AAO Foundation Award Final Report

Type of Award: Dr Fred Schudy Memorial Biomedical Research Award

Name of Principal Investigator: Sunjay Suri

Title of Project: Understanding the enigmatic, dwarfed mandible in non-syndromic Pierre Robin Sequence, its morphology, growth, associated clinical burdens and implications

Period of AAOF Support: 07-01-15 to 06-30-16 NCE till 12-31-16

Amount of Funding: USD 30,000

Summary/Abstract

This project aimed to study several of the enigmatic features of the mandible, its morphology and growth in Pierre Robin Sequence (PRS) and their clinical implications. This project was based on a collaboration between specialists from orthodontics and plastic surgery who routinely provide care for children with PRS, based in a tertiary-care university affiliated teaching hospital, The Hospital for Sick Children, Toronto and biostatisticians at the University of Toronto. There were 3 specific aims in this project and a summary for each specific aim of the project is included below:

Response to the following questions:

1. Were the original, specific aims of the proposal realized?

All 3 specific aims were realized. A summary is described in the detailed report in the following pages.

2. Were the results published? If not, are there plans to publish? If not, why not?

A paper prepared from specific aim 1 is undergoing final drafting for submission to the AJODO.

An MSc Orthodontics thesis resulting from that specific aim is nearing completion and being prepared for defense.

Manuscripts from specific aims 2 and 3 are underway and will be submitted soon upon completion of the upcoming 2nd International Robin Sequence Consensus Meeting to be held in May, 2017, where the original data will be presented.

AAOF support was and will be duly acknowledged in all publications emanating from this project.

3. Have the results of this proposal been presented? If so, when and where? If not, are there plans to do so? If not, why not?

The following conference presentations included findings that emanated from this project:

1. 'Longitudinal craniofacial growth in Pierre Robin Sequence (PRS) in comparison with unaffected children.'
   Pereira F, Fisher D, Lou W, Suri S. presented at "Latest Advances in Canadian Orthodontic Research" 68th Annual Session of the Canadian Association of Orthodontists, Charlottetown, PEI, Canada (September, 2016).

2. 'Longitudinal craniofacial growth in Pierre Robin Sequence (PRS) and Isolated Cleft Palate (ICP) in comparison with unaffected children.'
   Pereira F, Fisher D, Lou W, Suri S. to be presented at the 117th Annual Session of the American Association of Orthodontists, San Diego (April, 2017).

3. 'Longitudinal craniofacial growth in Pierre Robin Sequence (PRS) and Isolated Cleft Palate (ICP) in comparison with unaffected children.'
   Pereira F, Fisher D, Lou W, Suri S. to be presented at the 2nd International Robin Sequence Consensus Meeting, Toronto (May, 2017).

4. 'Permanent tooth agenesis in non-syndromic Pierre Robin sequence: a systematic review and meta-analysis.'
   Antonarakis G, Palaska K, Suri S. to be presented at the 2nd International Robin Sequence Consensus Meeting, Toronto (May, 2017).

5. 'Hospitalized burden of treatment in children with Pierre Robin Sequence: A retrospective chart review of 119 patients.'
   Palaska K, Suri S. to be presented at the 2nd International Robin Sequence Consensus Meeting, Toronto (May, 2017).

AAOF support was and will be duly acknowledged in all of these presentations.

4. To what extent have you used, or how do you intend to use, AAOF funding to further your career?

There are very few funding sources for clinical research studies and therefore, AAOF funding is of immense value in making many such clinical research projects possible that otherwise may suffer due to lack of resources available to conduct them. In my studies which have been supported by the AAOF, funds have helped to pay for remunerating research staff and assistants, equipment, covering costs for imaging and analysis of images, costs related to knowledge transfer of findings through publications as well as presentations in conferences. The true measure of an academician's career is the quality of their work published in peer reviewed scholarly journals and presentation in scientific conferences. I sincerely appreciate AAOF funding that has supported my research endeavors and strengthened the quality of work to allow meeting international standards.

Title of Project: Understanding the enigmatic, dwarfed mandible in non-syndromic Pierre Robin Sequence, its morphology, growth, associated clinical burdens and implications

PI: Sunjay Suri
Co-investigators (alphabetically): Gregory Antonarakis, David Fisher, Pinelopi-Kleio Palaska, Fay Pereira, Wendy Lou, Clinical Research Coordinator: Nicole Sidhu, Research Assistant: Lynn Cornfoot

Specific Aim 1: What are the characteristics of the mandibular morphology in PRS that make it unique in infancy, childhood and adolescence?

For this specific aim, we studied differences in craniofacial morphology and growth in non-syndromic PRS and unaffected children longitudinally during the period of active facial growth from age 6yr to nearly 17yr. This is the largest longitudinal study on a racially homogeneous sample with non-syndromic PRS to be studied and reported till date. Following REB approval, a retrospective chart review was conducted and lateral cephalometric tracings of 43 Caucasian subjects with non-syndromic PRS treated at the Hospital for Sick Children were completed using Dolphin imaging software. These tracings were compared with tracings of age- and sex-matched Caucasian unaffected Class I subjects selected from the Burlington Growth Centre archives.

