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ANATOMY OF TULP'S VALVE

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Abstract

Introduction: Tulp's valve is also known as ileocaecal valve which is situated at ileocaecal junction. Tulp's valve is a diverse anatomical valve where the ileum makes an access into the caecum. Earlier researchers have observed that there is occurrence of high densities of neurons in the Tulp's valve, though meticulous anatomical depiction about constitution of the myenteric plexus in and around the Tulp's valve has thus far to be obtained in humans. In array to add contribution to this vicinity of explore, the present work was performed to appreciate the anatomical composition of myenteric plexus in and around the Tulp's valve in human foetuses.

Materials and Methods: The research was performed on ileocaecal sections obtained from human foetuses (n=17) of various gestational ages after obtaining ethical authorization from the ethical clearance committee of Hind Institute of Medical Sciences, Sitapur. Cresyl Violet staining and NADPH- diaphorase enzyme histochemistry was performed over the obtained ileocaecal sections. Study Group-1(G-1) included foetuses of 9 to 14 week of gestational age group while Group-2(G-2) comprised of foetuses of 15 to 33 week of gestational age group. The Neuronal cell profiles (area, perimeter, ferret diameter) and Neuronal cell density were assessed in and around the Tulp's valve in human foetuses.

Results: In Cresyl violet stained sections, the difference in the neuronal cell profile area between G-1 (50.10±2.26 μm^2)and G-2 (61.25±4.07 μm^2) was found to be statistically significant (p=0.0028).The perimeter of myenteric neuronal cells in G-1 (26.32±0.51 µm) was significantly (p=0.0028) lower than G-2 (29.17±0.85 µm). The differences in Feret diameter of neuronal cells between G-1 (9.49±0.27 µm) and G-2 (10.53±0.21 µm) was statistically significant (p=0.0028). The neuronal cell density in Myenteric Ganglia (MG) in G-1 and G-2 was 60.01±9.77 and 52.27±6.54 respectively, which was statistically insignificant (p=0.1367) difference. The difference in the nitrergic neuronal cell area between G-1 (66.35±8.43 μm^2) and G-2 (74.93±0.53 μm^2) was statistically significant (p=0.0038). The mean perimeter of nitrergic neuronal cells in G-1 (32.01±2.57µm) was insignificantly (p=0.2001) lower than G-2 (33.83±0.73 µm). The mean Feret diameter of G-1 (11.97±1.26) was also insignificantly (p=0.2624) lower than G-2 (12.91±0.75). The nitrergic neuronal cell density in Myenteric Ganglia in G-1 was 22.41±4.13 and in G-2 it was 18.61±2.09, which was statistically insignificant (p=0.0983). acquaintance of the innervations of the Tulp's valve in human foetuses may help in restoration of it for improved movement of ileum inside into the caecum, as well as to check retrospective run of caecal inside into the ileum.

Keywords: Tulp's Valve, Cresyl Violet, NADPH- diaphorase, Nitrergic Neurons

Introduction

Enteric nervous system comprises principally of submucosal (Meissner's plexus) and Myenteric plexus (Auerbach's plexus) situated in submucosa and muscularis externa (in between circular and longitudinal muscle layers) respectively (Nezami et al, 2010). The neuronal cells found in the enteric nervous system are equivalent to or more than that of the neurons situated in the spinal cord (Cabarrocas et al., 2003).

The enteric nervous system is nearly all multifaceted and one of the prime allotment of autonomic nervous system(Nezami et al., 2010). It is situated inside the gut wall as a constant association of ganglionated neurons that reins gastrointestinal functions that includes the manage of confined blood run, motility

of gastrointestinal tract , mucosal transportation, secretions, immune inflection as well as endocrine functions (Furness JB, 1980). The function of enteric nervous system is free from the central nervous system. As for the reason that of its autonomous power over the gastrointestinal tract, it is also known as 'second brain'.

Enteric nervous system is consequential from neural crest cells at somite levels 1–7 cranially and caudal to 28 (Kapur, 2000; Le Douarin et al., 1973). The colonization of neural crest cells into the gut is dependent upon the migration of neural crest cells that utilizes about 25% of gestation age in mice and roughly 3 weeks of gestation age in human (J B Furness et al., 1980; Sasselli et al., 2012). In human beings, the entrance to the foregut and rostrocaudal migration i.e. reaching terminal hindgut of neural crest cells uses about 4 and 7 weeks respectively. (Kirchgessner et al., 1992). (Wallace et al., 2005). The neural crest cells liberated and detached originally, amalgamate to figure ganglia in the gut pipe with increasing gestational period (Fu et al., 2004; Wallace et al., 2005).

