 h) (Sobh, 2000; Christopher-Stine et al., 2003). The normal Pr:Cr for children over two years of age is <0.2. Finally, the RBC count in the urine sample can indicate the presence of hematuria in individuals with Alport syndrome. Typically, the number of RBCs in urine should not exceed five RBCs per high power field on microscopic examination of the urine sample. So, hematuria is defined as a secretion of more than 5 RBCs per high power field in the urine sample (Christopher-Stine et al., 2003).

Jacob's results from the above tests as are presented in Fig. 4. It is worthy to mention that Jacob's urine output revealed large amounts of blood and protein throughout the seven-year period. His initial test results revealed that his creatinine was at a normal level of 0.4 mg/dL, his Pr:Cr ratio was high at 2, and his serum albumin level was low at 2.4 g/dL. The Pr:Cr ratio indicated that Jacob had been experiencing proteinuria. His initial diagnosis was a general glomerulonephritis, but later in 2009 based on biopsy's results, he was diagnosed with Alport syndrome. In subsequent years, Jacob's creatinine levels remained stable and at normal levels. This indicates that his kidneys were adequately filtering creatinine. Only in 2012 did his creatinine levels begin to gradually elevate. In 2016, his creatinine levels were as high as 0.7 mg/dL. Unlike his creatinine levels, Jacob's Pr:Cr ratios fluctuated each year. For example, his ratio was 2.6 in 2012, 2.1 in 2013, 2.7 in 2014, and 3.5 in 2016. Lastly, Jacob's serum albumin levels remained somewhat stable. For example, the first four years his albumin levels remained just below 0.4 g/dL. Between 2012 and 2013, there was a slight increase and from then on, the albumin levels remained at around 0.6 g/dL.

Tyler's kidney test results are presented in Fig. 5. Similar to Jacob, Tyler also showed high amounts of blood and protein in his urine from 2009 to 2015. His initial creatinine was at 0.38 mg/dL suggesting that his kidneys were not filtering as well as they should have been. His Pr:Cr ratio was at 3.3, and his serum albumin level was at 3.2 g/dL. His Pr:Cr ratio level indicated that he was also experiencing proteinuria. He was also initially diagnosed with a general glomerulonephritis, but his kidney biopsy in 2009 showed signs of Alport syndrome. Tyler's creatinine levels did not fluctuate, however they always remained at high levels for his body size. In 2013, his levels increased by nearly 0.2 mg/dL, bringing his level to 0.54 mg/dL. It increased again to 0.76 mg/dL in 2015, and in 2016 it was 0.85 mg/dL. Similar to Jacob's Pr:Cr ratios, Tyler's
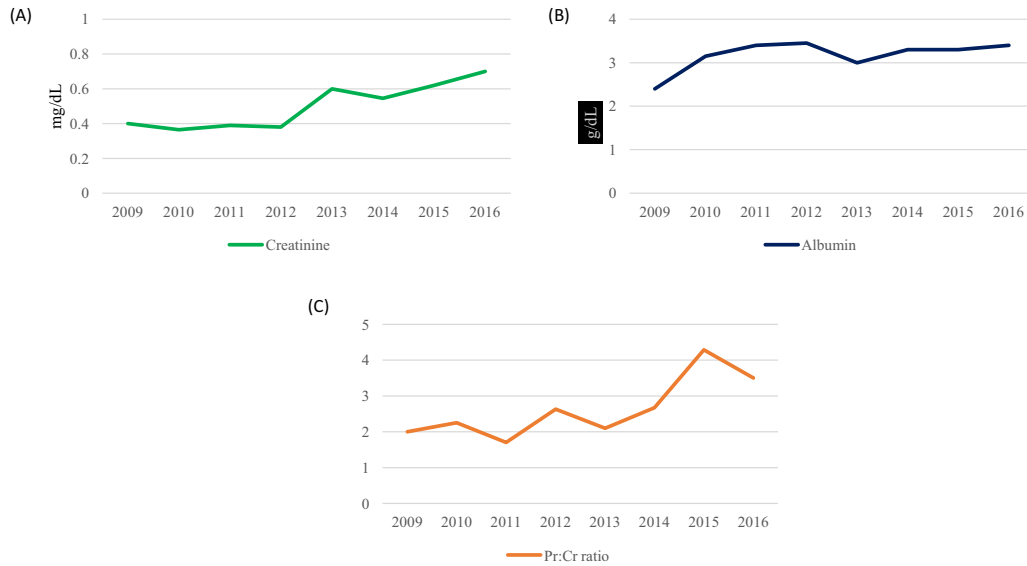
Fig. 4. Jacob's kidney function test results from 2009 to 2016. Panel (A) depicts the serum creatinine values. Normal creatinine levels range from 0.6 to 1.2 milligrams per deciliter (mg/dL). Panel (B) depicts the serum albumin values. Normal levels of albumin range from 3.5 to 5.5 grams per deciliter (g/dL). Panel (C) depicts the Pr:Cr ratio. The normal Pr:Cr for children over two years of age is <0.2.
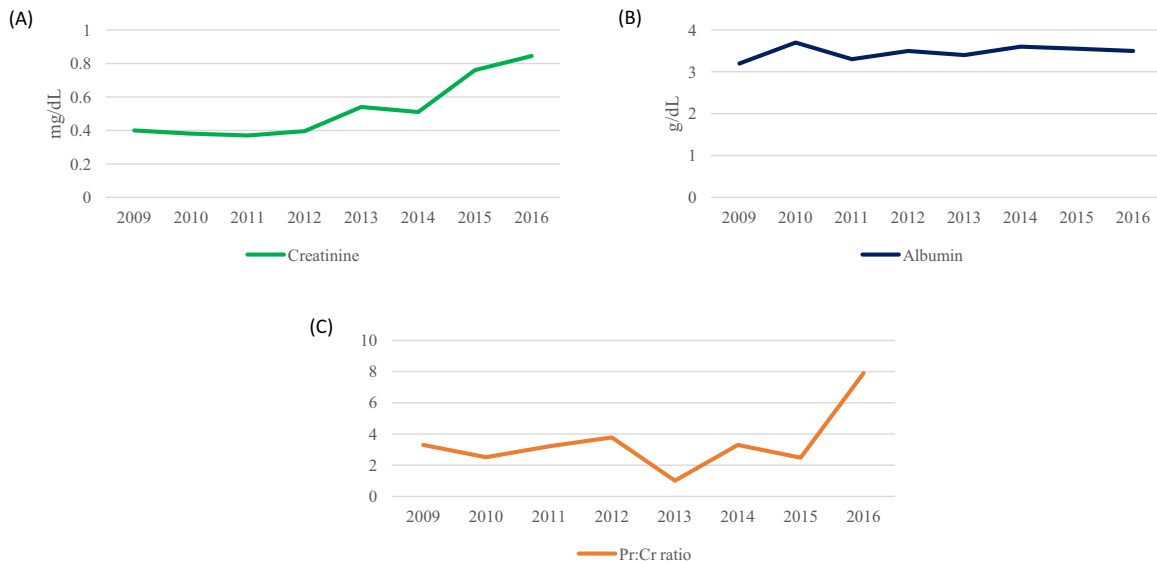

