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Development of the cerebellum vermis: A morphometric study on second trimester fetuses

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SUMMARY

The human cerebellum has a complex process of development. The cerebellum vermis is one of its main structures and its abnormal development has been related to different pathologies. There is still very little information about the normal measures of the cerebellum vermis during its development. Image techniques have a temporality limitation, plus they are operant dependent. The main objective of this research is to establish a nomogram of in vivo measures of human fetuses to contribute to the diagnosis of cerebellum malformations. We made an encephalic dissection of 33 human fetuses from the 14 to 21 weeks of gestation to expose the cerebellum. A dissection of the cerebellum was made to expose the cerebellum vermis, which was measured in three axes: craniocaudal, anteroposterior, and obliquus axes. Results were reported as the mean of each axis in millimeters and with the standard deviation. A Pearson´s correlation test was made between each of the axes with the gestational age.

The three measured axes showed an increasing growth pattern during the studied period. They also showed a strong correlation between these increasing measures as the gestational age increases. We described a series of measures of different axes of the cerebellum vermis. Our results help define the normal dimensions of this structure, which ultimately could ease the diagnosis of a malformation such as a cerebellum vermis hypoplasia or agenesis. Further research should be carried out to increase the validity of these results.

Key words: Cerebellum – Embryology – Abnormalities – Growth and development – Anatomy

INTRODUCTION

The cerebellum vermis is the structure that divides the cerebellum into a right and left hemispheres, and it is originated from the rombencephalic ventricle. The cerebellum vermis is formed from the fusion of the developing cerebellar hemispheres when they both join in the middle line. Thus, vermis could not be developed without the development of the cerebellar hemispheres. The main patterns of vermis malformation are The Dandy-Walker malformation

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spectrum, the Arnold Chiari malformation, Joubert´s syndrome, tectocerebelar dysraphism and rhombencephalosynapsis (Takanashi, 1999).

Dandy-Walker malformation, the Chiari malformation, and the cerebellum Hypoplasia are among the most common cerebellum malformations diagnosed in-utero. From this, the vermis is one of the most affected structures. Its study is difficult due to an inconsistent classification, unknown pathogenesis, and the lack of consensus about the normal dimensions of the cerebellum (Aldinger et al., 2019).

Dandy Walker´s disease is one of the most frequent malformations, and it is present approximately in 1 out of 25,000-35,000 newborns (Cignini et al., 2016; Jurca et al., 2017). Clinically, hypoplasia of the cerebellum vermis and its related syndromes may present with developmental delay and speaking problems (Wassmer et al., 2003).

Patients with Chiari Malformation present with a displacement of the cerebellar structures. In Chiari Malformation type I, the most affected structures are cerebellar tonsils and the inferior aspect of the vermis. This type of malformation presents with clinical manifestations in early adulthood and middle age (Barkovich, 1986).

Other malformation patterns of the vermis are represented by the Phelan-McDermid and Joubert Syndrome. The first one is caused by a deletion on 22q13.3, and it is defined by a development delay and a mild-to-severe absence of expressive speech, being the most frequent structural malformation of the cerebellum vermis hypoplasia. Joubert syndrome is defined by congenital ataxia with diffuse hypotonia, development delay, abnormal respiratory patterns, and oculomotor apraxia. Pathognomonic radiological findings of this syndrome are the molar tooth sign, that is the result of vermis hypoplasia, thickened and misoriented cerebellum peduncles, and an interpeduncular fossa abnormally deep (Aldinger, 2013; Zaki, 2008).

The prematurity period constitutes a critical period in cerebellar development. More than 19-37 % of the preterm infants evaluated with MRI are diagnosed with cerebellar bleeding, whilst more than 7-9% are diagnosed with the same pathology by ultrasound. The increasing use of MRI in preterm neonates has demonstrated that cerebellar hypoplasia is a relatively common finding on preterm infants particularly when the study is made during childhood (Gano and Barkovich, 2019).