Casper Bauhin (1579), was foremost to explain the Tulp's valve on human cadaver and dog (Bogers et al., 1993). He explained that Tulp's valve was a discrete anatomical composition where the ileum makes an entry into the caecocolon. Researches from anatomy and neuroanatomy of Tulp's valve recommend that the entry of ileum into caecum occurs as uncomplicated intussusception of the terminal ileum into the caecum on its posteromedial part at an acute angle (Cserni et al., 2009; Kumar et al., 1989). Earlier studies have observed that there are elevated densities of neurons in the Tulp's valve (Altdorfer et al., 1996), but exhaustive anatomical explanation about structure of the myenteric gland within the Tulp's valve has yet to be obtained in humans.

In order to additional contribute to this locale of research; the current study was performed to recognize the anatomical development of myenteric gland at Tulp's valve in human foetuses. Various studies could have been performed on the development of myenteric gland at various parts of the gastrointestinal tract however only some studies have been performed on the development of myenteric gland at Tulp's valve. As per our familiarity, no such research has been done on human foetuses, to observe the development of the myenteric gland in and around the Tulp's valve.

Materials and Methods:

The study was performed on human foetuses (n=17) of various gestational age groups after getting ethical permission from the human ethical clearance committee of Hind Institute of Medical Sciences , Sitapur, UP, India. The foetuses were collected from the Department of Obstetrics and Gynaecology, Hind Institute of Medical Sciences. The foetuses were obtained from the cases less than 20 Week of Gestation (WG) conferring medical termination of pregnancy for family planning or situations associated to spontaneous abortion more than 20 Week of Gestation (WG).

Merely foetuses from nondiseased mothers and those without any congenital abnormality were incorporated in the research work. The requisite foetal dimensions like weight, crown rump length, foot length, biparietal diameter were taken into account; tabulated and foetal gestational age was assessed (Mandarim-de et al., 1990).

Study Group-1(G-1) included foetuses of 9 to 14 week of gestational (WG) age group while Group-2(G-2) comprising of foetuses of 15 to 33 week of gestational (WG) age group and Group-3(G-3) had foetus of gestational age of 2 months. After making the para-median slit on the abdomen, the foetuses were immersed in 4% buffered para-formaldehyde to check autolysis.

Tulp's Valve was recognized and dissected out along with terminal fraction of ileum, caecum and inital part of the ascending colon. The obtained samples were fixed in 4% buffered para-formaldehyde and retained at 4^0C for further research.

For **Cresyl Violet Staining,** with descending grade of alcohol the cryo-sections were hydrated and stained with cresyl violet. 0.1% cresyl violet was prepared in distilled water for 2 minutes. Tissues sections were rinsed with distilled water after staining and were differentiated in 96% alcohol till Nissl substance started appearing purple. The sections were dehydrated swiftly in absolute alcohol. Finally tissues were mounted with DPX after clearing in xylene.

NADPH- diaphorase enzyme histochemistry was performed to study the nitrergic neurons. The foetal tissues ileocaecal junction was fixed in 4% buffered para-formaldehyde for 2 hours at 4^0C. After fixation tissue was washed carefully using chilled 0.1M phosphate buffer and was cryo-protected in 15% and 30% of sucrose at 4^0C for 3 hours and 8 hours

respectively. The samples were frozen in optimum cutting temperature compound LEICA and 12µm thick cryo-sections were obtained by using cryostat microtome. These sections were mounted on the glass slides coated with 1% gelatin and stored at -20^{0}C for additional enzyme histochemistry. Cryostat sections were washed with 0.1 M phosphate buffer (pH 7.4), thrice for 5 minutes each. The sections were held in reserve in ready solution of 10 ml of 0.1 M Tris-Cl (pH 7.8) buffer solution having 10 mg NADPH (Sigma, St. Louis, MO, USA), 1mg Nitrobluetetrazolium (NBT) and 0.3% Triton X-100 (utilized to increase the membrane permeability) at 37°C in the incubator for 45 min to 1 hour in the dark room. Staining was ended by washing the tissue in 0.1 M phosphate buffer subsequent to viewing under a dissecting microscope to see if the stain was adequately intense. NADPH and tetrazolium NADP respond to liberate formazan which shows blue colour. Processing of Sections was made with the descending grade of alcohol followed by two changes of xylene and mounted with DPX.

