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Determination of Lateral Ventricle and Brain Volume in Children with Stereological Method Using MRI

Determinación del Volumen del Ventrículo Lateral y del Cerebro en Niños Utilizando el Método Estereológico Mediante RNM

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SUMMARY: Although brain development is most active during the intrauterina period of life, the processes of myelination and arborization affect the structure of the brain throughout childhood and adolescence. Brain development is also very active in the early years of a child's life, and continues to be so for approximately 15 years after gestation. Volumetric changes in the brain are effected by sex. Understanding the variability of human brain volume during development is important for the interpretation of childhood neuroimaging studies. Hence the aim of this study is to determine the effects of sex difference on brain volume (BV), lateral ventricle volume (LV) and the ratio of brain volume and lateral ventricle volumes as a percentage (RLBV%) of 90 healthy children between the ages of 6-17 according to their sex with MRI. These children were divided into three age groups of 6-9, 10-13 and 14-17 also BV, LV were calculated using the Cavalieri principle, which is classified as a stereological method and than RLBV% were calculated.
Results: The BV of age group 6-9 was significantly smaller than the other two age groups (P < 0.05). General average BV of the age group 10-13 was higher than the other two age groups but this difference is insignificant. When the groups were compared according to sex, there was no important difference between girls and boys (P > 0.05). General average LV of the age group 6-9 was higher than the other two age groups but this difference insignificant. Moreover there was no sex difference. This study was presented that BV was continued to increase until the ages 10-13 for both of the genders. While LV was increased until the ages 10-13 for boys, it was had a negative relationship with changes of BV for girls.

KEY WORDS: Brain; Lateral ventricles; Magnetic resonance imaging; Stereology.

INTRODUCTION

Even during the process of a normal pregnancy, brain development is not completed at the time of birth (Ballesteros *et al*., 1993). The brain reaches 75% of its adult BV at 2 years, but changes of brain structure and physiology last a life time (Giedd *et al*., 1996). BV in a child reaches 80% of the adult brain size by age 3 years.The brain is % 95 volume of the adult brain by age 9 years. The brain completes the final 5% of its adult volume over a period l of time which is nearly as long as the time required for the initial 95% of volumetric acquisition (Caviness *et al.,* 1996; Giedd *et al*., 2010). There is a correlation between brain volume and particular medical conditions for both children and adults. For example, studies of various diseases emphasized brain volume changes in autism, hyperactivity disorder, schizophrenia, multiple sclerosis, epilepsy, premature birth, fragile X syndrome, Tourettes syndrome, and Alzheimer's. At the same time the lateral ventricle volume (LV) is affected by changes in BV. Studies emphasize a negative relationship between changes of BV and LV (Creasey *et al.*, 1986; Lawson *et al.*, 2000; Castellanos *et al.*, 2002; Wang *et al.*, 2002;Thune *et al.*, 2003; Kesler *et al*., 2004).

Brain imaging techniques are continually developing and the importance of brain imaging techniques in the field of child and adolescent psychiatry is increasing (Levene *et al.*, 1982; Sten *et al.*, 1997; Sowell *et al.*, 2007). Use of MRI is extremely safe and effective method for use in studies of child brain development because it does not have ionizing radiation (11-13). Therefore,the purpose of this study was to calculate BV, LV and brain/lateral ventricle volumes ratio (RLBV%), using MRI with stereological methods in children age between 6-17 years.

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MATERIAL AND METHOD

MRI was used to examine the relationship between age and sex difference with BV, LV and RLBV% in 90 healthy children and adolescents (50 girls and 40 boys), age 6-17 years. Subjects were selected from children undergoing health screening of the brain at the Cumhuriyet University Faculty of Medicine Research and Application Hospital Radiology Department between March 2007 and April 2008. Participants were normal volunteers and the official permissions were taken from the university. The research was performed according to the World Medical Association Declaration of Helsinki. Subjects were divided into there age groups of 6-9 (girls:11 boys:19), 10-13(girls:21 boys:9) and 14-17(girls:18 boys:12)by taking into consideration the sex differences.