Cerebellum vermis could suffer from morphological alterations not only from a congenital manner, being an example the infections that affect the cerebellum. Acute cerebellitis is considered an inflammatory syndrome that presents with fever, nausea, headache, and an altered mental status with cerebellar symptoms. The study of patients with rotavirus-related cerebellitis showed on the MRI that the most affected regions were the vermis and cerebellar cortex (Takanashi, 2010). Intracranial abnormalities in the cerebellum have also been described in the in-utero infection with B19 Parvovirus. However, it has been suggested that these were the result of the intrauterine treatment and not from the infection (Glenn et al., 2007).

Outer from the infectious causes, adverse effects on the development of the cerebellum have been described in patients that received corticosteroids either prenatally or neonatally. Preterm neonates are at risk of cerebellar hypoplasia, which is related to a delay in motor and cognitive functions (Tam, 2011).

A malformation on the cerebellum vermis could be detected prenatally either with an ultrasound technique or with a Magnetic Resonance Image (MRI). Nevertheless, image techniques have a temporality limitation. Ultrasonography does not identify cerebellum structures until the 18th week of gestation, and MRI is not recommended before this week because of fetal mobility and the small size of the structures. The intentional study of the human cerebellum before the eighteenth week of gestation increases the number of false-positive results of vermis dysplasia or abnormal communication of the fourth ventricle and cisterna magna (Chapman et al., 2015).

With the increasing availability and the better visualization of posterior fossa structures with MRI, cerebellar malformations are most frequently recognized. Even when they represent the most frequent structural malformations of the cerebellum, hemisphere and vermis malformations are poorly understood because of the scarce literature on them. Moreover, it is difficult to assure at the moment of diagnosis of a malformed cerebellum if this represents atrophy, hypoplasia, or another malformation in the cerebellum, since there are not enough and appropriate morphological descriptions. Patel and Barkovich (2002) proposed a morphological classification of the cerebellum malformations, which divides them into two main groups: cerebellar hypoplasia and cerebellar dysplasia, each group is divided posteriorly in focal hypoplasia or generalized hypoplasia and focal or generalized dysplasia, respectively (Patel and Barkovich, 2002).

Friede (1973) described the gestational periods in which cerebellum layers are developed. He also described the expected weight of the cerebellum in different gestational periods (Friede, 1973).

Cerebellum Hypoplasia might have a broad spectrum of manifestations and can be present either isolated or with a genetic syndrome (Sarnat and Alcala, 1980).

Many authors have described the cerebellum measures and growth patterns with similar results. Goldstein et al. (1987) did a prospective analysis in which they use ultrasound to measure the cerebellum growth prenatally. They studied 371 women with a normal evolutive pregnancy between 13 to 40 weeks of gestation. Three measures were taken: cerebellum diameter (CD), Biparietal Diameter (BPD), and Cephalic Circumference (CC). They found a statistically significant linear correlation between diameters and gestational age: Cerebellum Diameter ($R2= 0.948$; $P= 0.0001$), Biparietal Diameter ($R2= 0.956$; $P=0.0001$) and Cephalic Circumference ($R2=0.960$; $P=0.0001$) (Goldstein et al., 1987).

Co et al. (1991) measured 80 healthy newborns to describe the normal dimensions of the cerebellum based on their gestational age. They measured: the area, circumference, and vertical length of the vermis as well as the area, transverse length, and circumference of the main part of the cerebellum. They found a strong linear correlation between transverse dimensions and the measure lengths of the cerebellum and gestational age ($R=0.88$; $P < 0.0001$).

Chong et al., (1997) did the first evaluation of fetal cerebellum by magnetic resonance image (MRI). They studied 26 human specimens in the fetal period between 9 to 24 weeks of gestation. They reported the morphological development of the cerebellum structures depending on gestational age. They also suggested the use of MRI to reduce the delay on cerebellum malformation diagnosis and the usage of a nomogram to avoid confusion on the cerebellum size.

Cerebellum vermis has been less studied than other posterior fossa structures. However, important findings related to this structure have been found.

