

(a)Title: Feeding, communication, hydrocephalus and intracranial hypertension in patients with severe *FGFR2*-associated Pfeiffer syndrome.

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(d) Acknowledgements:

Dr Jo Byren, Dr Fintan Sheerin, Megan Cooke, Shahida Kiani, Dr Lotte Meteyard, Mr Tim Lawrence.

(e) Funding:

A.O.M.W. was supported by the National Institute for Health Research (NIHR) Oxford Biomedical Research Centre (BRC). The views expressed are those of the author(s) and not necessarily those of the NHS, the NIHR or the Department of Health.

Abstract

Background: Pfeiffer syndrome is associated with a genetic mutation of the *FGFR2* (or more rarely, *FGFR1*) gene, and features the combination of craniosynostosis, midface hypoplasia, broad thumbs and broad great toes. Previous research has identified a wide spectrum of clinical phenotypes in patients with Pfeiffer syndrome. This study aimed to investigate the multifactorial considerations for speech, language, hearing and feeding development in patients with severe genetically-confirmed Pfeiffer syndrome.

Methods: A 23-year retrospective case-note review of patients attending the Oxford Craniofacial Unit was undertaken. Patients were categorized according to genotype. Patients with mutations located in *FGFR1*, or outside the *FGFR2* IgIII domain-hotspot, or representing known Crouzon/Pfeiffer overlap substitutions were excluded. Twelve patients with severe *FGFR2*-associated Pfeiffer syndrome were identified.

Results: Patients most commonly had pansynostosis (n=8) followed by bicoronal (n=3), and bicoronal and sagittal synostosis (n=1). Seven patients had a Chiari I malformation. Four patients had a diagnosis of epilepsy. Ten patients had with hydrocephalus necessitating ventriculoperitoneal shunt insertion.

Feeding difficulties were common (n=10/12) and multifactorial. In 5/12 cases, they were associated with pansynostosis, hydrocephalus, tracheostomy and tube feeding in infancy.

Hearing data were available for 10 patients, of whom 9 had conductive hearing loss, and 8 required hearing aids. Results indicated that 3/4 patients had expressive language difficulties, 3/4 had appropriate receptive language skills. 6/12 patients had a speech sound disorder and abnormal resonance.

Conclusion: This study has identified important speech, language, hearing and feeding issues in patients with severe *FGFR2*-associated Pfeiffer syndrome. Results indicate that a high rate of motor-based oral stage feeding difficulties, and pharyngeal stage swallowing difficulties necessitating regular review by specialist craniofacial speech and language therapists

Key Words: Pfeiffer syndrome, *FGFR2*, speech, language, feeding, hearing.

Introduction

Pfeiffer syndrome (PS) is a genetic condition affecting ~1 in 100,000 individuals, defined by a mutation in either the *FGFR1* or *FGFR2* genes.¹ Mutations usually occur *de novo*, but milder phenotypes may be inherited in an autosomal dominant fashion.^{2,3} The clinical presentation of individuals with PS typically includes bicoronal or other multisuture synostosis (including pansynostosis), midface hypoplasia, broad thumbs, and broad big toes (Figure 1).¹⁻³ Additional clinical features may include respiratory, ocular, otologic and neurologic difficulties that add complications to the course of patient treatment.⁴⁻⁸ The limb anomalies together with the presenting craniofacial phenotype constitute the criteria for clinical diagnosis, and distinguish PS from Crouzon syndrome, in which the extremities are grossly normal. Both Pfeiffer and Crouzon syndromes are most commonly caused by heterozygous mutations in the *FGFR2* gene; although the patterns of mutation are overlapping, a partial genotype-phenotype correlation is evident.⁹⁻¹²

Hence, genetically-defined case definition, combined with clinical assessment, is paramount to provide homogenous case series of PS, but this is frequently lacking in the literature. Previous research has sought to classify patients with PS clinically, to facilitate the study of this syndrome. Cohen et al. (1993) proposed a sub-classification into type I – less severe, type II – severe with a cloverleaf skull, and type III – severe without a cloverleaf skull,¹³ however this classification predated the discovery of *FGFR2* mutations in PS. Grieg et al. (2013) proposed an alternative classification system based on a functional assessment of respiratory, ocular, otologic and neurologic problems. Greig et al. (2013) classified a series of 42 patients with PS into three groups: type A, B, or C and investigated whether surgical treatment resulted in improved functional outcome for patients.¹⁴ Although, this series included only patients classified clinically as PS, not all were genetically-confirmed, and the authors acknowledged they may have inadvertently included patients with other diagnoses in their study. Due to the heterogeneity in these groups, limited clear conclusions can be drawn for clinical practice.