Only subjects who met all of the following conditions were used in this study: 1) subjects had no previous brain disease; 2) no signal abnormality and cerebral tumors, infarction or hemorrhage were found on MRI; 3) no history of prenatal confounds that may influence brain maturation, such as prenatal exposure to substances or pregnancy and birth complications; 4) no positive trauma or maltreatment history; 5) no significant medical, neurological or psychiatric disorder or history of head injury or loss of consciousness. The radiologicaly evaluation was performed using a standard head coil with a 2001 model 1.5-T MRI machine (Exelart, Toshiba, Tokyo, Japonya). All of the patients images were obtained through the T2 weighted fast spin echo technique and with the following parameters: time to repeat TR=5000 ms; time to echo TE=94 ms; Flip angle (FA)=90/160; NEX=2; field of view FOV=180x220 mm; matrix=224x320 and section thickness= 6.2 mm.

Stereological volume measurements were based on the Cavalier principle. According to the rule of this principle, sections were taken equidistant, parallel and serial for the most accurate calculations of the volume of interest (14-15). Related fields in the MRI which were taken at an equal distance of 6,2 mm and axial T2 sequence were measured using a 1 / 16 scale compound-point of the measurement scale (d = 0.2 to 0.8) . The measurement scales were taken randomly in the related field and thus prevented partisanship. Points which corresponded to each cross-section were counted separately three times and the number of average points were found to be suitable for the brain and lateral ventricle (Fig. 1).

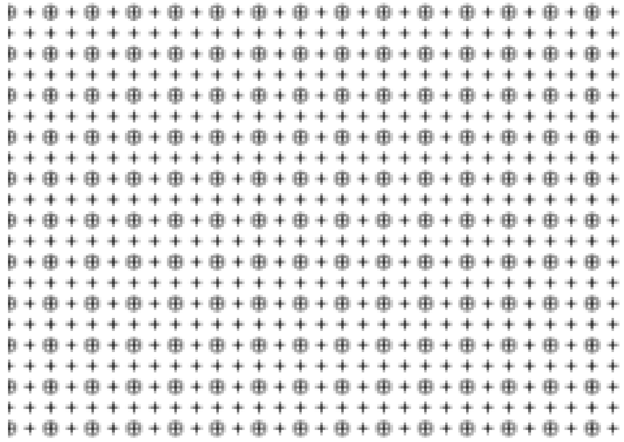

Fig. 1. Scale compound-point of the measurement scale

The cross-sectional area was calculated following the number of points. The volume was calculated by using a equipment for finding the value and slice thickness. The following formula was used for volume estimation(14,16,17,18,19).

$$V = t \times [\,((SU) \times d)/SL]^2 \times \Sigma P \qquad (1)$$

(V: volume, t: slice thickness, SU: length represents the scale which shows the magnification of image d: the length between the two points of the compound-point of the measurement scale, SL: the length of the image scale as measured by f the ruler or caliper, ΣP: number of the points corresponding to all sections)

After the point count values were completed, BV and LV data was entered into the appropriate places on the macro program that was prepared using Microsoft Excel. The findings of volume values were loaded onto the SPSS (ver: 14) program and were used to test which were analysis of variance, Kruskal-Wallies, test of Tukey, significance test of difference between two points for the evaluation . The tables of data reported the arithmetic mean (x) ± standard deviation (S) with an error level of 0.05.

RESULTS

According to sex in all ages (without dividing into age group) comparisons of BV,LV and RLBV% are presented in Table I. The difference between girls and boys was insignificant for BV, LV and RLBV% (p>0,05). The relationship between BV and LV were found in girls and boys r = -0.029 and r = 0.077, respectively. This correlation was insignificant (p>0,05).

According to age groups comparisons of BV, LV and RLBV% without sex difference are shown in TableII. When BV was compared between age groups, the difference was

Comparison of BV(cm^3), LV(cm^3) and RLBV% in all age groups.