NADPH- diaphorase and Cresyl Violet stained sections, were observed under the light microscopy and pictures were captured by means of a Charged Coupled Device Camera linked to an IBM computer having a frame grabber card interfaced with a Zeiss binocular microscope. Captured pictures were saved as TIFF files. The pictures were subsequently analyzed using ImageJ –Fiji. Ahead of making the assessments the system was calibrated by means of a micrometer scale of Carl Zeiss for the magnification at which the pictures were acquired. Area, Perimeter and Feret diameter were chosen ahead of captivating measurements by means of imageJ software. Pictures were subsequently opened with imageJ software and analysis of following parameters was carried out.

-Neuronal cell profiles (area, perimeter, ferret diameter)

-Neuronal cell density is the number of neuronal cells in the ganglionic vicinity and it is calculated as number of neuronal cells per ganglion.

The SPSS software was utilized to evaluate the statistical data with the help of biostatistics department. Student t-test was used to evaluate the data. Probability levels of less than or equal to 0.05 was measured significant.

Results:

Observations in Cresyl violet stained sections

Smaller size of the ganglia was noted at 9 WG when compared to later gestational periods within the group. Dissimilar sized neuronal cells were observed at 9 WG. The size and number of the myenteric ganglion and neuronal cells augmented at 12 WG compared to 9 WG. The neuronal cells of myenteric ganglion were somewhat enlarged in size at 13 and 14 WG than those of the 12 and 9 WG.

Neuronal cell profiles (area, perimeter, ferret diameter) of myenteric ganglion in all three groups were compared with one another. The mean neuronal cell profile area in G-1 was 50.10±2.26 µm^2 and G-2 was 61.25±4.07 µm^2. The difference in the neuronal cell profile area between G-1 and G-2 was statistically significant (p=0.0028). An enhance in neuronal cell area (69.53±1.47 µm^2) in G-3 as compared to G-2 was observed. The perimeter of myenteric neuronal cells in G-1 was 26.31±0.52 µm which was significantly (p=0.0028) lower as compared to G-2 (29.18±0.86 µm). The Feret diameter of neuronal cells in G-1 was 9.49±0.27 µm and G-2 10.53±0.21 µm, and the differences between G-1 and G-2 was statistically significant (p=0.0028). Feret diameter in G-3 was higher as compared to G-2. The overall size of the neuronal cells in the MP was increased significantly from G-1 to G-2 (Table-1).

Table 1: Cresyl Violet stain (statistical data)

	Group-1 (9 to 14 WG)						Group-2 (15 to 33 WG)						
Variables	*Mean*	*Median*	*SD*	*Min*	*Max*	*IQR*	*Mean*	*Median*	*SD*	*Min*	*Max*	*IQR*	*p value*
Area (µm^2)	50.10	51.65	2.26	49.39	52.51	3.15	59.58	61.27	4.07	55.71	62.33	6.65	0.0028
Perimeter (µm)	26.31	26.77	0.52	25.91	26.90	1.12	29.01	29.19	0.86	28.21	29.61	1.39	0.0028
Feret diameter (µm)	9.49	9.43	0.27	9.27	9.67	0.39	10.53	10.47	0.21	10.23	10.75	0.51	0.0028

WG-weeks of gestation; SD- standard deviation; Min-minimum; Max-maximum; IQR- inter quartile range; p= probability (< 0.05, statistical significant)

Neuronal cell density: The neuronal cell density of per 10 mm^2 profile area of the myenteric ganglion in G-1 is 60.01±9.77 and in G-2 it is 52.27±6.54, which is statistically insignificant (p=0.1367). Mean neuronal density of G-3 (33.65±5.45) is decreased when compared with G-1 and G-2.

Observation of diaphorase positive neurons

Nitrergic neurons were observed having mean profile area of 66.35±8.43 μm^2 and 74.93±0.53 μm^2 in G-1 and G-2 respectively. The difference in the nitrergic neuronal cell profile area between G-1 and G-2 was found to be statistically significant (p=0.0038). A raise in the neuronal cell area (80.27±0.28) in G-3 was observed as compared to G-2. The mean perimeter of nitrergic neuronal cells in G-1 and G-2 was 32.01±2.57 µm and 33.83±0.73 µm respectively. This was statistically insignificant (p=0.2001) between G-1 and G-2. The mean Feret diameter in G-1 and G-2 was 11.97±1.26 and 12.91±0.75 in µm respectively, which was also statistically insignificant (p=0.2624). The mean Feret diameter of neuronal cells in G-3 was more than the G-1 and G-2. The profile area of the nitrergic neurons was significantly increased (Table-2).

Neuronal cell density: The nitrergic neuronal cell density per 10 mm^2 profile area of the MP in G-1 was 22.41±4.13 and in G-2 it is 18.61±2.09, which was statistically insignificant (p=0.0983). Mean neuronal density in G-3 (13.01±1.10) was decreased when compared with G-1 and G-2.

