Speech and Language development in Siblings with Alport syndrome: A Seven-year Longitudinal Retrospective Case Study

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Abstract

Alport syndrome is a syndrome that results in nephritis, renal failure, sensorineural hearing loss, and various eye deficits. As a result of sensorineural hearing loss, these individuals are likely to experience difficulties in the area of speech and language. While many studies examine the speech and language characteristics of children with syndromic sensorineural hearing loss at a given time, we did not find any that followed these children over a long-term basis. This study addresses this limitation by observing two twin brothers with X-linked Alport syndrome over a seven-year period. Information regarding hearing function, as well as speech and language skills, renal function, and visual acuity are mentioned in order to provide a holistic view of the participants' health and to make functional comparisons between body systems. Over the seven years, Jacob and Tyler's health correlated to their diagnosis of Alport syndrome. Jacob's health remained relatively stable in each area, while Tyler's health fluctuated each year. The medical records support information regarding the functional relationship between the kidneys and the cochlea, though they appear to be independent of one another. It is likely that various body systems influence the function of others. Therefore, because syndromes affect many different areas of the body, interdisciplinary collaboration is vital between each medical specialist that is treating a patient with a syndrome in order to gain a holistic view of the person they are providing care for.

1. Introduction

Hearing loss is the most common birth defect in developed countries and affects about 6-8% of the population [1, 2]. Hearing loss is commonly categorized as either conductive, sensorineural, or mixed types [2]. Sensorineural hearing loss is typically characterized by damage to the inner ear and is often irreversible. The incidence of sensorineural hearing loss at birth is about 1-2 per 1000 births [3]. Approximately 50% of cases of sensorineural hearing loss are caused by genetic factors [2]. Out of this 50%, about 70% of the cases of sensorineural 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 a syndromic hearing loss [3]. A syndrome is defined as a disease or disorder that has significant and unique characteristics and symptoms. They can be hereditary or appear with no family history. Many well-known syndromes present with hearing loss as one of the associated characteristics [3]. 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 as a symptom include Mohr-Tranebjaerg syndrome and Alport syndrome [4]. 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 after providing amplification. For example, Hassanzadeh and Farhadi [5] studied the effects of cochlear implantation in six children with Waardenburg syndrome. The results post-implantation 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 [6, 7]. Although these studies help us understand the speech and language characteristics of children with different syndromic hearing loss, the 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, in this retrospective longitudinal case study we provide some background information on a rare syndrome called Alport syndrome and report the development of speech and language of twins born with this syndrome.

1.1 Alport Syndrome

Alport Syndrome is a heterogeneous disease that is known primarily for progressive renal failure and sensorineural deafness. It is the most common form of glomerulonephropathy, an umbrella term for kidney diseases [8]. Alport syndrome is associated with mutations on the α3, α4, and α5 chains of the type IV collagen (COL_4). These collagen chains are located in the glomerular (kidney-filtering) and cochlear basement membranes, thus affecting the function of the kidneys and cochlea [9]. As a result of Alport syndrome, the glomerular basement membrane splits and

acquires a ‘basket-weave’ appearance [10]. There is no exact rate of prevalence for this disease. Prevalence has been known to range from every 1 in 10,000 individuals to every 1 in 50,000 individuals [11]. There are many unique characteristics and symptoms associated with Alport syndrome. First, there is nephritis and progressive renal failure. The risk of renal failure is equal for every male under the age of 30 affected by the disease [12]. Second, there is progressive bilateral high-frequency sensorineural hearing loss. This syndrome accounts for at least 1% of congenital hearing loss occurrences [13]. Hearing loss typically presents itself during school age for those living with the disease [14]. Other prominent features of Alport syndrome include hematuria, proteinuria, and various eye complications [9]. 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 [11, 15]. Any person with Alport syndrome may experience all, some, or none of the eye complications mentioned.

1.2 Inheritance of Alport Syndrome

Alport syndrome can be inherited through three different genetic routes that include X-linked, autosomal recessive, and autosomal dominant types of inheritance. X-linked and autosomal recessive forms of the disease are most common, while autosomal dominant is extremely rare [8]. X-linked Alport syndrome and autosomal recessive appear nearly identical. The main difference between the two is that autosomal recessive Alport syndrome affects females and males more equally than the X-linked form [8]. Females are carriers of X-linked Alport syndrome, living relatively symptom-free, but are likely to pass the disease on to their children. Half of a woman’s sons and half of her daughters are predicted to inherit the same mutations [12]. Males with X-linked Alport syndrome tend to experience more intense symptoms than

those with autosomal recessive. If the male reproduces and has sons, they will not inherit the disease; however, if he has daughters, they will inherit the mutations [12]. Autosomal recessive Alport syndrome can be associated with the following histories: no family history of renal disease or failure; the presence of hematuria in both of the individual's parents; and/or if the individual is the child of a consanguineous marriage, or a marriage between two people who share ancestors [12]. Males and females with autosomal recessive Alport syndrome experience symptoms equally; therefore, if a female exhibits many symptoms, it is likely that she has this form of the disease [8].