Sex	BV $\overline{X}$ ±S	LV $\overline{X}$ ±S	RLBV% $\overline{X}$ ±S
Girl (n=50)	1085,72 ± 101,82	10,76 ±3,09	0,99 ± 0,32
Boy (n=40)	1112,20 ± 134,46	11,00 ±4,37	0,94 ± 0,40
	p=0,290	p=0,762	p=0,548

Table II. Comparison of BV, LV and RLBV% between age groups

Age groups	BV $\overline{X}$ ±S	LV $\overline{X}$ ±S	RLBV% $\overline{X}$ ±S
6–9	1019,43 ± 115,01	11,20 ± 4,45	1,04 ± 0,46
10–13	1154,20 ± 92,70	10.30 ± 4,15	0,89 ± 0,36
14–17	1118,83 ± 102,22	11,10 ± 2,10	0,98 ± 0,19
	p=0,000 p<0,05	p=0,592	p=0,284

Table III. Comparison of BV,LV and RLBV% values in girls for each age group.

Age groups	BV $\overline{X}$ ±S	LV $\overline{X}$ ±S	RLBV% $\overline{X}$ ±S
6–9 (n:11)	1012,42 ± 121,66	11,20 ± 4,45	1,04 ± 0,46
10–13 (n:21)	1123,50±94,39	10.30 ± 4,15	0,89 ± 0,36
14–17 (n:18)	1100,05±66,50	11,10 ± 2,10	0,98 ± 0,19
	p=0,018 p<0,05	p=0,09 p>0,05	p=0,29 p>0,05

Table IV. Comparison of BV,LV and RLBV% values in boys for each age group.

Age groups	BV $\overline{X}$ ±S	LV $\overline{X}$ ±S	RLBV% $\overline{X}$ ±S
6–9 (n:19)	1024,76±113,16	11,06±4,27	0,96±0,42
10–13 (n:9)	1200,25±70,93	11,33±6,06	0,95 ± 0,52
14–17 (n:12)	1151,27±143,23	10,55±2,16	0,91 ± 0,19
	p=0,00 p<0,05	p=0,75 p>0,05	p=0,91 p>0,05

Table V. Comparison of BV,LV and RLBV% values according to sex difference for each age group.

Age groups (girls and boys)	BV $\overline{X}$ ±S (girls and boys)	LV $\overline{X}$ ±S (girls and boys)	RLBV% $\overline{X}$ ±S (girls and boys)
6–9	1012,42±121,66 1024,76±113,16	11,20 ± 4,45 11,06±4,27	1,04 ± 0,46 0,96±0,42
10–13	1123,50±94,39 1200,25±70,93	10.30 ± 4,15 11,33±6,06	0,89 ± 0,36 0,95 ± 0,52
14–17	1100,05±66,50 1151,27±143,23	11,10 ± 2,10 10,55±2,16	0,98 ± 0,19 0,91 ± 0,19
6-9	p=0,818 p>0,05	p=0,850 p>0,05	p=0,414 p>0,05
10-13	p=0,023 p<0,05	p=0,639 p>0,05	p=0,799 p>0,05
14-17	p=0,077 p>0,05	p=0,183 p>0,05	p=0,093 p>0,05

found significant (p<0,05). The BV of children that 6-9 age group was significantly smaller than other groups. The relationship between BV and LV were found into three age groups of 6-9, 10-13 and 14-17, r = -0.049, r = 0.098 and r =0,198 respectively.

According to age groups comparisons of BV,LV and RLBV% in girls are given in the Table III. When BV of girls for each age group were compared among themselves, results was found significant between 6-9 age group and other groups. When RLBV% of girls for each age group were compared among themselves, results was found significant between 6-9 age group and 10-13 age group. But the comparison of LV for girls among themselves was insignificant.

According to age groups comparisons of BV,LV and RLBV% in boys are given in the Table 4.When BV of boys for each age group were compared among themselves, results was found significant between 6-9 age group and other groups. But the comparison of LV and RLBV% for boys among themselves was insignificant.The comparison of BV,LV and RLBV% values according to sex in same age groups, BV was found significant between girls and boys in 10-13 age group while LV and RLBV% values was found insignificant.