Using morphological characteristics and predetermined measures of the posterior fossa, Paladini and Volpe (2006) evaluated 51 normal fetuses and 20 fetuses with Dandy Walker´s malformation to identify in an early period malformation on the cerebellum vermis development. They used 3D ultrasound and MRI to measure cerebellum vermis and to evaluate abnormal characteristics such as a cephalic rotation of the vermis and a delay in the development of the vermis. They compared their ultrasound observations with those of the MRI, showing a very small variation.

One of the main findings of the studies that have measured the cerebellum vermis is that, unlike other cerebellar structures, the cerebellum vermis has a linear growth pattern that is highly related to gestational age. Dudek et al. (2018) described a mathematical analysis with measures obtained directly from cerebellum specimens from 101 human fetuses from 15 to 28 weeks of gestational age. They evaluated the normal development of the cerebellum measuring the transverse and ventrodorsal diameters of the cerebellum vermis in the transverse axis and rostrocaudal dimensions from the cerebellum vermis and cerebellum hemispheres on the frontal axis. The analysis showed a linear growth following the gestational week.

It has been described that, in neonates, vermis height is a sensitive marker to evaluate a normal cerebellar development. Moreover, during the prenatal stage, the evaluation of the transversal diameter of the vermis is more precise to evaluate normal development (Pogliani, 2008). Scott et al. (2012) did 3D reconstructions based on MRI to evaluate cerebellar development and described that cerebellum volume increases its size 7-fold between 20 to 31 weeks of gestation. They measured trans-cerebellar diameter, vermis height, and anteroposterior diameter of the vermis, and, from their results, they calculated linear, quadratic, and exponential estimations of the growth of the cerebellar hemispheres. Unlike the cerebellar area, which is better predicted with a quadratic model, vermis dimensions showed a linear growth pattern, which increased in the same period at about 3.5-fold (Scott et al., 2012).

These findings represent a highly relevant finding for this research, since the study of the cerebellum vermis through ultrasound, the most available image study, should not be done before the 18th week. However, since many authors agree that the vermis has a linear growth pattern, measures before the 18th week could be very useful to predict either retrospectively or prospectively the normal size of the vermis. This could be particularly helpful when vermis hypoplasia in a neonate or infant patient is suspected and a previous measure of his cerebellum vermis was taken. Moreover, as many authors have described, vermis dimensions are a sensitive predictor of cerebellar development, so its measure at the second trimester could predict which should be the normal dimensions of that patient's cerebellar structures in later stages of development.

MATERIALS AND METHODS

This research followed the directions of the Helsinki declaration and was approved by our institutional ethics committee with approbation number PI20-00128. 33 human fetuses, which were product of abortions from ages of 14 to 21 weeks of gestation, were dissected (17 female and 16 male). The sample size was taken under our laboratory availability of human fetuses. Although an increased number of patients would have been ideal, availability of human fetuses, embryos and cadavers for research is scarce at our institution, and most representative and morphologically normal fetuses for gestational week were intended to be included. An encephalic dissection was made, dissecting by planes first the skull, then the encephalon, and then the encephalic trunk. Once isolated, the encephalic trunk was impregnated with mangold solution for 24 hours to harden encephalic tissue. Cerebellum was dissected with a cut in the median sagittal plane, using the medium dorsal groove, dividing it into right and left hemispheres. For the cerebellum vermis measure three axes were used: The anteroposterior axis (APA) which goes from cerebellum fastigium to the posterior region of the middle line; the obliquus axis (OA), from the anterior region of the central lobule to the posterior region of the cerebellar folia; and finally the cranio-caudal axis (CCA), from the cranial region of the culmen to the caudal region of the uvulae. Measures were taken using a digital stereomicroscope (ZEISS Stemi 2000-C, ZEISS AxioCam ICc 1) using a 0.65 scale. The taken measures are showed in fig. 1. A database with the results was made using Microsoft Excel 365 and was analyzed using the IBM SPSS 24 Software. A Kolmorov Smirnoff test was made to certify the normal distribution of data in terms of mean (standard deviation). A Pearson correlation test was made to determine if a linear relationship between the measures taken and the gestational age exists.