2. Methods

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 sibling, 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 2007 another couple legally adopted them. All of the participants' information related to birth history (post-natal), developmental history, medical history, and treatment from 2009 until 2016 were collected through two sources: (1) verbal interview with the participants' legal guardian and (2) inspection of their medical records. The only source of information about both of the participants prior to 2009 was obtained through inspection of their medical records that were available at the time of their recruitment in this study as the biological

mother of the participants was unavailable for a verbal interview at the time of data collection. 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 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. The participants had a different biological father than their sibling, and both paternal histories are unknown. Both of 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 three months in the hospital's neonatal intensive care unit due to neonatal jaundice. He was also born with an incomplete unilateral cleft lip and an incomplete cleft palate which caused difficulties with breathing and feeding. Many corrective surgeries were performed during his stay in the neonatal

intensive care unit. Jacob had a number of surgeries prior to his adoption, and he has had four since his adoption. He still experiences hypernasality when he speaks, especially since he received a partial adenoidectomy in 2015. During his first year of life, Jacob suffered from chronic ear infections. 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 obtain new hearing aids until age 7. Tyler was born at 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. Though there was no access to specific information regarding Jacob's speech, language, and motor development in the first few years of life, it was noted that he was delayed in speech and language. In contrast, Tyler's development was typical as he did not experience any speech or language delays until after the onset of his hearing loss.

Both of 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 present at a check-up with their primary care physician. The two participants and their sibling were diagnosed with Alport syndrome~~,~~ in 2009~~,~~ through a renal biopsy performed on Tyler. Both 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 Medical History

3.2.1 Hearing Function

Both of the participants received a comprehensive audiological evaluation on a regular basis (at

least once each 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 2 and 3, respectively.

Jacob's hearing loss ranged from moderate to severe from 2009 to 2016. From 2009 to 2011, he experienced a mild conductive hearing loss in his left ear due to chronic middle ear infections. These infections were caused by his cleft palate. Initially, Jacob was prescribed behind-the-ear Phonak Eleva 311 hearing aids and a MicroLink FM system. In 2010, he was provided with Phonak Certena P hearing aids. He used the hearing aids consistently and removed them only while he slept and bathed. In 2012, one of the hearing aids as well as the FM transmitter were not working. Jacob was provided a loaner hearing aid until the repaired hearing aid and FM transmitter were repaired, two weeks later. That same year, his hearing loss worsened. He required more amplification, so he was provided the Phonak Naida S III UP hearing aids. The gain of hearing aids was evaluated whenever he visited his audiologist on at least 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. The results of his unaided speech audiometry revealed that he could perceive the presented words at 57.5 dB HL in 2009 and over the years, his unaided speech perception gradually worsened. According to the initial pure tone audiometry (PTA) test performed in 2009, Jacob's hearing loss severity ranged from moderate to moderately severe. Hearing loss was slightly worse in the left ear due to reduced middle ear mobility from 2009 to 2012. Binaural soundfield testing revealed that, with his hearing aids, he could hear sounds in the normal to mild loss range. This gave Jacob the ability to hear others without having to depend on visual support, such as lip-reading. Jacob's hearing remained stable until 2014, at which time it gradually improved to moderate-to-moderately severe.

Tyler began hearing evaluations in 2009, but not because of hearing concerns. Due to his diagnosis of Alport syndrome, it was recommended that all three siblings receive hearing evaluations at least on an annual basis. Tyler's severity of hearing loss ranged from mild to moderate from 2009 to 2016. During these seven years, his hearing loss worsened dramatically between 2009 and 2012, but changes were subtle thereafter. After the initial hearing loss in his right ear and the improvements afforded by a loaner Oticon Vigo Pro hearing aid, Tyler was prescribed behind-the-ear Phonak Nios Micro III hearing aids as well as a Phonak Inspiro FM system. In 2012, he was provided with another loaner hearing aid when one of his prescription hearing aids ceased to function. His new hearing aid was picked up two weeks later. The same issue occurred in 2013, when Tyler was provided with new hearing aids, the Phonak Bolero Q50 M-13 hearing aids. He did not use the hearing aids consistently due to self-consciousness, so he began wearing the Lyric in-canal hearing aids as a part of a study in 2013. The Phonak hearing aids were then used as a backup. The severity of his hearing loss was unable to be treated by the Lyric hearing aids in 2014, so he had to return to the full-time use of the Phonak hearing aids. The gain of hearing aids was evaluated whenever he visited his audiologist on at least 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. In 2015, Tyler was provided a Phonak Roger Pen and Roger 15 receivers, a new type of FM system. The results of his unaided speech audiometry revealed that he could perceive the presented words at 25 dB HL in 2009 and over the years, his unaided speech perception gradually worsened. In 2016, he could perceive the presented words at no less than 50 dB HL. According to the initial pure tone audiometry (PTA) test performed in 2009, Tyler's hearing loss severity was mild. Binaural soundfield testing revealed that, with his hearing aids, he could hear sounds in the normal to mild hearing loss

range. His hearing quickly deteriorated until 2013, when it began to stabilize.