According to sex difference in age groups comparisons of BV, LV and RLBV% are given in the Table 5. When BV for each age group were compared between girls and boys, results was found significant in 10-13 age group although LV and RLBV% was insignificant in all groups.

DISCUSSION

Although the development of the brain is more active in the intrauterine period of life, brain structure is affected by many other processes such as myelination and arborization throughout childhood and adolescence (Giedd, 1999). The development process of the human brain continues for approximately 15 years; including the period of pregnancy. The growth rate is very fast during the intrauterine period and the first few months after birth (3). The total intracranial volume and the volume of different cerebral parts increase rapidly in the first two years of a child's life and this change continues, but more slowly, up to adolescents. In a variety of studies related to this field of investigation there is conflicting findings. For example, according to Caviness *et al.*, 1996, Giedd, 1999 and Lenroot *et al.*, 2006, 95% of brain volume is completed at 9 years, 5 years and 6 years, respectively. In spite of myelination of white matter generally increases with age, gray matter decreases. Corpus callosum, which contains most white matter in the brain, increases 1.8% between 3-18 years in each year. While the number of cells which is cited at front of brain and brain stem increase, water volume decreases until the age of eight from pre-natal development (Zhang *et al*, .2005). The findings from studies in the literature on BV are presented in TableVI.

When BV values of this study were compared with other studies, results were generally similar. Our values were found to be close with the values of Reiss *et al.*, 1996, Lange e*t al.*, 1997 and Giedd *et al.,* 1999 but were found to be lower than the values of Bellis *et al.*, 2001. This study revealed that brain volume was greater in boys than girls between 6-17 years and age groups (6-9, 10-13, 14-17). It is not entirely clear how sex factors affect the changes in the brain with the increasing of age, but it is thought that both internal and external factors influence these volume changes. For example, sex hormones play a significant role in terms of changes in the brain as the level of sex hormones remains relatively constant in organisms. Also, the volumetric changes of the brain may be affected by environmental conditions, nutrition and genetic factors. In addition, height and weight are known to affect the volume of the brain which is thought to explain the change in brain volume of boys and girls (Xu *et al.*, 2000; Manjunath *et al*., 2002). However, it is not known whether the differences in total brain size constitute a functional advantage or not. Different functions such as large structural measurements, neural relationships and receptor sensitivity cannot be related to sexually dimorphic differences (Lenroot *et al.*, 2006).

The studies performed after the ages of 16-17 demonstrated that brain volume is greater in boys than in girls. However, it also demonstrated that the loss of BV is greater in boys than in girls (Courchesne *et al*., 2000).

The morphometric measurements of LVV are more variable because lateral ventricles share a common border with other brain structures (Thune *et al.*, 2000; Wang *et al.*, 2002; Giedd *et al.*, 2010). LVV can change more or less because of an abnormality in any area of the brain. The changes of the forebrain structures such as the hypothalamus, thalamus, limbic system and basal ganglia is affected by lateral ventricles.Cortical and especially subcortical atrophy is associated with ventricular enlargement. Many studies related with this matter show that an increase of LVV results in a decrease in BV (Courchesne *et al.*, 2000;Wang *et al*., 2002). However, it is not possible to know to what extent the reduction in any area of the brain tissue is caused by ventricular enlargement (Creasey *et al.*, 1986; Wang *et al*., 2002).

Lange *et al.* (1997) reported a mean value of LVV 10, 08 among healthy children according to age and sex. This value was expressed as 9.28 for boys and 10.68 for girls. Giedd *et al.*, 1996, reported that LVV increased with age and this was more significant in boys. Reiss *et al*., 1996, reported value of LVV 11.9 ± 5.7 for boys and 15.5 ± 9.5 for girls (29). Our study demonstrated that the relationship between LVV and BV is positive for boys but negative for girls with age. Also, the numerical results of our study were found to be compatible with other pediatric studies. Compared with findings from other studies, the mean LVV estimated was greater in boys than in girls in all age groups and the result is consistent with the study of Giedd *et al.,* (1996). Moreover, values of LVV in our study was found to be more than Lange *et al.*, (1997), but less than Reiss *et al.*, (1996).