Fig. 5. Tyler's kidney function test results from 2009 to 2016. Panel (A) depicts the serum creatinine values. Normal creatinine levels range from 0.6 to 1.2 milligrams per deciliter (mg/dL). Panel (B) depicts the serum albumin values. Normal levels of albumin range from 3.5 to 5.5 grams per deciliter (g/dL). Panel (C) depicts the Pr:Cr ratio. The normal Pr:Cr for children over two years of age is <0.2.

fluctuated significantly. For example in 2012 his Pr:Cr ratio was at 3.8, but in 2013 it dropped to 1.0 and rose again to 3.3. In 2015, it did not drop significantly, but it increased considerably in 2016 to 7.9. On the other hand, Tyler's albumin levels remained relatively stable throughout the seven year-period.

3.5. Eye function

Although the number of individuals with Alport syndrome presenting with these eye deficits are relatively low, Alport syndrome is known to have numerous effects on the individual's eyes. Both the participants experienced some loss of eye function. From 2010, Jacob as well as Tyler started exhibiting periorbital edema. In 2011, Tyler additionally started showing signs of perimacular flecks. Tyler as well as Jacob's visual acuity started gradually deteriorating over the years, but as per the physician's report the loss of visual acuity was not related to their Alport syndrome. Both participants were prescribed eye-glasses to accommodate their deteriorating visual acuity, and they visited their optometrist at least on an annual basis.