Table 2: NADPH-diaphorase histochemistry

	Group-1 (9 to 14 WG)						Group-2 (15 to 33 WG)						
Variables	*Mean*	*Median*	*SD*	*Min*	*Max*	*IQR*	*Mean*	*Median*	*SD*	*Min*	*Max*	*IQR*	p value
Area (μm^2)	66.35	68.79	8.43	62.29	72.79	10.51	74.87	75.13	0.52	74.69	75.47	0.79	0.0038
Perimeter (µm)	32.01	31.98	2.57	30.31	33.91	3.58	33.83	33.86	0.73	33.31	34.31	0.95	0.2001
Feret diameter (µm)	11.97	11.91	1.26	10.82	12.93	2.15	12.91	12.75	0.75	12.33	13.29	0.97	0.2624

The NADPH-diaphorase nitrergic neuronal cells profile (Area, perimeter and Feret diameter) was significantly (p=0.028) increased when compared with the Cresyl violet stained neuronal cell profile, both in group-1 and group-2 (Table-3).

Table 3:

	Group 1 (9-14 WG)												
	Cresyl violet stain						**NADPH-d stain**						
Variables	*Mean*	*Median*	*SD*	*Min*	*Max*	*IQR*	*Mean*	*Median*	*SD*	*Min*	*Max*	*IQR*	p value
Area (μm^2)	50.10	51.65	2.26	49.39	52.51	3.15	66.35	68.79	8.43	62.29	72.79	10.51	0.028
Perimeter (µm)	26.31	26.77	0.52	25.91	26.90	1.12	32.01	31.98	2.57	30.31	33.91	3.58	0.028
Feret diameter (µm)	9.49	9.43	0.27	9.27	9.67	0.39	11.97	11.91	1.26	10.82	12.93	2.15	0.028
	Group 2 (15-33 WG)												
	Cresyl violet stain						**NADPH-d stain**						
Variables	*Mean*	*Median*	*SD*	*Min*	*Max*	*IQR*	*Mean*	*Median*	*SD*	*Min*	*Max*	*IQR*	p value
Area (μm^2)	59.58	61.27	4.07	55.71	62.33	6.65	74.87	75.13	0.52	74.69	75.47	0.79	0.028
Perimeter (µm)	29.01	29.19	0.86	28.21	29.61	1.39	33.83	33.86	0.73	33.31	34.31	0.95	0.028
Feret diameter (µm)	10.53	10.47	0.21	10.23	10.75	0.51	12.91	12.75	0.75	12.33	13.29	0.97	0.028

WG-weeks of gestation; SD- standard deviation; Min-minimum; Max-maximum; IQR- inter quartile range; p= probability (< 0.05, statistical significant)

Discussion:

The morphological development of the enteric nervous system in various parts of the gastrointestinal tract has been studied by various scientists. However, the writing is scarce on the development of the myenteric plexus at Tulp's valve in human, which is a spot of a variety of congenital and acquired anomalies. Hence, this study is planned to assess the developmental changes in the innervations of Tulp's valve at different gestational ages in array to appreciate the pathophysiology.

(Furness JB, 1980), (Fu et al, 2004) and (Singh et al, 2015), verified that, with rising age, the ganglionic plexus enlarged in size with additional neuronal cells, intra plexus nerve fascicles and enteric glial cells. The similar findings are also noted in the present study. Research by Mandic et al., (2015) found that there was an enlarge in the size of neuronal cells as age advanced, however the neuronal cells decreased in number with advancement of age in proximal part jejunum of human cadavers (aged from 20 to 84 years old). The consequences of the current study show that profile area and number of neuronal cells increase with age throughout intra uterine and post natal life.

Ultrastructural observation of human foetal ileum by Gabella, (1972), exposed that myenteric ganglion was heavily engaged by neuronal cells, and neuropil and enteric glial cells. The neuronal cells were of different shapes and sizes with hefty oval or round nuclei. These cells were there within the myenteric ganglion and were partially encircled by enteric glial cells (Fekete et al., 2000; Gabella, 1972). In the current study, NADPH-d staining discovered that the myenteric ganglion had neuronal cells of different sizes, extensive neuropils and glial cells. The nuclei of the neuronal cells were large, round to oval and eccentric.

Pollard et al., (2012) observed that the myenteric ganglion was denser in the terminal piece of ileum than in the papilla of ileum and adjacent large gut in human cadavers. The authors were not sure whether the innervation of ileum step by step decreased from the proximal part to the distal part including Tulp's Valve. They postulated that the gradual declining innervation would explicate the one-way promulgation from ileum to caecum (Pollard et al., 2012). In the present study, it is verified that the density of the Myenteric plexus was superior at the upper lip in comparison to the lower lip of the Tulp's Valve.

