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Review Article

Role of forkhead box protein 2 (FOXP2) in oral-motor abilities of preterm infants: A brief literature review

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Abstract

Preterm infants, born before the 37-week gestation period, have limited storage for nutrients at birth and are vulnerable to poor feeding, severe nutritional deficits and growth retardation. The immature gastrointestinal system leads preterm infants to experience a delay in initiating enteral nutrition. Inappropriate feeding can cause acute and long-term morbidity, prolonged hospitalization and increased treatment cost. Generally, preterm infants that are born after 32 weeks of gestation without severe comorbidities do not have dysphagia and should start oral feeding soon after birth. Preterm infants should have well-developed sucking-swallowing-breathing coordination by 32–34 weeks of gestational age. However, some infants take days or weeks to master the skill. The oral feeding development involves forkhead box protein 2 (FOXP2)-expressing neurons that are found in the deep layers of the cortex, basal ganglia, parts of the thalamus and Purkinje cells of the cerebellum. In mammals, these areas belong to the brain network circuits working for motor coordination in learning and acquiring sensorimotor skills. This review aimed to describe the role of FOXP2 in oral-motor skills in preterm infants, including oral feeding, sucking-swallowing-breathing coordination and language development. The oral-motor skills development could be an early predictor for language delay in premature infants, representing a vulnerable group susceptible to such delays.

Keywords: FOXP2, oral-motor ability, preterm infant, feeding, prematurity

Introduction

Prematurity or preterm birth is one of the causes of global neonatal mortality. An estimated 13.4 million babies were born preterm in 2020, with nearly 1 million dying from preterm complications [1]. The World Health Organization (WHO) reported the percentage of neonatal death due to prematurity has continued to increase for more than a decade, which it was 14% prematurity death in 2000 and reached 17% in 2009–2011 [2]. In Indonesia, the preterm incidence rate with perinatal mortality was higher than global number at around 19% in 2010, rendering it the leading cause of perinatal mortality [3].

Oral-motor skills, particularly oral feeding is a highly complicated developmental task requiring maturation and integration of the nervous, gastrointestinal, sensory, musculoskeletal and hypothalamic systems. Impaired or delayed maturation of one or more of these systems can cause choking, feeding aversion and delayed growth [4]. Factors contributing to feeding difficulties in premature infants include impaired oral structure-function, impaired sucking pattern, impaired sucking-swallowing-breathing coordination and transition to oral feeding [5]. A prior study revealed that the expression of forkhead box protein 2 (*FOXP2*) gene in saliva was

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Received: May 31, 2023 - Accepted: August 27, 2023 - Published online: August 31, 2023

linked to successful oral feeding in preterm neonates [6]. However, there has been no study discussing comprehensively about the oral-motor abilities, such as oral feeding, sucking-swallowing-breathing coordination and language development, that are related to *FOXP2* gene, particularly in the preterm infants. Therefore, this review aimed to describe the role of *FOXP2* in oral-motor skills in preterm infants.

Preterm infant

WHO defines a preterm infant as a baby born alive before the 37-week gestation period [2]. The preterm birth is categorized based on gestational age, i.e., extremely preterm (less than 28 weeks); very preterm (28–32 weeks); moderately to late preterm (32–<37 weeks); very preterm (<32 weeks or very low birth weight <1,500 grams); and late preterm infants (LPIs) (34–36 weeks) [3,7]. LPIs are physiologically and metabolically immature, representing a critical developmental period and a high risk of medical complications, morbidity, mortality and hospital re-admission compared to full-term infants [8, 9]. The birth of an LPI in the last six weeks of gestation disrupts normal fetal development, especially the development of the brain and lungs [10].

Preterm labor forces preterm infants to breathe and eat before their respiratory and digestive systems are fully developed. Most premature infants require a feeding tube until they can suck [11]. During fetal development, the perioral region develops in response to tactile stimuli as early as seven weeks while sucking or swallowing patterns begin at 15–18 weeks [5].