3.6. Educational history

Jacob as well as Tyler received Individualized Education Plans (IEPs) in their schools to accommodate their hearing deficits. The IEPs required them to have access to optimal listening environment such as the use of FM systems and preferential seating. Jacob enjoyed science classes and earned passing grades in those classes. However, he struggled significantly in mathematics and English, ultimately failing in these areas. As a result, he worked one-on-one with a teacher in these subject areas. Tyler enjoyed science and social studies classes, but he also struggled in mathematics and English. He earned passing grades in science and social studies, but not in mathematics and English. He too, was taken out from the classroom and received private tutoring from a teacher in the school. Due to the lack of appropriate resources at school to accommodate the participants' hearing loss and their comorbid conditions, as well as to accommodate the schedule of their adoptive mother's new traveling job, both the participants were home-schooled from 2014. The siblings are now able to benefit from one-on-one learning environment in all the subject areas. As a result, Jacob and Tyler now receive passing grades in the subject areas they previously struggled with.

4. Discussion and conclusion

It is not unusual for children with syndromic conditions to present with hearing loss and/or speech and language deficits (Daneshi et al., 2005; Loundon et al., 2003). But what remains unknown is the long term development of speech and language in children with various syndromes. The current study addressed this deficit by reporting the speech, language, and hearing function in twins diagnosed with Alport syndrome across a seven-year period. Additionally, information regarding the twins' developmental and education history, kidney and visual function were also presented. Evidence reporting the association between kidney dysfunction and malformations of the external ear is weak. However, there has been strong association between kidney dysfunction and inner ear (cochlear) abnormalities in several syndromes, among which Alport syndrome is one of them (Torban and Goodyer, 2009). In order to understand the abnormal development of speech, language, and hearing function in individuals with Alport syndrome, it is vital to know the relationship between the kidneys and the cochlea.

The mammalian external, middle, and inner ears develop from the ectoderm and endoderm, whereas the mammalian kidneys develop from progenitor cells of the mesoderm (Torban and Goodyer, 2009). Although these two organs seem to be superficially different, it is intriguing that children with Alport syndrome have deficits in both these organs. This is basically attributed to two important aspects. First, the kidneys and ear share similar physiological mechanisms. The active transportation of fluids and electrolytes is performed by the glomerulus of the kidney and the stria vascularis of the inner ear, respectively. The normal functioning of the cochlea is assumed to be dependent on electrolytic stability within the body, which maintains cochlear homeostasis, and this is achieved through normal kidney functioning. The composition of fluids within the cochlea ensures electromotility of the outer hair cells of the cochlea. The endolymph in the inner ear is rich in potassium ($K+$) and has low concentrations of sodium ($Na+$) and calcium ($Ca+$) and it bathes the apex of the membranous labyrinth. Whereas the perilymph is rich in $Na+$ and low in $K+$, and it is housed in the perilymphatic space between the membranous and bony labyrinth (Couloigner et al., 2006). The adequate balance of $Na+$, $Ca+$, and $K+$ is essential for cochlear micro and macromechanics. It is logical to assume that any interruption to this electrolytic balance within the body, which is frequently seen in individuals with Alport syndrome results in a disturbance to the fluids of the inner ear, thereby causing cochlear dysfunction (Torban and Goodyer, 2009). However, the direct relation between electrolytic imbalance and hearing loss is yet to be established. Most of our knowledge in this area stems from studies that have used "otoacoustic emissions" to assess cochlear hair cell functioning in individuals with electrolytic imbalance. These studies indicate that individuals with electrolytic imbalance are likely to present with sub-clinical hearing loss. The second aspect is related to the mutation of specific genes that are responsible for adequate development of kidney as well as the cochlea. Around 85% of the Alport syndrome cases present with mutations of the Col4A5 gene on the X chromosome, and this results in loss of type IV collagen leading to hematuria, proteinuria and patchy segments of thickened glomerular basement membrane. The remaining 10–15% of the cases present with autosomal recessive mutations of Col4A3 and Col4A4 on chromosome 2 (Torban and Goodyer, 2009). As both Col4A3 and Col4A5 play a prominent role in the development of basilar membrane and the spiral ligament of the cochlea, mutations of either of the gene can affect cochlear micromechanics resulting in SN hearing loss (Mancini et al., 1996).