RESULTS

Results from the measured axes are summarized in Table 1. Each measure is described as the mean (standard deviation) of each week from 14 to 21 weeks of gestation. All the axes showed an ascendant pattern related to gestational age.

Although each of the axes measured followed an increasing pattern that correlates with gestational age, they did it at different rates. The cranio-caudal axis was the structure with the most constant growing rate. This was the case, however, by a minimum difference with the other axes.

All of the measured structures increased in an equivalent rate since they doubled the mean length at the 14th week of development: the first

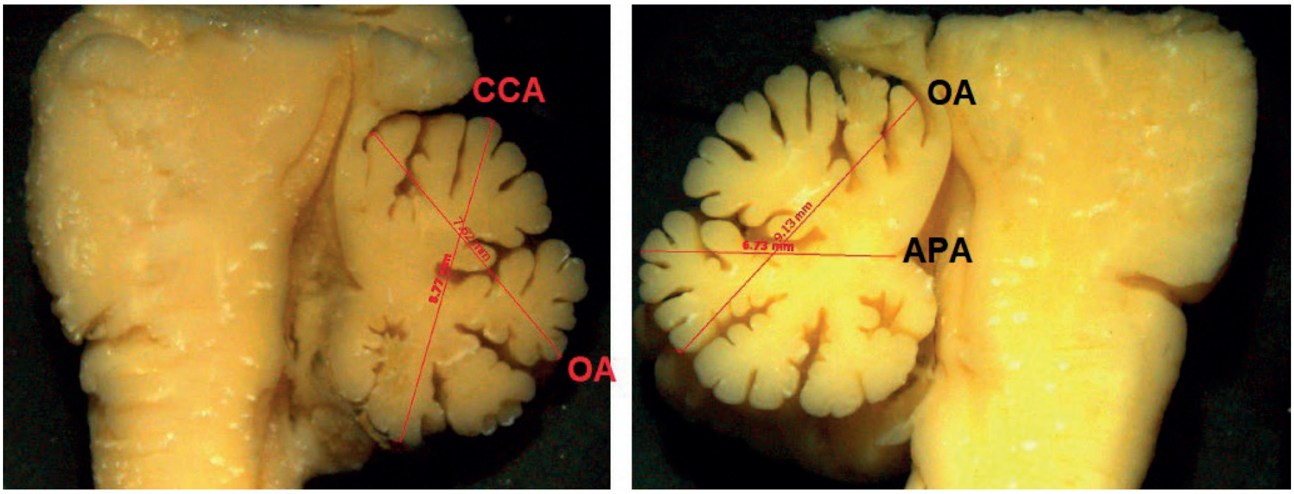

Fig. 1.- Measures of the cerebellum vermis. CCA: cranio-caudal axis. APA: anteroposterior axis. OA: obliquus axis.

one studied, at the 17th week of development and triplicated at the 21st week of development, the last one measured. These results support the knowledge that the cerebellum vermis has a linear growth pattern.

There are certain differences in the growing of the three different axes measured among the studied weeks. While cranio-caudal axis (CCA) and anteroposterior (APA) had their higher increase in length between the 14th to 15th week of development, obliquus axis had its higher increase in length between the 16th to 17th weeks of development, although, as CCA and APA, OA did show a relatively high increase between the 14th to 15th week, suggesting that this might be a period of greater growing and maturation of the vermis.

These measures help set a standard for normal dimensions of the cerebellum vermis and to distinguish an hypoplastic or hypertrophic structure. Although it is not ideal to establish the diagnosis of an hypoplastic or aplastic vermis so early in the development (before 18 weeks), measures at these stages could help predict the normal dimensions of a certain patient´s vermis in later stages, which could be especially useful in patients with suspicion of a disease involving this structure.

As shown in Table 2, Pearson´s correlation tests were made to identify whether the cerebellum vermis has a constant growth pattern depending on gestational age. All the measured axes showed a strong correlation with gestational age, which shows that the measure of this structure could be a reliable parameter to estimate fetal age. Although the difference on the Pearson´s correlation of each axis with gestational age were minimum, the cranio-caudal axis resulted in the strongest correlation, and thus it could be a

Table 1. Average value of cranio-caudal axis (CCA), anteroposterior axis (APA) and obliquus axis (OA) of the cerebellum vermis.