3.2.1.1 Eye Function

Alport syndrome is known to have numerous effects on the individual's eyes, but the number of those presenting these effects is relatively low. Both participants experienced some loss of eye function. Jacob's visual acuity had deteriorated, but not as a result of Alport syndrome. In 2010, he began to experience periorbital edema, or swelling around the eyes. The edema has persisted since then. In 2010, Tyler also began to experience periorbital edema. In 2011, the presence of perimacular flecks were noted. Perimacular flecks are a result of Alport syndrome, but they are not a cause of vision loss. Both of these eye deficits persisted throughout the rest of the study. His vision loss is also unrelated to Alport syndrome. Both participants treat their vision loss solely with prescription glasses, and they visit their optometrist at least on an annual basis.

3.2.2 Speech and Language Assessment and Treatment

Both participants received speech and language evaluations on an annual basis from a certified speech-language pathologist. Speech and language evaluations consisted or were comprised of the administration of standardized tests, such as the CELF and GFTA tests. The CELF (Clinical Evaluation of Language Fundamentals, 4th and 5th editions) is a test that evaluates language function for people ages 5 – 21. The GFTA-2 (Goldman-Fristoe Test of Articulation, 2nd edition) is an articulation test that assesses the sound production abilities of people ages 2-21 at the word, phrase, and sentence levels. Sound production abilities are checked in the initial, medial, and final word positions using the GFTA-2. The results of the standardized tests are presented in figures 3 and 5 for Jacob and 4 and 5 for Tyler. In addition to standardized tests, the speech-language pathologist used informal measures to assess the speech and language skills of the participants. Informal measures included dialogue exchange, monologue, and recognition of the

Ling 6 sounds, and they evaluated mean length of utterance (MLU), conversational skills, and vocabulary. The Ling 6 Sounds are a set of 6 sounds ranging from lowest frequency to highest (“m,” “ah,” “ee,” “oo,” “sh,” and “s”), and the recognition of these sounds ensure that the client has auditory access to the minimum number of sounds necessary to hear and understand speech. MLU, or mean length of utterance, is the average number of morphemes spoken in a sentence. Conversational skills include turn-taking abilities, eye contact, and topic maintenance.

Jacob’s initial speech and language evaluation revealed that he was below the 10th percentile in each subtest of the CELF evaluation and he was in the 19th percentile in GFTA. Errors noted by the CELF included the absence of irregular plurals and the use of past tense markers. Errors noted by the GFTA included the use of the sound “sh” in place of “s” and the use of “b” instead of “v”. Over the years, his speech and language gradually improved and results 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 21stpercentile in GFTA. The errors found in 2009 had since been mastered, though new errors were identified. These included the use of non-content words in place of specific nouns (e.g., that, those, stuff) and reciprocal eye gaze during a conversation. This suggests that he had attained improvement in speech and language skills, but he still has skills to improve upon. Similarly, informal tests revealed that Jacob made considerable progress. For example, in 2009 his single word vocabulary was at age level and his conversational skills were delayed, with difficulty maintaining a topic as well as difficulty comprehending non-canonical or open-ended interrogative sentences. In 2014, the Ling 6 sounds were introduced to Jacob. At 3 feet, he had confusion between “oo” and “mm” and between “ss” and “sh.” In 2015, his vocabulary was expanding by at least 3 words per week and his conversational skills were at an appropriate level, with only mild difficulties with topic

maintenance and perspective taking. He was also able to detect and discriminate all 6 Ling sounds up to 9 feet away. However, with the presence of background noise and the absence of an FM system, there was confusion between "ee" and "oo" and between "ss" and "sh," even in short distances. Jacob received auditory-verbal therapy 2 times per week from a certified auditory-verbal therapist from 2010 to 2016. Short-term goals are presented in table 6. Inspection of therapy records revealed that Jacob had achieved his goals on a consistent basis, which explains his improvement on standardized assessments.

Tyler's speech and language therapy has been intermittent since 2010. 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 the CELF evaluation, and he was above the 30th percentile in GFTA. Errors found in CELF included difficulty following a conversation and the need for many repetitions as well as errors of syntax (e.g., verb tense, relative clauses, and use of descriptors). Tyler's speech and language gradually improved and results from his most current evaluation, in 2014, revealed that his CELF subtest scores ranged from below the 10th percentile to the 50th percentile in CELF and he was above the 24th percentile in GFTA. The errors found in 2009 had since improved, although new errors had been identified. These included difficulty with topic maintenance and grammatical errors (e.g., use of pronouns). Similarly, informal tests revealed that Tyler made progress in some areas while continuing to struggle in others. For example, in 2012 he was able to detect all Ling-6 sounds, his MLU was 9.5 and his conversational skills were delayed, with moderate difficulty following a conversation and requiring many repetitions of utterances, explanations of unknown words, and/or rephrasing in order to comprehend. In 2014, he was able to detect all Ling-6 sounds with 3 feet of distance, but experienced confusion between "oo," "ee," and "s" sounds with 9 feet of

distance. His MLU was 10.3 and his conversational skills remained delayed, with difficulty maintaining a topic and effectively initiating and ending a conversation. In 2016, his detection of the Ling-6 sounds remained unchanged, his MLU increased to 11.5, and his conversational skills were only slightly delayed. Tyler received intermittent auditory-verbal therapy once per week from a certified auditory-verbal therapist from 2012 to 2016. Short-term goals are presented in table 7. Inspection of therapy records revealed that Tyler had progressed towards his goals on a consistent basis, which explains his progress on standardized assessments.