The importance of normal audition on speech and language development cannot be overlooked. In the current study, it is likely that the sensorineural HL in Jacob and Tyler affected their normal development of speech and language. Hearing loss in Alport syndrome is not always congenital, it begins by age 10 in nearly half of the affected individuals and in 85% by adulthood (Torban and Goodyer, 2009). In line with previous report(s), Tyler had post-lingual hearing loss (by 7 years of age), and his speech and language skills were relatively better than Jacob. On the other hand, Jacob had congenital hearing loss, as a result his speech and language development was severely delayed. Izzedine et al. (2004) reported that severity of renal and auditory features do not correlate in individuals with Alport syndrome. Similar to the findings of Izzedine et al. (2004), the current study revealed that the participants' protein and blood levels in their urine showed no clear correlation with their hearing function. However, it is possible that the electrolyte imbalance due to chronic kidney dysfunction could have contributed to hearing loss in the participants. It is important to be aware that Jacob and Tyler had multiple complications including Asperger's syndrome. It is possible

that the additive effects of AS and co-morbid conditions could have delayed the speech and language development in the twins. As both Jacob and Tyler received speech and language therapy as well as auditory-verbal therapy, their speech and language skills improved over the years. However, as this was an observational study and not a controlled study it is difficult to rule out maturational factors that could have aided in the improvement of participants' speech and language skills.

In the current study, we did not intend to demonstrate a "cause and effect" relationship between kidney dysfunction and the resulting hearing, speech and language deficits, but rather to highlight a rare clinical scenario. To our knowledge, this is the first longitudinal seven-year case study to report speech, language, and hearing function in twins with Alport syndrome. Although it is not very common for a speech-language pathologist and/or an audiologist to have clients with rare syndromes such as Alport syndrome on their case load, one cannot exclude the possibility of encountering them. Clients like Jacob and Tyler can prove quite challenging to health care professionals, especially to a speech-language pathologist due to multiple health complications. Recently, the University of Minnesota's Department of Pediatrics has developed the "Alport Syndrome Treatments and Outcome Registry" (https://astor.ahc.umn.edu/index.cfm?page=home) that aims to increase knowledge about Alport syndrome and also identify different lines of treatment. Currently, the registry focuses on treatment intended for improving kidney function, but it is possible that in the future the registry could start providing information on speech, language, and hearing management in these individuals. As the research pertaining to speech and language development of individuals with Alport syndrome is still at its infancy, it is essential to document the speech, language, and hearing function in these individuals to improve evidence-based practice.

Finally, an important aspect that needs to be emphasized when treating patients like Jacob and Tyler is the role of interdisciplinary approach. It is very important for the healthcare team members to be in constant contact with one another to understand the holistic development of the affected individual. Unfortunately, in the current study we found that the speech-language pathologist, audiologist and nephrologist who provided services to the twins were not working closely as a team and there was a lack of active communication among them. It is possible that treatment provided by a healthcare professional can impact the other functions. For example, medications provided to improve kidney function can negatively impact hearing and subsequently speech and language development as well. Thus, it is essential that speech-language pathologists and audiologists (as well as other healthcare providers) adopt a team approach when treating such complex medical conditions such as Alport syndrome to achieve ideal outcomes.

Appendices

Appendix 1
Jacob's speech and language therapy goals and progress achieved across the seven-year period.

Goals	Progress achieved
1. Answer and ask closed- and open-ended "wh" questions with 80% success, given visual support	2011: He answered "wh" questions with 60−70% success. 2015: He answered "wh" questions with 90% success and asks "wh" questions with 80% success. Goal met: Yes
2. Identify an appropriate compensatory strategy to utilize in instances of word-retrieval difficulty with 80% accuracy given a list of strategies	2011: He identified compensatory strategies to facilitate word retrieval with 50% success. 2012: He identified synonyms with 60% success, antonyms with 60−70% success, multiple meanings with 70% success, and feature description with 70−80% success. Goal met: Partially
3. Maintain a topic for at least 3−4 conversational turns in 3 of 4 attempts given a verbal prompt	2012: 4 out of 4 attempts on average Goal met: Yes
4. Describe objects/words, giving at least 3 salient characteristics with 80% success	2011: He described objects giving only 1 salient characteristic. 2012: He described objects/words, giving at least 3 salient characteristics with 70% success. Goal met: No
5. Produce grammatically correct utterances of at least 8 words in length in 80% of attempts given a delayed model	2012: 80% success. Goal met: Yes
6. Listen to a 3−5 min story and then answer 3−4 questions with 80% success	2011: He listened to the stories, but could not answer questions consistently. 2012: He listened to the stories and answered questions with 60−70% success. Goal met: No
7. Follow 6−7 element directions with at least 80% success	2012: He followed 6 element directions with 60% success. 2015: He followed 6 element directions with 70−80% success. Goal met: No
8. Listen to a paragraph and answer closed- and open-ended "wh" questions with 80% accuracy	2012: He listened to stories and answered questions at 50% success. 2015: He listened to stories and answered questions at 70−80% success. Goal met: No

Appendix 1 (*continued*)