Over 40 different heterozygous mutations of *FGFR2* causing PS have been reported,¹⁵ each of which is associated with a unique, albeit overlapping phenotype.^{9,15} For example, a limited subset of *FGFR2* mutations (typically encoding the amino-acid substitutions p.Trp290Cys, p.Tyr340Cys, p.Cys342Arg and p.Ser351Cys)^{12,16} may be associated with severe multisuture synostosis and neonatal lethality,^{1,17,18} whereas the p.Cys342Ser substitution has been reported in the literature with diagnoses of both Pfeiffer and Crouzon syndromes.¹⁹ More rarely, PS is caused by a specific heterozygous variant encoding p.Pro252Arg in *FGFR1*; this is characterized by a much milder phenotype and craniosynostosis is not always evident.^{20,21}

This work focuses on severe *FGFR2*-associated PS, in which the complex combination of craniofacial, respiratory and neurologic presentation raise particular challenging implications for patients' feeding and communication development. Specifically, craniofacial anomalies such as mid-face hypoplasia, glossoptosis, tracheal stenosis and choanal atresia, which create potential airway obstruction can

have a significant impact on feeding and swallowing efficiency and safety.^{16,22} Airway difficulties in patients with PS are commonly managed by tracheostomy. Tracheostomy insertion may have further implications for feeding and swallowing,^{22,23} and communication.^{24–29} This research seeks to examine the multifactorial presentations of patients with severe *FGFR2*-associated PS through the perspective of a specialist craniofacial speech and language therapist, to better understand the implications of these factors for speech, language, feeding and hearing in this patient population.

Materials and Methods

A retrospective case-note review was undertaken of all patients with a clinically and genetically-confirmed diagnosis of PS, who attended the Oxford Craniofacial Unit during a twenty-two-year period (1995 to 2017). Inclusion criteria were patients with severe *FGFR2*-associated PS, and available speech, language hearing and/or feeding data.

Classification of severe FGFR2-associated PS

A clinical diagnosis of PS requires craniosynostosis to be associated with broad thumbs and big toes,² hence it is unsurprising that the craniofacial features can be variable. For the purposes of this research, we excluded patients with PS who had atypical mutations, either involving the *FGFR1* gene (n=2), or located in atypical domains of *FGFR2* (IgII [n=1]³⁰, tyrosine kinase [n=1]¹¹, or presenting with the Crouzon/Pfeiffer overlap mutations p.Cys278Phe (n=1) or p.Cys342Ser (n=1). Following these exclusions, we reviewed in detail the clinical features of the twelve remaining patients, all of whom have mutations associated within the *FGFR2* IgIII domain hotspot.¹¹ For this study, we will refer to this group of patients as having 'severe *FGFR2*-associated PS'.

Criteria for hydrocephalus

Patients who required treatment in the form of cerebrospinal fluid (CSF) diversion (e.g. via ventriculoperitoneal shunt insertion) were classified as having hydrocephalus.

Criteria for intracranial hypertension

The criteria for intracranial hypertension were in accordance with the well-established specification of a baseline average above 15 mm Hg or more than 3 B-waves in a 24-hour period.³¹ Monitoring was conducted over a 24- to 48-hour period using an intraparenchymal Codman microsensor (Codman Microsensor, Johnson & Johnson Professional Inc.) placed in the right frontal lobe under a general anaesthetic. A recent review of 385 cases of intracranial pressure monitoring in the Oxford Craniofacial Unit identified a low complication and morbidity rate relating to the use of this procedure in the craniofacial population.³²

Criteria for feeding difficulties

The criteria for feeding difficulties included a sensory or motor difficulty affecting feeding safety, efficiency or typical age-appropriate feeding development across the following domains:

- 1) Oral-motor stage: difficulty achieving a normal range of movement, or difficulties controlling/ manipulating the tongue, lips, jaw and/or palate when eating and/or drinking.
- 2) Oral-respiratory co-ordination: difficulties due to airway obstruction affecting oral stage of feeding or suck-swallow-breath synchrony.
- 3) Pharyngeal stage: delayed swallow initiation, impaired airway protection, reduced or slow laryngeal elevation.
- 4) Oesophageal stage: swallow dysfunction including gastro-oesophageal reflux.
- 5) Food or fluid aversions or selectivity as observed by the speech and language therapist or reported by the child or family as being problematic.