Oral-motor ability

The effectiveness of oral-motor abilities, including oral feeding, sucking-swallowing-breathing coordination and language development, play fundamental roles in facilitating the transition of newborns from the intrauterine to the extrauterine phase. The development starts from the branchial arch [12]. Ectoderm, mesoderm and endoderm are formed, each of which will underlie the formation of fetal organs at three weeks of gestation. The ectoderm will form the skin and nervous system; the mesoderm will form smooth muscle, connective tissue, and blood vessels; and the endoderm will form the gastrointestinal and respiratory systems [12]. At 9–40 weeks of gestation, all organs are maturing in the fetal period and the oral reflexes appear, i.e., pharyngeal swallow (12 weeks), suction (18–24 weeks), vomit reflex (26–27 weeks), rooting (28 weeks) and phasic bite (40 weeks) [13]. In this process, the coordination of swallowing and breathing functions will mature gradually by at least 34 weeks of gestation [13].

Oral feeding and breathing skills

Infant feeding combines sucking, swallowing and breathing with one process separable from the other. Reflexes influence newborns and automatically generate oral movements. Coordination among the three activities is crucial to prevent choking. Breathing is coordinated with swallowing, which the infant sucks and swallows after the inspiration phase of breathing [14].

Infants do two different types of sucking, nutritive sucking (fluid ingestion) and non-nutritive sucking (no fluid involved, e.g., pacifier) [15, 16]. The maturity of the latter occurs earlier [16]. Full-term infants do one nutritive suction per second and two non-nutritive suctions per second [16], while preterm infants have higher sucking and swallowing frequency, bolus size, and suction amplitude. It is speculated that their feeding difficulties are more likely to result from inappropriate swallow-breath interfacing than sucking-swallowing interaction [17].

The swallowing behavior emerges sequentially from basic to complex movement patterns in the weeks closer to full-term age. Jaw and lip movements are developed from simple mouth opening to repetitive mouth opening and closing for effective sucking. The complexity of tongue movements progresses from simple cupping and forward-thrusting to anterior-posterior movements required for successful sucking. In contrast, laryngeal movements evolve from superficial movements to complex adduction-abduction patterns required to protect the airway during swallowing [11].

As maturity advances, the swallowing process will become more adaptable to accepting larger sizes and amounts of fluid, as evidenced by the increased swallowing frequency [17]. Oral feeding will be safe if swallowing occurs at the right time when the trachea closes, preventing aspiration into the lungs [15]. Aspiration can occur before swallowing due to large amounts of

fluid, the larynx not closing properly during swallowing, or the residue around the vallecula and pyriform sinus due to poor pharyngeal cleansing [15].

However, preterm infants often suffer from respiratory problems, such as respiratory distress syndrome and bronchopulmonary dysplasia. Healthy preterm infants usually have fewer episodes of oxygen desaturation or apnea during oral feeding [18]. Clinically, coordination succeeds when the infant feeds by mouth with the sucking:swallowing:breathing ratio of 1:1:1 or 2:2:1 and without aspiration, oxygen desaturation, apnea or bradycardia [15].

The relationship between feeding difficulties and language delay

Notably, feeding and sucking behavior represent early manifestations of motor control in newborns and involve shared neural pathways associated with feeding and language development [19]. Preterm babies often encounter challenges related to feeding [19]. A prior study revealed that premature infants (≤26 weeks of gestation) with breastfeeding challenges are at a higher risk of experiencing language delays at 18 months of corrected age [20]. The long-term neurological development of surviving preterm infants is of significant concern. The susceptibility to adverse outcomes depends on the brain structure maturation, development, and differentiation, including those responsible for feeding and language. This neuropathological risk aligns with clinical evidence demonstrating that preterm infants are more prone to experiencing language delays compared to their full-term counterparts [19].

FOXP2 gene and oral-motor ability

In 1990, a rare pedigree was discovered where about half of the family members exhibited speech and language disorders, primarily indicated by problems in coordinating the sequence of mouth movements while speaking [21]. In 2001, an investigation found that fifteen members of the family had mutation in a single base transition (G/A) in exon 14 of the *FOXP2* gene, resulting in an arginine to histidine substitution (R553H) in the DNA binding domain of the encoded protein [19], therefore, *FOXP2* was the first gene associated with speech and language disorders [22].