3.2.2.1 Educational History

The diagnoses of ADHD and ASD, along with hearing loss, led to the development of Individualized Education Plans (IEPs) for both participants. In these IEPs, it was determined that both participants needed optimal listening environments (the use of FM systems, preferential seating, etc.) in order to obtain as much information in the classroom as their peers.

Jacob enjoyed science classes and earned passing grades for those classes. However, he struggled significantly in mathematics and English, ultimately failing in these areas. As a result, he was taken from the class during these courses and worked one-on-one with a teacher to ensure he was able to comprehend the information. 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 the classes he struggled in. He, too, was taken from the classroom and received private tutoring from a teacher in the school.

Due to the lack of resources provided by the schools and teachers in order to accommodate the participants' hearing loss, as well as the adoptive mother's new traveling job, Jacob, Tyler, and their younger sister transitioned from the public school setting to home schooling in 2014. Along with the ability to stay with their mother as she travels, the siblings are now able to benefit from

one-on-one learning in all subject areas. As a result, Jacob and Tyler now receive passing grades in the areas in which they previously struggled.

3.2.3 Renal Function

To monitor renal function, the participants visited their pediatric nephrologist at least on an annual basis. During each visit, vital signs and body systems were noted, a physical exam was performed, and various tests were run to evaluate renal function. The tests that were performed monitored levels of blood, protein, creatinine, and serum albumin in the urine and/or blood. Creatinine is the chemical waste of creatine, a substance created by the body to produce muscle energy. This waste travels through the blood and is filtered out in the kidneys. Creatinine levels are tested to predict renal function as high levels of creatinine indicate that the kidneys are not adequately filtering waste products in the body [16]. Albumin is a protein created in the liver and it helps transport small molecules through the blood. It is common for those with Alport syndrome to have lower albumin levels because this protein~~,~~ as well as others~~,~~ are lost in their urine [17]. The protein-to-creatinine ratio is a measure taken from the urine sample. A positive result indicates the presence of protein in the urine and a negative result indicates the absence of protein [18]. The results from these tests are presented in tables 8 and 9 for Jacob and Tyler, respectively. Blood and protein were present at alarming rates for both participants throughout the seven years.

During the initial visit with his pediatric nephrologist, test results showed large amounts of blood and protein in Jacob's urine. His creatinine was at a normal level of 0.4 mg/dL (milligrams per deciliter), his protein-to-creatinine (Pr:Cr) ratio was high at 2 mg/dL, and his serum albumin level was low at 2.4 mg/dL. The Pr:Cr ratio and serum albumin level indicated that Jacob had been experiencing proteinuria. His initial diagnosis was a general glomerulonephritis, but later in

2009, the biopsy performed on Tyler revealed the diagnosis of Alport syndrome. In subsequent years, Jacob's creatinine levels remained stable and at normal levels. This indicates that his kidneys were adequately filtering the creatinine out of his blood and into his urine. Only in 2012 did his creatinine levels begin to gradually rise. In 2016, his creatinine levels reached a high of 0.7 mg/dL. Unlike his creatinine levels, Jacob's Pr:Cr ratios fluctuated each year. For example, his ratio was 2.6 mg/dL in 2012, 2.1 mg/dL in 2013, 2.7 mg/dL in 2014, and 3.5 mg/dL in 2015 mg/dL. Lastly, Jacob's serum albumin levels remained somewhat stable. For example, the first four years his albumin levels remained just below 0.4 mg/dL. Between 2012 and 2013, an increase in albumin levels appeared. From then on, the levels remained at around 0.6 mg/dL. Tyler also showed high amounts of blood and protein in his urine during his initial visit with the nephrologist. His creatinine was at 0.38 mg/dL, his Pr:Cr ratio was at 3.3 mg/dL, and his serum albumin level was at 3.2 mg/dL. Tyler's creatinine level showed that his kidneys were not filtering as well as they should. His Pr:Cr ratio and serum albumin level indicated that he was also experiencing proteinuria. He was also initially diagnosed with a general glomerulonephritis, but his kidney biopsy later in 2009 showed signs of Alport syndrome. Tyler's creatinine levels did not fluctuate, however they always remained at high levels for his 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 in 2015, and ended at 0.85 in 2016. Similar to Jacob's Pr:Cr ratios, Tyler's fluctuated significantly. In figure 9, many peaks and dips in Pr:Cr ratios can be observed. An example can be seen in 2012, when his Pr:Cr ratio reached a level of 3.8 mg/dL. In 2013, that ratio dropped to 1.0 mg/dL and rose, again, to 3.3 mg/dL. A less significant drop occurred again in 2015, but the ratio ended in 2016 with a high of 7.9 mg/dL. Lastly, Tyler's albumin levels remained relatively stable throughout the seven years. His peak albumin level occurred in 2013, with a level of 3.7 mg/dL,

but by the next year his level returned to 3.3 mg/dL and it remained around 3.5 mg/dL until 2016.