It did not include feeding issues falling under ICD-10 CM codes of eating disorder.³³

Criteria for Speech Sound Disorder:

Speech was assessed using a combination of the *Great Ormond Street Speech Assessment* (GOS.SP.ASS'98) and clinical assessment.³⁴ The presence of one or more delayed or disordered articulation or phonological errors indicated a speech sound disorder, in accordance with the standardized norms in Dodd et al (2006).³⁵

Criteria for Language Difficulties

Language was assessed using Clinical Evaluation of Language Fundamentals – Preschool – second edition (CELF-P2)³⁶ and Clinical Evaluation of Language Fundamentals – Third Edition (CELF-3).³⁷ The criteria for language difficulties were defined as a standard score of less than 1.3 standard deviations below the mean score on one or more of the above standardized-measures, or a score of less than seven on a series of subtests of one of the standardized measures.^{36,37}

Criteria for Velopharyngeal Dysfunction and Resonance Disorders:

Hypernasal resonance was defined as the occurrence of excessive nasal resonance perceived during speech production, resulting from an abnormal coupling of oral and nasal resonating cavities when the velopharyngeal sphincter is in an open position.³⁸ Hyponasal resonance was defined as the reduction or absence of expected nasal resonance associated with nasal consonants and their adjacent vowels in English. This is usually due to the reduction of the size of the velopharyngeal port and/or nasal airway, as might be expected if an individual's adenoids are large.³⁸ Normal resonance was defined as nasality expected in normal voice production resulting from the appropriate coupling of the oral and nasal resonating cavities.³⁹

Criteria for hearing impairment

Where possible the average hearing loss (HL) was calculated from the hearing thresholds using Play or Pure Tone Audiometry and minimal response levels using Visual Reinforcement Audiometry or Distraction Testing at 500, 1000, 2000 and 4000 Hz.

Abnormal test results were defined in accordance with the British Society of Audiology guidelines: 21-40 dB HL = mild; 41-70 dB HL = moderate; 71-95 dB HL = severe; >95 dB HL = profound.⁴⁰ For the majority of cases, minimum hearing levels obtained using Soundfield Audiometry used a screening level of 25 dB HL. Due to changes in departmental protocol over time, older cases were screened to a minimum level of 30 dB HL. For these cases, hearing levels of 30 dB HL were classified as satisfactory.

Results of Tympanometry were analysed to determine the compliance of the tympanic membrane. Results were classified in accordance with Jerger's (1970) definitions of Type A, B or C tympanograms. Type A is normal. Type B is flat and correlates with either middle ear effusion, occlusion of the external auditory canal with wax, perforation of the tympanic membrane or presence of a grommet which can be differentiated by the ear canal volumes.⁴¹ A Type C tympanogram usually indicates eustachian tube dysfunction or mastoid abnormality.

Results

Patient characteristics

A total of 12 patients (five males, seven females) had *FGFR2* mutations (11 previously reported missense, one novel in-frame duplication) typically associated with a severe PS phenotype⁷ (Table 1). **We excluded six other patients diagnosed with PS but with atypical mutations (see Methods).** One patient (Patient 1) died at the age of two years, however their early medical and developmental history are included in this review.

Eight patients had pansynostosis, four had multisuture synostosis (one with bicoronal and sagittal synostosis, and three had bicoronal synostosis). Additional craniofacial features are outlined in Table 1.

In respect of surgical management, the patients all underwent multiple surgical procedures.

Neurological Features

Four patients had a confirmed diagnosis of epilepsy with a predisposition to unprovoked seizures in later childhood requiring regular anti-epileptic medication. Ten patients (83%) developed hydrocephalus, necessitating ventriculoperitoneal shunt insertion in all cases. Patient 1 initially received an external ventricular drain (EVD), followed by a ventriculoperitoneal shunt, Patient 7 received a lumbar peritoneal shunt as part of treatment for a post-operative cerebrospinal fluid leak and went on to develop hydrocephalus which was treated with a ventriculoperitoneal shunt. Radiological imaging indicated that seven patients had a Chiari I malformation, of whom 2/7 were asymptomatic and 3/7 had mild gross motor symptoms, which did not require intervention. Patient 1 had a severe Chiari I malformation and underwent early foramen magnum decompression. This patient continued to present with a severe bulbar signs and underwent a secondary procedure, which was abandoned due to venous anomalies and intraoperative bleeding. Patient 7 required foramen magnum decompression to treat a symptomatic Chiari I malformation, which was contributing to a presentation of oropharyngeal dysphagia.