It is stated in the literature that there is a correlation between the BLVVR and the LVV changes. The studies related to BLVVR by Giedd *et al.*, demonstrated that the increase in BLVVR is in correlation with the increase in LVV and minimal changes occurred with the changes of the ventricular volume (Giedd *et al.*, 1996). In studies related to LVV changing by age changing. Barron *et al*., (1976) emphasized that LVV increased with age. For instance, they reported BLVVR as 1.8 ± 0.4% between 0-9 years and as 3.3% ± 0.7 between 10-19 years.

When the values of our study were compared between age groups, it was found that LVV was decreased between 10-13 years and was increased between 14-17 years. But

Table VI. The litterateur of BV changes according to age and sex (BV; cm^3)

Authors	Age groups	Subjects	Girls (BV)	Boys (BV)
Giedd *et al.* (2)	4-18	104	BV is great in boys more than girls	
Giedd *et al.* (28)	4-22	145	1260	1382
Lange *et al.* (10)	4-20	115	1072,82	1169,63
Reiss *et al.* (29)	5–17	85	1182,5 ± 104,7	1290,6 ± 147,4
Bellis *et al.* (30)	6–17	118	1188,5 ± 85,7	1344,53 ± 123,41

BLVVR was decreased between 10-13 years and was increased between 14-17 years.

Our study can provide very important data for neuroanatomical development .The aim of our study is to create a model in a group which includes healthy children between the ages of 6-17 and to show the brain and lateral ventricle volume change and produce their relationship with age and sex. Fundamental changes in the brain between these age groups can be a reflector or predictor for the normal development of behavioral patterns. Changes in brain structures are important indicator of many psychiatric disorders. However, most childhood neuropsychiatric disorders are diagnosed in children between the age group of 4-18. Thus, the normal values which were found in this study can be an extremely important guide for further research.

KARACAN, K.; KOSAR, M. I.; ÇIMEN, M.; SOLAK, O. & SAHIN, B. Determinación del volumen del ventrículo lateral y del cerebro en niños utilizando el método estereológico mediante MRI. ***Int. J. Morphol., 31(1)***:211-216, 2013.

RESUMEN: Aunque el desarrollo del cerebro es más activo durante el período de la vida intrauterina, los procesos de mielinización y arborización afectan a la estructura del cerebro durante la infancia y la adolescencia. El desarrollo del cerebro es activo en los primeros años de la vida, y sigue siendo así durante unos 15 años después de la gestación. Cambios volumétricos en el cerebro son afectados según el sexo. La comprensión de la variabilidad del volumen del cerebro humano durante el desarrollo es importante para la interpretación de los estudios de neuroimagen en la infancia. Por lo tanto, el objetivo de este estudio fue determinar, a través de resonancia nuclear magnética, los efectos de las diferencias de sexo en el volumen cerebral (VC), en el volumen del ventrículo lateral (VL) y la relación porcentual de los volúmenes del cerebro y del ventrículo lateral (% VLVC) de 90 niños sanos entre 6-17 años de edad, en ambos sexos. Los niños fueron divididos en tres grupos de edad: 6-9, 10-13 y 14-17. El VC y el VL se calcularon utilizando el principio de Cavalieri, además de la relación porcentual RLBV. El VC del grupo 6-9 años fue significativamente menor que el de los otros dos grupos (p <0,05). El promedio del BC del grupo 10-13 años fue superior a los otros dos grupos de edad, pero esta diferencia fue mínima. Cuando se compararon los grupos en cuanto al sexo, no hubo diferencia entre niños y niñas (P> 0,05). El promedio general del grupo VL de 6-9 años fue mayor que los otros dos, sin diferencia significativa entre ambos sexos. El VC siguió aumentando hasta los 10-13 años en ambos sexos. Mientras LV aumentó hasta los 10-13 años de edad en los niños, se observó en las niñas una relación negativa con cambios de BV.

PALABRAS CLAVE: Cerebro; Ventrículos laterales; Imágenes por resonancia magnética; Estereología

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