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Development of the human fetal cochlear nerve: a morphometric study

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Abstract

Ontogenesis of the human peripheral auditory pathway is relatively less explored. While the distal part of the auditory perception apparatus (i.e. the cochlea) received attention, studies on the neural element carrying information to the brainstem (i.e. the cochlear nerve) are scarce. In the present study, axonal differentiation, maturation and myelination of the distal end of the human cochlear nerve (CN) were assessed using light and electron microscopy. Seven human fetuses of 12, 15, 18, 20, 22, 28 and 38 weeks' gestation (WG) were analyzed. Light microscopy revealed nerve fascicles as early as 12 WG, initially arranged loosely but later compacted by 18 WG. Myelinated fibers were clearly detected at 28 WG. Ultrastructurally, at 12 WG developing Schwann cells were present between the thin unmyelinated axons. At 15 WG, the fascicular arrangement was distinct with blood vessels in the perineurium. The maximum number of axons was found at 20 WG, which subsequently reduced to reach the adult level at 22 WG. The myelinated axons in the CN were first observed on the left side at 20 WG, following which the number and proportion of myelinated axons increased until term, incorporating both small and large axons. The right CN lagged behind in maturation. Axon size also increased with age. Thus, the maturation of the human CN commences during the mid-gestation period and produces exuberant axons that are eventually pruned at a time when axons start to myelinate. During this developmental period the human CN maintains maturational asymmetry, the functional consequences of which remain to be elucidated.

Keywords: Auditory nerve; Ontogeny; Myelination; Asymmetry; Stereology

1. Introduction

The auditory information is transmitted to the brainstem through the cochlear division of vestibulocochlear nerve, the ganglionic neurons of which reside mainly in the Rosenthal's canal, partly encroaching into the modiolus of the cochlea. The peripheral processes of these ganglionic neurons innervate the organ of Corti while the central processes or the axons join together to form the cochlear nerve (CN). The CN axon fibers constitute the first order neuron circuit to carry impulses from the sensory hair cells in the cochlea to the brainstem cochlear nucleus. Apart from these afferent fibers carrying sensory inputs to the brainstem, the nerve also has efferent fibers that convey information in the opposite direction from the brainstem to the hair cells.

Abbreviations: ABR, auditory brainstem response; CN, cochlear nerve; E, embryonic day; IHC, inner hair cell; OHC, outer hair cell; P, postnatal day; SD, standard deviation; TEM, transmission electron microscopy; VCN, ventral cochlear nucleus; WG, weeks gestation

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Morphological development of the sensory hair cells in the organ of Corti has been observed in the human fetuses and alongwith comparative studies in the mammals suggests that both structural and functional maturation occur by 20 weeks' gestation (WG) (Romand et al., 1970; Pujol et al., 1991). Despite early maturation of the cochlea, the auditory function starts late and occurs only after the neural element mature (Sanes and Constantine-Paton, 1985; Sanes et al., 1992). Structurally, appearance of myelin in a nerve fiber during development is an important event as it has close relationship with the onset of rapid and synchronized axonal conduction. Axonal maturation and myelination influence conduction velocity, such that larger and/or more thickly myelinated axons conduct faster impulses (Rushton, 1951; Ritchie, 1982). Pujol and Hilding (1973) noted the presence of myelin sheaths on axons within the cochlea several weeks before the onset of recordable action potentials, and hypothesized that the delay in onset of auditory function may be due to synaptic immaturity. There are also reports stating that human fetus can hear at 22nd WG (Moore and Jeffery, 1994).

While there are multiple studies on the response of the developing human auditory system to acoustic stimuli (Dwornicka et al., 1964; Barden et al., 1968; Sakabe et al., 1969; Grimwade et al., 1971; Goodlin and Schmidt, 1972), the precise time at which the auditory function begins is still unknown. Using morphological techniques for assessing the onset of myelination (as an index of maturity) in the auditory pathway, it was observed that the entire process is sequential (i.e. the peripheral part followed by the central part) (Moore et al., 1995; Moore and Linthicum, 2001). However, these studies were performed using light microscopy, where the fibers are identifiable only when they are sufficiently myelinated. Analysis of the onset of myelination in the neural tissue will require detailed examination using the transmission electron microscope (TEM). Further, as the peripheral part of the CN is myelinated by Schwann cells (Moore and Linthicum, 2001), the study of Schwann cell development is also important for evaluating changes associated with congenital conditions, aging process, pathological conditions or diseases.

Additionally, determination of fiber count, axon size and myelin thickness is a goal in many studies that investigate nerves in various physiological, experimental and pathological conditions (Geuna et al., 2001). Developing fetuses may be subjected to various drugs/teratogens during the intrauterine period that may affect the auditory system (e.g. administration of ototoxic drugs to expectant mothers). Similarly, endocrinopathies involving the fetus or the mother are known to have deleterious effect on the developing nervous system (Usson and Saxod, 1988; Paternostro and Meisami, 1996). However, there is no data available on the morphology of the fetal CN to determine the changes that occur during the prenatal period. Therefore in the present study, the maturation of the CN is analyzed quantitatively by light and electron microscopic examination of the peripheral auditory pathway at different time-points during the prenatal period. The onset of myelination and maturation of the Schwann cells in the distal CN were noted, in particular.

2. Materials and methods

2.1. Fetus collection and tissue preparation

All the fetuses used in the study were collected in accordance with the protocol approved by the Ethics Committee, All India Institute of Medical Sciences, New Delhi, India under the guidelines of Helsinki declaration. The CN of seven human fetuses (aged 12, 15, 18, 20, 22, 28 and 38 WG) was examined. The fetuses less than 20 WG were obtained from cases where medical termination of pregnancy was performed for family planning (legalized in India under MTP Act, 1971) while those more than 20 WG were still-births. Prior to the use of abortuses and stillborn fetuses written consent was obtained from the mothers or legal representatives of the demised fetuses. The consent to participate in the study was entirely voluntary and dissociated from the abortion decision. None of the mothers suffered from any medical illness during pregnancy and the fetuses used in the study had no congenital anomalies. However as the cause of death of the stillbirths were undetermined, there may be a possibility of some adverse effects on the development of CN. All of the specimens used in the present study were obtained within 4 h of delivery and were preserved at 4 °C to minimize the post-mortem changes. Details of the fetal material used in the study are shown in Table 1.

The fetuses were weighed and measured for crown-rump length, foot length and biparietal diameter (Sailaja

Table 1
List of fetal material used for morphometric analysis of developing cochlear nerve

Fetus no.	Age of the fetus (in WG)	Side of the cochlear nerve
AIM 4	12	Left
		Right
AIM 9	15	Left
		Right
AIM 31	18	Right
AIM 19	20	Left
		Right
A 5	22	Right
AIM 1	28	Left
		Right
AIM 5	38	Left
		Right

WG – weeks of gestation.