4. Discussion

For this study, it is important to understand the relationship between the kidneys and the cochlea. At first it appears that these two organs are unrelated. However, these two organs develop from the same cells in utero. The kidneys are developed from the embryo's mesoderm, while the outer, middle, and inner ears are formed from the ectoderm and endoderm. Within the embryo, the bilateral nephric ducts descend toward the cloaca, and progenitor cells cause the nephrons to multiply. This process is complete around the 36^{th} week of gestation, and at the time of birth the infant has 600,000-800,000 nephrons in each kidney. Around the fourth week of gestation, the ears begin to develop. The embryo's ectoderm begins to invaginate and form otic vesicles. These vesicles, then, begin to form the outer, middle, and inner ear. In Alport syndrome, sensorineural hearing loss is a result of the loss of the type IV collagens responsible for the kidneys' basement membrane development [19].

In the current study, we reported information on the speech and language development of twins diagnosed with Alport syndrome. Information on their medical history, specifically hearing function, kidney function, and visual acuity, was also presented. The information provided a holistic understanding of the speech and language development of these twins. Even though the protein and blood levels in their urine showed no clear correlation with hearing function, it is possible that antigens could have contributed to hearing loss.

Jacob was born with an incomplete unilateral cleft lip and an incomplete cleft palate, as well as sensorineural hearing loss. He had received several corrective and cosmetic surgeries for his cleft lip and cleft palate prior to his adoption in 2007, and he has received several surgeries after the

adoption. His most recent surgery, in 2015, included a partial adenoidectomy, which resulted in a slight hypernasal resonance. Due to the presence of hearing loss at birth, Jacob did not have the opportunity to learn speech and language as well as Tyler, who was born with typical hearing. In 2009, he was diagnosed with a moderate to moderately severe sensorineural hearing loss. He experienced middle ear infections in his left ear from 2009 to 2011 due to his cleft palate. These infections resulted in a mild conductive hearing loss in his left ear. In 2009, his expressive and receptive speech and language skills were delayed, with poor pragmatic skills, the excessive use of substitutions, and the inability to follow directions. As a result of Tyler's renal biopsy, both twins were officially diagnosed with Alport syndrome later in 2009. The only other symptoms of the diagnosis that Jacob presented was nephrotic-range proteinuria and hematuria. In 2011, his conductive hearing loss improved, but his sensorineural hearing loss increased. His hearing deteriorated to a moderate to severe loss. He also began to experience vision loss, though it was not due to Alport syndrome. He did experience periorbital edema which was a result of his renal syndrome. Speech and language therapy helped improve his delays, but all of his deficits were still present. In 2012, Jacob was able to follow directions and his pragmatic skills improved significantly. He was better able to maintain eye contact and he knew how to properly begin, maintain, and end a conversation. He was also able to remember details in a story and participate in a discussion about that story. In 2013, Jacob was diagnosed with Asperger's syndrome and reached an elevated creatinine level of 0.84 mg/dL. His hearing, speech, and language remained the same. In 2014, he was introduced to the Ling-6 sounds and he was able to detect these sounds at distances up to 9 feet. From 2014 to 2016, no major changes in vision, speech and language, hearing function, or renal function were noted. Overall, Jacob's vision, hearing, and renal function deteriorated slowly and steadily. With speech and language therapy, he consistently

made improvements.

Due to Tyler's uneventful birth and typical hearing, he was able to develop speech and language skills as any other child with typical hearing would. Because he did not experience hearing loss until 2009, and it did not have a negative effect on his speech and language skills until 2012, his speech and language reports are fewer in number compared to Jacob. In late 2009, Tyler was diagnosed with a mild hearing loss in his right ear. Due to his hematuria and proteinuria, a renal biopsy was performed on him, and the diagnosis of Alport syndrome was made for him as well as his siblings. By early 2010, his mild hearing loss became present bilaterally. In just a few months, his hearing function deteriorated to a moderate level. Tyler also began experiencing vision loss, though it was unrelated to Alport syndrome. In 2011, his hearing loss stabilized, but he began to experience periorbital edema and perimacular flecks, a result of Alport syndrome. In 2012, Tyler's hearing loss began to affect his speech and language skills. His hearing loss as well as ADHD caused great difficulty in remaining on task during various situations. He was diagnosed with a moderate receptive and expressive language delay, though his expressive language was worse than his receptive. In 2013, Tyler's hearing function worsened to a moderate level. He refused to wear his behind-the-ear hearing aids due to self-consciousness, so he participated in a study that allowed him to wear in-canal hearing aids. In the same year, he was diagnosed with Asperger's syndrome and his creatinine levels elevated, for the first time, to a level of 0.66 mg/dL. In 2014, his hearing loss remained at a moderate level, but it worsened just enough in which the in-canal hearing aids did not provide enough gain, so he returned to behind-the-ear hearing aids. His speech skills improved, but he still had great difficulty in pragmatics. In 2015, his hearing function stabilized again, but his creatinine levels elevated further to 0.98 mg/dL. By 2016, his creatinine levels lowered to 0.64 mg/dL. His speech and language skills

improved enough to warrant dismissal from speech and language therapy.