A comprehensive cephalometric analysis previously published by Suri et al, was used to describe the morphological characteristics of the maxilla, mandible and cranial base at 3 time points

	PRS group		Control group	
N	18 M	25 Female	18 Male	25 Female
T1	6yr 5mo	6yr	6yr 4mo	6yr 5mo
T2	11yr 8mo	12yr 3mo	11yr 7mo	12yr
T3	16yr 5mo	16yr 10mo	16yr 5mo	16yr 10mo

Comparisons between the groups at each time point were made using generalized linear models adjusted for gender effects. Longitudinal comparisons across all time points were made using mixed model adjusted for gender effects as well as their interactions with time. Results showed that the craniofacial morphology and longitudinal facial growth in subjects with PRS differed significantly from comparable unaffected Class I children. The most significant morphological differences were in the mandible. Mandibular length, external and internal ramal length, ramal width, symphyseal thickness and internal body length were significantly smaller in the PRS subjects. These morphological differences were seen at the 6yr time point and continued to be deficient at the 12yr and 17yr time points, with little improvement during this period of active facial growth. The longitudinal facial growth trends from childhood to maturity revealed that the growth increments in several areas of the mandible as well as in the length of the maxilla and cranial base remained deficient in this large racially homogeneous sample of patients with PRS.

Specific Aim 2: Are there associations between patterns of tooth agenesis and mandibular morphology and growth in PRS?

In our previously published work on a multiracial sample with PRS, we had observed that the overall prevalence of permanent tooth agenesis was 32.9% in a sample of 146 patients with PRS, with about two thirds having bilateral tooth agenesis.

We conducted a meta-analysis of prevalence and patterns of permanent tooth agenesis in non-syndromic PRS, which led to synthesis and analysis of data based on 448 individuals with non-syndromic PRS, who were included in 6 studies that met our inclusion criteria. We found that the permanent teeth with the highest reported prevalence of agenesis were mandibular second premolars (26%). The most common tooth agenesis patterns included the agenesis of both mandibular second premolars. These studies corroborated our previously reported data and indicated that prevalence and pattern of tooth agenesis is quite similar in children with PRS. In order to explore whether specific patterns of tooth agenesis were associated with peculiarities in mandibular morphology and growth, for specific aim 2, we explored whether the most commonly reported pattern, i.e. the bilateral absence of mandibular second premolars was associated with altered mandibular morphology and growth.

Focusing on a racially homogeneous group of subjects with PRS with lateral cephalograms at ages 6, 12 and nearly 17yr, dental agenesis of one or more teeth (excluding the third molars) was studied using the longitudinal radiographs comprising panoramic and 45^{O} lateral cephalometric radiographs at these time points. Dental agenesis (excluding the third molars) was noted in 34.8% of the sample of 43 subjects (33.3% males and 36% females), which corroborated our previously published prevalence figures. Within the 15 subjects with dental agenesis (not including 3^{rd} molar agenesis), 7 (46.7%) exhibited bilateral agenesis of the mandibular second premolars.

A cephalometric comparison of subjects with this agenesis pattern (N=7) was made against those subjects with PRS who had a complete complement of permanent teeth (also including the presence of 3^{rd} molars), N=17. Cephalometric comparison showed that at the mean age 16.8 yr, there were small differences in overall mandibular length (3.0mm), ramal length (2.8mm), body length (0.6mm) and symphyseal height (0.5mm), all shorter in the mandibular second premolar agenesis group, and this group also exhibited a more open cranial base angle (by 2.3^{O}) and internal mandibular flexure angle (by 1.3^{O}). However, adjusting for the effects of gender and age, these differences were statistically not significant. Using a mixed model approach, when the estimated mean differences for changes from T1 to T3 were compared, adjusting the analysis for age and gender revealed no significantly differential length gains among the two groups.

Specific Aim 3: What are the short and long term treatment burdens in PRS?

The purpose of this specific aim was to examine in a holistic approach, the overall burden of treatment at The Hospital for Sick Children in Toronto for children born with PRS. This study documented the types of multidisciplinary interventions for PRS care from infancy onwards. A descriptive analysis of data collected from a comprehensive chart review of patients treated in the approximately last 25 years was undertaken. The study sample comprised 119 children (57

M, 62 F) with PRS who had received their primary treatment at the Hospital. Airway management in infancy and early childhood involved positioning (90.74%), nasopharyngeal airway (5.55%), tracheostomy (2.77%) and distraction in 0.92% of the sample. Feeding with gastrostomy and gastrojejunostomy tubes was used in 38.18% while Haberman feeders were used in 59.09% and Mead Johnson feeders in 2.7% of the sample. Gastroesophageal reflux disease was documented in at least 5.88% of the cases. A pharyngeal flap surgery was conducted in 20.17%, and 12.61% of the sample had a second palatal surgery. Audiological management included the use of tympanostomy tubes in 58.82% of the sample with many subjects needing the PE tubes to be replaced several times. At least 14.28% of the sample had a positive diagnosis of obstructive sleep apnea and received treatment for it through CPAP or BPAP. Adenoidectomy or adenotonsillectomy was conducted in 4.20% of the sample included in this retrospective review. Orthodontic management noted significant crowding despite the commonly seen dental agenesis of one or more permanent teeth, and interceptive guidance of occlusion through planned extractions was documented frequently. Among the additional medical conditions that were noted with a significant frequency were cardiac defects (6.72%) and clubfoot (4.20%). These data show that implications and burdens related to several systems are common in infants and children with PRS. Conservative management strategies such as prone and/or lateral positioning were employed very frequently in a supervised hospital setting. This knowledge of the frequencies of use of these treatment interventions is useful for clinicians and families as well as hospital management and healthcare funding stakeholders.