Hydrocephalus and Intracranial Pressure

Ten patients (n=10/12) had hydrocephalus. Hydrocephalus was managed via ventriculoperitoneal shunt in all ten cases. Table 2 provides a breakdown of the patients who had treatment for hydrocephalus as part of their care.

Patient Number	Hydrocephalus	Shunt	Clinical Features/ Intervention	Evidence of Intracranial Pressure (age, result)
Patient 1	Y	Y	Cranio-cerebral disproportion.	1 year 8 months = abnormal
			Transcranial surgery and shunt revision	1 year 11 months = borderline
Patient 2	Y	Y		
Patient 3	Y	Y		
Patient 4	N	Y		
Patient 5	Y	Y		
Patient 6	Y	Y		
Patient 7	Y	Y	Shunt	1 month = abnormal
			Transcranial surgery	2 years 7 months = abnormal
			Shunt revision to allow Monobloc	5 years 7 months = abnormal
			Cranio-cerebral disproportion	5 years 11 months = abnormal
Patient 8	Y	Y	Raised pressure identified in another Unit. Treated with subtemporal decompression in another Unit.	
Patient 9	Y	Y	Primary surgery elsewhere. Presented late. Treated with calvarial expansion.	4 years 7 months = abnormal
Patient 10	Y	Y		6 years 8 months = abnormal
Patient 11	N	N		
Patient 12	Y	Y		

Table 2. Hydrocephalus and Intracranial Pressure

Hydrocephalus, Reflux and Feeding

Seven patients presented with both hydrocephalus and oral-motor feeding difficulties, which became apparent under five years of age. Five patients with hydrocephalus were reported to have gastro-oesophageal reflux.

Respiratory

92% (n=11/12) of patients were diagnosed with upper airway obstruction. Six patients were tracheotomized for obstructive sleep apnoea, two patients (Patients 10 and 12) underwent prophylactic tracheostomy insertion prior to Le Fort III advancement (Patient 10 at one year; Patient 12 at five years) according to Unit protocol. Patient 10 was decannulated after 6 months, Patient 12 after 12 months. Patients 2,3, 4 and 11 did not require a tracheostomy

Feeding

Results indicated that 92% (n=11/12) of patients with severe *FGFR2*-associated PS had feeding difficulties (Figure 2, Table 3).

66% of patients (n=8/12) experienced structurally-based upper airway pathology that impacted on their oral stage of feeding due to the presence of choanal atresia, choanal stenosis, relative macroglossia or more generally documented upper airway obstruction. Six patients had documented obstructive sleep apnea. The impact of this was typically uncoordinated suck-swallow breath patterns when feeding during infancy; with some reports of subsequent feed-induced apnea, feeding fatigue, poor weight gain, mouth breathing and consequent inability to create an oral seal when feeding due to nasal obstruction and reduced oral sensation. Patient 8 reported that nasal obstruction continued to cause some difficulty with eating at 14 years of age. Patient 11 continued to have slow feeding at seven years of age due to reliance on mouth, rather than nasal breathing. Six of these patients had a placed tracheostomy to manage their respiratory difficulties (excluding those with tracheostomy placed as a preventative measure prior to surgical procedure), five during infancy and one (Patient 6), at 13 months of age. No patients in this cohort with unit-based Ear Nose and Throat notes (n=6) had a documented cartilaginous tracheal sleeve. Results indicated that 5/6 patients with a tracheostomy (not including preventatively inserted tracheostomies) experienced both oral and pharyngeal stage swallowing difficulties, and 4/6 of these patients had reflux.

66% (n=8/12) of patients had documented motor-based, oral stage feeding difficulties. These consisted of a reported weak suck, reduced lip seal resulting in drooling and loss of food/fluid from the mouth, gagging, chewing difficulties and residual food remaining in the mouth after eating. Of these eight patients, six patients were reported still to have oral motor-based feeding difficulties persisting beyond five years of age (one died aged two years).

All patients with documented pharyngeal stage swallowing difficulties (and consequent risk of aspiration during feeding) (n=5/12) had pansynostosis, hydrocephalus requiring a shunt in the first year of life, a tracheostomy *in situ*, and a need for tube feeding during infancy. Four out of five of these patients required tube feeding beyond two years of age and a further two of these (one child deceased)

patients required tube feeding beyond 10 years. Pharyngeal stage swallowing difficulties never occurred in isolation and none could be managed by diet modification or therapeutic management alone. In addition to tube feeding, one case required foramen magnum decompression to manage their swallowing difficulties. No patients with isolated oral motor (n=1), or oral-respiratory (n=2) based feeding difficulties required tube feeding.