5. Conclusion

It is likely that twins in the current study had developed sensorineural hearing loss over the course of years as a result of chronic kidney dysfunction. The current longitudinal retrospective case study highlights how Alport syndrome can affect not only hearing function but also speech and language development. To our knowledge, this is the first longitudinal (i.e. 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 such clients. This study highlighted how systemic disease associated with Alport syndrome (i.e. glomerulonephritis) can also affect hearing and speech and language development. Unfortunately, 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 the healthcare professionals. It is possible that treatment provided by a certain healthcare professional can impact the other functions. For example, medications provided to improve kidney function can negatively impact hearing. Thus, it is essential that speech-language pathologists and audiologists adopt a team approach when treating such complex medical conditions to achieve ideal outcomes.

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Tables and Figures

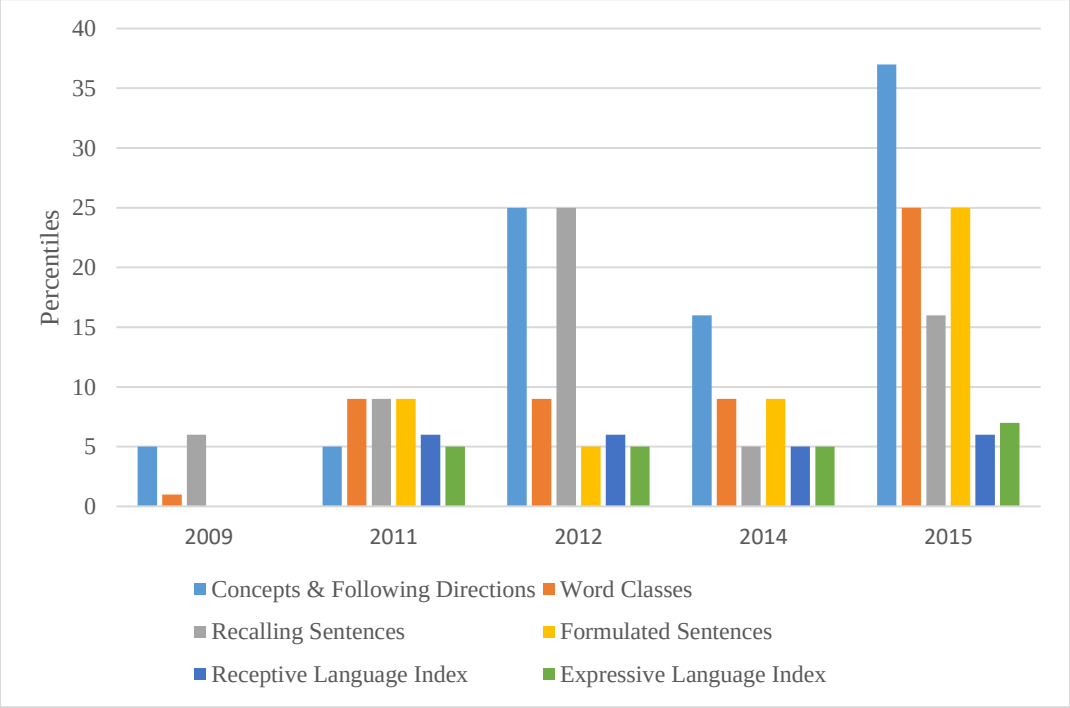
1. Audiological Assessments for Jacob, by Year.
PTA = pure tone audiometry, SRT = speech recognition testing, Word Rec. = word recognition testing

Year	Ear	Audiological Assessment			
[redacted]		PTA	SRT	Word Rec	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

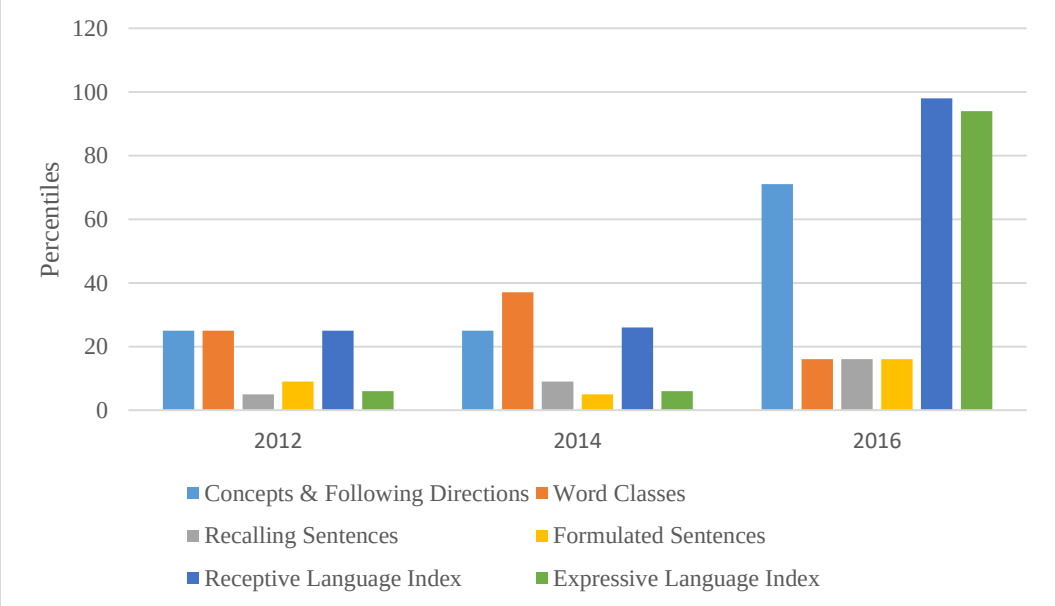
2. Audiological Assessments for Tyler, by Year.
PTA = pure tone audiometry, SRT = speech recognition testing, Word Rec. = word recognition testing