The *FOXP2* gene is 607,446-bases length and located on chromosome 7q31.1 (chromosome 7, long arm, position 31) (**Figure 1**) [23]. Neurons expressing *FOXP2* are located in the deep layers of the cortex, basal ganglia, parts of the thalamus and Purkinje cells of the cerebellum. In mammals, these areas belong to network circuits involved in motor coordination, learning, and acquisition of sensorimotor skills, essential components in developing oral feeding [24].

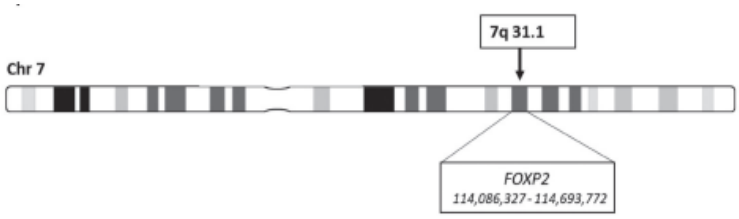

Figure 1. Location of FOXP2 gene [23].

FOXP2 plays a vital role in speech development because it involves in regulating the expression of many genes involved in the embryonic development of neural structures required for speech and language development [25]. Human and animal studies confirmed that *FOXP2* plays a role in the function and development of motor skills and vocal behavior-related neuronal circuits [26]. Abnormalities of *FOXP2* are associated with speech-language delay and language disorders such as in spelling and reading [6, 24, 27, 28] as well as for the application of imaging genetics in dyslexia study [29]. The same neural paths as language are involved in feeding and sucking behavior as one of the earliest manifestations of newborn motor control [20].

FOXP2 gene polymorphisms

Genetic and environmental factors lead to phenotypic variation [30]. When comparing the genomic deoxyribonucleic acid (DNA) sequences on the same chromosome from two individuals, substantial variations are present at many points in the sequences across the genome. Single nucleotide polymorphism (SNP) is one of genetic variations that occur when a single nucleotide

(adenine, thymine, cytosine or guanine) in the genomic sequence changes [30]. Scanning the genome for SNPs can help identify millions of potentially informative biomarkers [31]. SNPs associated with loci in the *FOXP2* gene are widespread. Three consistent SNPs were initially identified in the haplotype linked to schizophrenia within the range of 113.5 Mb to 114.0 Mb: rs923875, rs2396722 and rs17137124. Recent investigations have demonstrated that rs923875 is associated with word reading behavior, rs2396722 with speech sound disorder and rs17137124 with specific language impairment. rs17137124 has been found to modulate frontal degeneration in elderly subjects [32]. Studies using functional neuroimaging also reinforced the association between *FOXP2* polymorphisms and language, showing the involvement of the left inferior frontal gyrus T, including Broca's area and putamen in rs1456031 TT and rs17137124 TT [33].

This research is an early predictor for language delay in premature infants, representing a vulnerable group susceptible to such delays. The limitations of this study are the lack of quantitative data and the reliance on parent reports in measuring breastfeeding competence during the neonatal period.

Conclusion

Preterm infants are forced to breathe and eat before their respiratory and digestive systems are fully developed. Therefore, they experience difficulties in developing oral-motor abilities, including oral feeding, sucking-swallowing-breathing coordination and language development. Our study elaborated the essential role of *FOXP2* in oral-motor skills development, particularly in determining feeding success in neonates and regulating the general form of speech-language ability, which could be applied as an early predictor for language delay in premature infants, representing a vulnerable group susceptible to such delays.

Ethics approval

Not required.

Competing interests

The authors declare that there is no conflict of interest.

Funding

This study did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

Underlying data

All data underlying the results are available in the article and no additional data sources are required.

How to cite

Mauliza M, Dimiati H, Akmal M, *et al.* Role of forkhead box protein 2 (FOXP2) in oral-motor abilities of preterm infants: A brief literature review. Narra J 2023; 3 (2): e237 - http://doi.org/10.52225/narra.v3i2.237.

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