Sensory aversion was noted in three patients. This occurred alongside oral-respiratory, oral-motor and pharyngeal feeding problems and tube feeding for all three children. For 2/3 patients, reflux was an additional feature.

Hearing

Hearing data were available for ten patients. Hearing loss was most commonly bilateral (n=8/10) and conductive in nature (n=9/10). Severity varied, but was most often moderate (n=4). 6/10 patients had documented structural abnormalities, including absent or narrow external auditory meati and pinna abnormalities.

Speech and Resonance

Results reflect the most recent speech outcome for each patient (range 5-21 years) (Table 4). Speech data were available for 6/12 patients. Results indicated that all patients had a speech sound disorder, or abnormal resonance. Five of these six patients had tracheostomy and two had a two-way valve. Five patients had hyponasal resonance. Patient 6 had a diagnosis of dysarthria and velopharyngeal incompetence. Structural factors, particularly a class III malocclusion impacted on speech sound production in this group, with 4/6 patients with speech errors and malocclusion having lateralization, dentalization and palatalization. For Patient 7, chronic open mouth posture had a significant effect on speech sound production, specifically their ability to produce bilabial sounds (/b/ and /m/), and consequently impacted on intelligibility.

Language

Language data were available for four patients. Three patients had appropriate receptive language skills, and one child had receptive language difficulties. Three patients had expressive language difficulties, all of whom had a history of tracheostomy insertion and conductive hearing loss. Patient 11 had appropriate receptive and expressive language skills. This patient had a c.940-2A>T splice site mutation, appropriate hearing and did not require tracheostomy insertion.

Discussion

This is the first study to investigate the multifactorial considerations for speech, language, hearing and feeding in a homogenous group of patients with severe genetically-confirmed *FGFR2*-associated PS. Of note, over half (n=7/12) of the patients harbored the identical p.Cys342Arg substitution, which is recognized to be the most frequent single mutation causing PS, and is associated with a severe phenotype.^{11,12,15} In this study, the combination of rigorous genetic classification of severe *FGFR2*-associated PS, together with the perspective of a **specialist craniofacial speech and language therapist**, provides a distinct contribution to the literature.

The relationship between PS and epilepsy is not described in the literature, but is to our knowledge mentioned in a single case-report featuring a child with PS type III who developed status epilepticus with fever and cerebral oedema.⁴⁴ Our results indicated that four patients had a diagnosis of epilepsy. Previous literature has predicted the potential for broad neurological abnormalities in patients with a severe PS phenotype.²

Our finding that four patients developed abnormal ICP results after primary transcranial surgery, necessitating surgical intervention corresponds with reports of elevated post-operative ICP reported elsewhere.^{42,43}

It is well known that patients with syndromic craniosynostosis may be at risk of developing hydrocephalus.^{45–47} This finding was mirrored in our group, with 10/12 patients developing hydrocephalus requiring management with cerebrospinal fluid diversion procedures (external ventricular drain, or ventriculoperitoneal shunt insertion).

The results in the present study indicated that six patients (50%) had a history of obstructive sleep apnea. This has been identified previously in the literature.^{42,48} Additional multi-level upper airway obstruction was noted in our group, with six patients requiring a tracheostomy for reasons of respiratory compromise (two of whom had a tracheostomy prophylactically prior to midface surgery in accordance with evolving Unit policy). These two patients would have required a tracheostomy had they not undergone midface advancement. Patients with PS typically present with upper airway obstruction secondary to midface hypoplasia and resultant nasal obstruction.² Upper airway obstruction is known to have implications for oral feeding in infants.⁴⁹ Infants may have resultant difficulties with suck, swallow, and breath coordination. Furthermore, inefficient feeding together with difficulty protecting the airway during swallowing may have profound implications for a child's respiratory health as well as ability to gain weight appropriately.⁴⁹

A point of interest in the present study is that there appears to be a link between reflux and hydrocephalus, which is in keeping with previous reports in the literature of reflux co-occurring with hydrocephalus in neurologically-impaired patients.⁵⁰ The hypothesis for the co-occurrence of reflux and hydrocephalus is based on animal studies that have identified that an acute elevation of ICP may result in a decrease in lower oesophageal sphincter pressure.⁵¹ Research has also identified an increased prevalence of gastro-intestinal difficulties in patients with PS including intestinal or bowel malrotation (associated with the p.Cys342Arg mutation).⁵² In the general population, an association between reflux and intestinal malrotation has been identified.⁵³ The possible link between raised ICP, hydrocephalus and reflux in patients with severe *FGFR2* associated PS requires further investigation.