Weeks of gestation	Cranio-Caudal Axis (CCA) mm Mean (SD)	Anteroposterior Axis (APA) mm Mean (SD)	Obliquus Axis (OA) mm Mean (SD)
14 (n=4)	3.65 (0.45)	2.86 (0.29)	3.73 (0.46)
15 (n=4)	4.96 (0.95)	3.64 (0.55)	4.58 (0.88)
16 (n=4)	5.16 (0.90)	3.59 (0.38)	4.69 (0.60)
17 (n=3)	6.84 (0.46)	4.29 (0.43)	6.11 (0.64)
18 (n=6)	7.46 (0.98)	5.03 (0.53)	6.57 (0.72)
19 (n=4)	8.68 (1.05)	6.12 (0.77)	8.37 (1.20)
20 (n=4)	9.27 (0.76)	6.16 (1.02)	8.88 (0.96)
21 (n=4)	10.23 (1.54)	7.06 (0.63)	9.79 (1.46)

sensitive marker of adequate vermis development in the second trimester of gestation. These strong correlations also support the knowledge about the linear growing pattern of the vermis.

DISCUSSION

The human cerebellum has a complex development mechanism. Thus, it is highly susceptible to congenital malformations. The cerebellum vermis, the dividing structure of the cerebellum, has a constant growth during prenatal development.

As described by Dudek et al. (2018) and Scott et al. (2012), the vermis has a linear growth pattern, unlike other cerebellar structures that show exponential growth and thus the prediction of their normal dimensions could be less precise.

As we report, the three axes that were measured (cranio-caudal axis, anteroposterior axis, and obliquus axis) represent appropriate measures to evaluate the normal growth and development of the cerebellum. Each of them showed to have an increased size with a strong correlation to gestational age. Although the diagnosis of hypoplasia or aplasia of the vermis should not be established before the 18th week of development, its normal dimensions could be predicted with models like the proposed by Scott et al. (2012) using the measures that we report. Moreover, we support that this linear pattern that previous authors report at the third trimester of pregnancy is present also during the second trimester.

These results support the knowledge that the vermis is the structure with the most constant growth rate in the cerebellum, and their dimensions are a representative marker of normal cerebellar development. As Paladini and Volpe (2006) suggested, the variation in the measurements of cerebellar structures with ultrasound compared with MRI is minimum, we suggest that the evaluation of vermis and other cerebellar structures could be evaluated correctly using ultrasound techniques. Moreover, as more specific types of ultrasonography such as neurosonography become available, the evaluation of the cerebellum should be more precise. This is one of the main reasons to increase morphometrical studies of the cerebellum and other neurological structures, since the descriptions of normal dimensions of many structures are scarce, and the early identification of a malformed structure could improve patient care by the early referral to a specialist.

Our results could be used to set a nomogram for the study of normal dimensions of the cerebellum vermis, and results could be used and compared with measures taken using image techniques such as ultrasound or magnetic resonance image (MRI). Since most of the pathologies that affect the vermis also affect other structures, an intentional search for these should be done in patients with hypoplastic or aplastic vermis.

Our research has certain limitations, as our population is limited in size and further studies should be made to increase the validity of the results. Nevertheless, they bring an important orientation in evaluating if a cerebellum vermis has normal dimensions and could be used with previously established models to predict the future size of the vermis in normal conditions and compare them with the patient´s vermis dimensions in which cerebellar malformations are suspected.

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Table 2. Pearson´s correlation test of the measures taken with gestational age.

Parameter	Gestational Age (Pearson´s correlation test) (r)	p value
Cranio-Caudal Axis (CCA)	0.925	0.000
Anteroposterior Axis (APA)	0.916	0.000
Obliquus Axis (OA)	0.918	0.000

then improve patient care. Therefore, these donors and their families deserve our highest gratitude.

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