Year	Ear	Audiological Assessment			
[redacted]		PTA	SRT	Word Rec	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

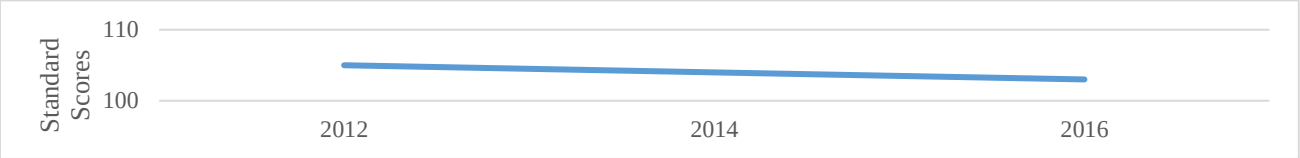
3. Jacob's CELF Scores by Year.
This chart shows the results of each CELF (Clinical Evaluation of Language Fundamentals) test during each year.



4. Tyler's CELF Scores by Year
This chart shows the results of each CELF (Clinical Evaluation of Language Fundamentals) test during each year.



5. GFTA Standard Scores for Each Participant, by Year
   This chart shows the results of each GFTA-2 (Goldman-Fristoe Test of Articulation, 2nd edition) during each year it was used on the participants.



6. Jacob's Short Term Goals and Progress
   This table presents the goals set for Jacob by his certified auditory-verbal therapist as well as the progress made.

Short Term Goal	**Progress**
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.
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. Progress made – goal not met.
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.
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. Progress made – goal not met.
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.
6. Listen to a 3-5 minute 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. Progress made – goal not met
7. Follow 6-7 element directions with at least	2012: He followed 6 element directions with

80% success	60% success. 2015: He followed 6 element directions with 70-80% success. Progress made – goal not met
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. Progress made – goal not met
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.
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.
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. Progress made – goal not met.
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. Progress made – goal not met.
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.
14. Participate in the CLIX auditory discrimination program achieving 90% success at all levels of listening skills.	2014: He achieved an overall score of 60% on the CLIX. 2015: He achieved an overall score of 100% on the CLIX. Goal met.
15. Demonstrate expanded receptive and expressive vocabulary for all parts of speech	2014: New vocabulary words were not being documented.

by establishing the ability to utilize at least 3 new vocabulary words weekly.	2015: At least 3 new vocabulary words were being documented each week. Goal met.
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. Progress made – goal not met.
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.

7. Tyler’s Short Term Goals and Progress

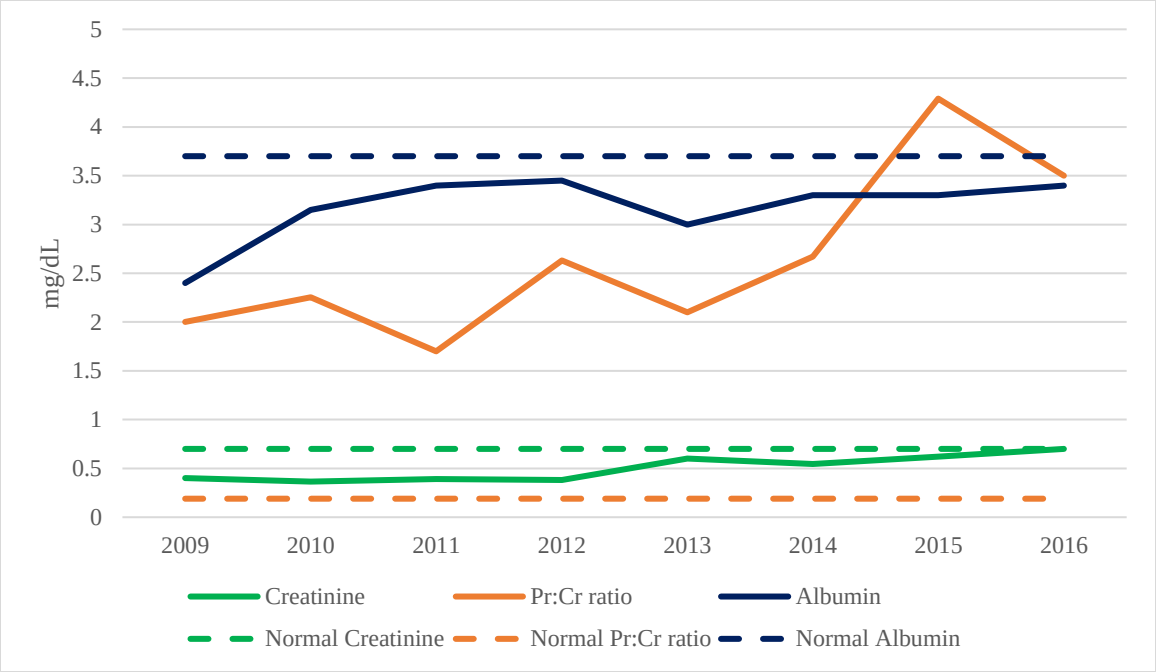
This table presents the goals set for Tyler by his certified auditory-verbal therapist as well as the progress made.