Limited literature has explored the feeding needs of patients with PS. Our results indicate that the following factors co-occurred with pharyngeal stage swallowing difficulties: pansynostosis, hydrocephalus requiring a shunt in the first year of life, a tracheostomy *in situ* and requiring tube feeding in infancy. Surprisingly, although seven patients had a Chiari I malformation, only one patient had related oropharyngeal dysphagia requiring foramen magnum decompression (Patient 7). Effective management of dysphagia is required to prevent aspiration, associated

pneumonia and other sequelae. No patient in our cohort had a documented tracheal cartilaginous sleeve, which has previously been identified in patients with PS.^{54–56} Wenger et al. (2017) identified tracheal cartilaginous sleeves in 100% (n=5/5) of patients with a p.Trp290Cys mutation of *FGFR2*,⁵⁶ but this was not present in Patient 9 who had the identical mutation. A tracheal cartilaginous sleeve can impact on the effectiveness of airway clearance when coughing and put a child at risk of tracheal occlusion, or aspiration.

The impact of hearing loss on expressive language in patients with severe *FGFR2*-associated PS has not previously been considered. Our results indicated that all patients with expressive language difficulties had a history of conductive hearing loss. However, this is the first study to consider only patients with severe *FGFR2*-associated PS. Our results indicated that all patients had presumed conductive hearing loss in the absence of bone conduction and in the context of structural anomalies.

Limited literature exists regarding communication development in patients with PS, and much of it is characterized by methodological limitations.⁵⁸ Results of the present review indicated that six patients had a speech sound disorder in the context of a combination of tracheostomy insertion (n=5/6), a class III malocclusion (n=4/6), chronic open mouth posture (n=1/6), and/or hearing loss (5/6) that may have impacted on speech sound production. Limited language data were available in the present review - results indicating that 3/4 patients had appropriate receptive language skills, and one child had receptive language difficulties. Three out of four patients had expressive language difficulties. These three patients had the p.Cys342Arg mutation, which in all cases was associated with pansynostosis, concurrent speech and expressive language difficulties, hearing loss and a history of tracheostomy insertion. Research into the consequences for tracheostomy insertion on communication development in the general population has shown variable outcomes, and is therefore inconclusive. Research has indicated that a tracheostomy inserted around the time of speech emerging may result in delayed speech development,²⁶ reduced canonical babbling,⁵⁹ delayed receptive language,²⁵ and delayed expressive language,²⁶ whereas other studies have reported age appropriate language skills.²⁷ Long-term tracheostomy insertion may increase the extent of expressive language delay,²⁷ resulting in phonological impairment.²⁹ It is important to note that this research has been conducted within heterogeneous populations, and the impact of tracheostomy insertion on speech and language development has not been investigated specifically in patients with PS.

Although this study demonstrated that these patients had co-morbid speech and hearing impairments, causation was not established. Current literature suggests that the degradation of auditory speech sound signal in patients who have impaired hearing can negatively impact phonological development,⁵⁹ and language development.⁶⁰ Future research should focus on looking at the association between these three variables with a larger sample of patients.

Study numbers were limited by the strict inclusion only of patients with available speech, language, hearing and feeding data; further restricting a sample size already constrained by the relative rarity of the severe *FGFR2*-associated PS diagnosis. The nature of retrospective data analysis also resulted in gaps in available information for

some patients. However, strengths of this study are that only patients with genetically-confirmed severe *FGFR2*-associated PS were included, meaning that less inter-patient variability was observed thus painting a comprehensive picture of the management challenges faced by this group of seriously affected children.

Conclusion

This study has identified important speech, language, hearing and feeding issues in patients with severe *FGFR2*-associated PS. Results indicate that a high rate of motor-based oral stage feeding difficulties, and pharyngeal stage swallowing difficulties, hearing difficulties, and speech and expressive language difficulties were noted in these patients necessitating regular review by specialist craniofacial speech and language therapists.

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Figure Legend

Figure 1. Patient with severe FGFR2-associated Pfeiffer syndrome

Figure 2. Feeding Difficulties in Patients with FGFR2-related Pfeiffer Syndrome