The researches on the development of enteric nervous system in trial models of a range of animals such as rat, horse, sheep, pig and chick formerly demonstrated that the density of neuronal cells was decreased as age advanced (Gabella, 1971; Gabella, 1987; Doxey et al., 1995; Zhang et al., 2004; Young et al., 2004; Donnell et al., 2007). A study by Singh et al., (2015) reported parallel results in sigmoid colon of human foetuses (Roy, Singh, Shariff, Das, & Rani, 2015). As said by Cserni et al., (2007), the intussusceptions of gut in mature chick could be prohibited by decreasing neuronal density with growing gestational age and creation of the lip of the ileocaecal junction in foetal being is one of the examples which happened as a consequence of the presence of elevated density of neuronal cells. It had also been observed that decreased neuronal cell density throughout the growth of human foetus resulted in amplified interspacing between myenteric ganglion (Kwong & Tam, 1997). Alike changes were reported in the present study. The density of NADPH-d-positive neuronal cells is decreased in the myenteric plexus of human Tulp's valve, which might be due to the development and elongation of the gut. Though, this disparity was not statistically significant stuck between G-1 and G-2 stained by means of Cresyl violet (p=0.1367) and NADPH-d (p=0.0983).

As said by Ruhl, (2005), the cell bodies of the gut glial cells were smaller in size than those of the neuronal cells and presence of nuclei could be differentiated from those of neuronal cells by the existence of clumps of chromatin within the nucleus. The enteric glial cells offer functional and structural prop up to the neuronal cells by liberating neurotrophic factors for their development and growth. enteric glial cells Loss leads to the degeneration of neurons and changes in the neurochemical coding (Rühl, 2005). In the current study, smaller sized gut glial cells along with pale cytoplasm inside the myenteric ganglion in Cresyl violet stained sections were reported.

One of the markers used for the nitrergic neurons is NADPH-d. earlier it was observed that in the chick embryo, there was an raise in the number of myenteric ganglion of small gut from caudal to cranial track (Bagyánszki et al., 2000). Whereas in a study conducted by Cserni et al., (2007), they noticed that the numbers of myenteric neuronal cells amplified in the terminal ileum and Tulp's valve, which might

describe the formation of ileocaecal junction due to intussusception of the terminal ileum. The current study demonstrated that the nitrergic neuronal cells were fewer in number and outsized as compared with Cresyl Violet stained neuronal cells. Nitrergic neuronal cells are a subpopulation of the neurons situated in the myenteric ganglion and it was noted that 30 to34% of the total myenteric ganglion neurons are the nitrergic in character (Sengupta et al., 1995; Wester et al., 1999), which too happened to be the case in the present study. There was no response with NADPH-d in the tissue sections of 33 WG, which might be because of loss of gaseous NO by diffusion due to long-standing storage of the sample.

It was found that the number of neuronal cells per ganglia was more in G-2 when compared with G-1 in both Cresyl Violet and NADPH-d stained sections. The comparison was statistically significant. Earlier studies observed that the number of cells per ganglion decreased in the late second trimester and this might be due to concrete decline in the cell number (Hitchcock et al., 1992). The maturation of the neurons was evaluated by analyzing neuronal morphometry which depicted a statistically significant enhance in the area, perimeter and Feret diameter from G-1 to G-2 in Cresyl Violet stained sections. Analogous increase in these parameters was also noted in NADPH-d stained sections.

Conclusion:

This study evaluated a morphological analysis of the development of innervations of human foetal Tulp's valve from 9 WG to 2 months post natal. There is an enhance in neuronal cell size from 9 WG to birth and up to 2 months of age, infant suggesting maturational progression. There is a decline in the numerical density of neuronal cells per 10 mm^2 of the ganglionic area at Tulp's valve. At 9 WG, there were sprinkled tiny sized neurons noted in the myenteric ganglion of the Tulp's valve. At 14 and 15 WG, there was constant band of neuronal cells noted at Tulp's valve. In afterward ages (from 19 to 33 WG), appearance of neuronal processes, the size of the neurons and the neuropil inside the myenteric ganglion were gradually more prominent with growing gestational age. It was noted in the two months old infant, that the myenteric ganglion were elongated, large and well separated from one another. Neuronal cell density was more at lower lip in comparison to upper lip of Tulp's valve. The awareness of the innervations of Tulp's valve may assist in reconstruction of Tulp's valve for healthier movement of ileal contents into the caecum as well as to check retrograde run of caecal content into the ileum.

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