Short Term Goal	**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. Progress made – goal not met
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. Progress made – goal not met
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. Progress made – goal not met
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. Progress made – goal not met
5. Verbally produce an 8-10 element story	2012: He produced a 4-step story narrative

narrative with at least 80% success	with 70% success. 2013: He produced a 6-step story narrative with 70% success. Progress made – goal not met
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.
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. Progress made – goal not met
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 Progress made – goal not met
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. Progress made – goal not met

8. Jacob's Nephrology Results by Year

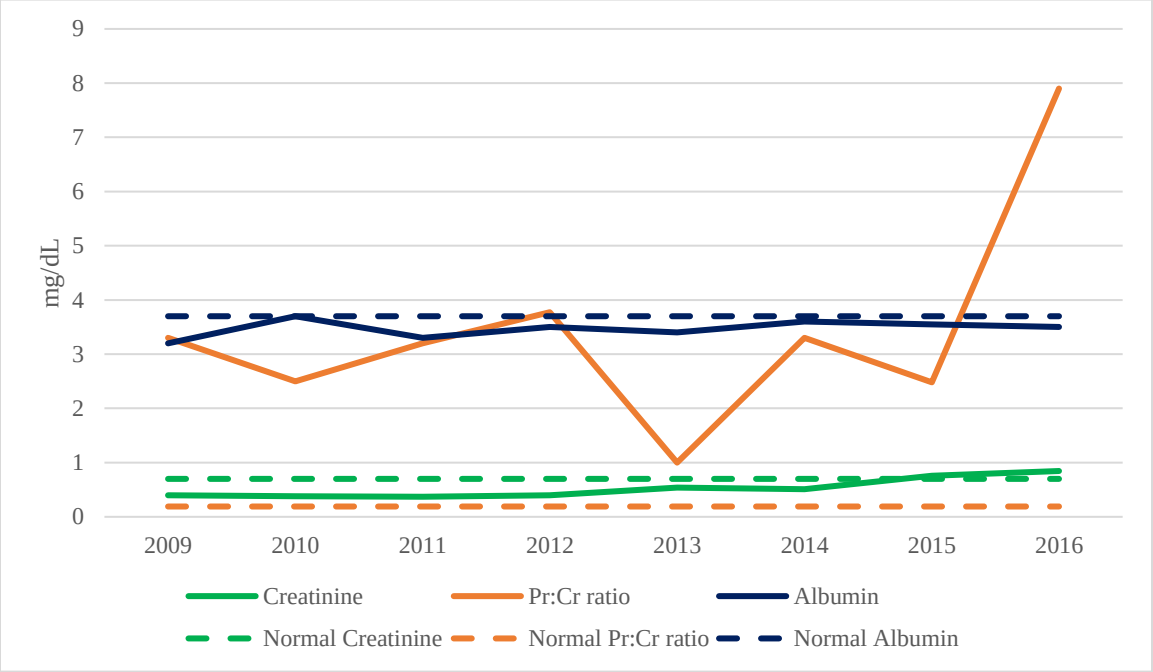
This table presents the results of urine and blood samples taken to monitor renal function.



Note: Normal levels of creatinine in the blood vary due to the size and muscle mass of each person. Normal levels of creatinine for adult males range between 0.7 and 1.3 mg/dL (milligrams per deciliter). The protein-to-creatinine ratio is a measure used to monitor proteinuria. A positive result indicates the presence of protein in the urine, while a negative result indicates the absence of protein. Levels of serum albumin that are considered to be normal in urine range between 0 and 23 mg/dL.

9. Tyler's Nephrology Results by Year

This table presents the results of urine and blood samples taken to monitor renal function.



Note: Normal levels of creatinine in the blood vary due to the size and muscle mass of each person. Normal levels of creatinine for adult males range between 0.7 and 1.3 mg/dL (milligrams per deciliter). The protein-to-creatinine ratio is a measure used to monitor proteinuria. A positive result indicates the presence of protein in the urine, while a negative result indicates the absence of protein. Levels of serum albumin that are considered to be normal in urine range between 0 and 23 mg/dL.