Goals	Progress achieved
9. Participate in a conversational exchange, answering at least 5 questions each session regarding activities in his life	2012: He participated in a conversational exchange, answering 1−2 questions regarding activities in his life. 2015: He participated in a conversational exchange, answering at least 5 questions regarding activities in his life. *Goal met: Yes*
10. Verbally produce an 8−10 step procedural or story narrative with at least 80% success	2012: He verbally produced a 6-step procedural narrative with 60−70% success. He verbally produced an 8 element story narrative with 50−60% success. 2015: He verbally produced 8−10 step procedural or story narratives with 80% success. *Goal met: Yes*
11. Write an 8−10 step procedural and/or story narrative with at least 80% success	2012: He was unable to write a procedure. He was able to write a 4−5 sentence story. 2015: He wrote 8 steps with assistance. *Goal met: No*
12. Produce sentences using a variety of relative clauses and a variety of descriptors with at least 80% success	2012: He used primarily simple sentences in conversation. 2015: He produced sentences using relative clauses and a variety of descriptors with 70% success. *Goal met: No*
13. Consistently respond to Ling 6 sound test at a variety of distances and levels	2014: He discriminated the Ling 6 sounds at 6 feet with 70% success. 2015: He discriminated the Ling 6 sounds at 9 feet and at different levels with 100% success. *Goal met: No*
15. Demonstrate expanded receptive and expressive vocabulary for all parts of speech by establishing the ability to utilize at least 3 new vocabulary words weekly.	2014: New vocabulary words were not being documented. 2015: At least 3 new vocabulary words were being documented each week. *Goal met: Yes*
16. Produce "sh," "ch," and "j" in sentences and conversation with at least 90% success.	2014: He produced "sh," "ch," and "j" in sentences with 70% success. He produced the sounds in conversation with 60−70% success. 2015: He produced "sh," "ch," and "j" in sentences with 80% success. He produced the sounds in conversation with 70−80% success. *Goal met: No*
17. Will discuss and practice a variety of ways to initiate, maintain, and effectively end a conversation.	2014: He was unable to describe ways to initiate, maintain, or end a conversation. 2015: He was able to list ways to initiate, maintain, or end a conversation without appearing rude. He is able to practice these techniques with at least 80% success. *Goal met: Yes*

Appendix 2

Tyler's speech and language therapy goals and progress achieved in 2012 and 2013.

Goals	Progress
1. Follow 6−8 element directions with at least 80% success	2012: He followed 4−5 element directions with 70% success. He followed 6 element directions with 50−60% success. 2013: He followed 4−5 element directions with 80% success. He followed 6 element directions with 70−80% success. *Goal met: No*
2. Listen to a paragraph being read and then answer closed and open-ended "wh" questions with 80% accuracy given intermittent visual support	2012: He listened to a paragraph and answered "wh" questions with 50−60% success. 2013: He listened to a paragraph and answered "wh" questions with 70% success. *Goal met: No*
3. Participate in a conversational exchange, answering at least 5 specific questions each session regarding activities in his life	2012: He answered 2 questions about life. 2013: He answered 4 questions about life. *Goal met: No*
4. Verbally produce an 8−10 step procedural narrative with at least 80% success	2012: He produced a 4-step procedural narrative with 70% success. 2013: He produced a 6-step procedural narrative with 70% success. *Goal met: No*
5. Verbally produce an 8−10 element story narrative with at least 80% success	2012: He produced a 4-step story narrative with 70% success. 2013: He produced a 6-step story narrative with 70% success. *Goal met: No*
6. Participate in the CLIX auditory discrimination program achieving 90% at all levels of listening skills	2012: He achieved 70% correct. 2013: His test score was 98% correct. *Goal met: Yes*

Appendix 2 (*continued*)

Goals	Progress
7. Write an 8—10 step procedural narrative with at least 80% success	2012: He wrote an 8-step procedural narrative with 50% success. 2013: He wrote an 8-step procedural narrative with 60% success. *Goal met: No*
8. Write an 8—10 element story narrative with at least 80% success	2012: He wrote an 8-step story narrative with 50% success. 2013: He wrote an 8-step story narrative with 70% success. *Goal met: No*
9. Produce sentences using regular and irregular verb tenses, relative clauses, and a variety of descriptors with at least 80% success	2012: He produced regular past tense verbs with 70% success and irregular past tense verbs with 40% success in sentences. 2013: He produced regular past tense verbs with 80% success and irregular past tense verbs with 60% success. *Goal met: No*

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