The development of cerebellum in Chinese children-A study by voxel-based volume measurement of reconstructed 3D MRI scan

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Abstract

Cerebellar disorder was frequently reported to have relation with structural brain volume alteration and /or morphology change. In dealing with such clinical situations, we need a convenient and non-invasive imaging tool to provide clinicians with a means of tracing developmental changes in the cerebellum. Herein, we present a new daily practice method for cerebellum imaging that utilizes a work station and a software program to process reconstructed 3D neuroimages after MRI scanning. In a 3-year period, 3D neuroimages reconstructed from regular MRI scans of 50 normal children aged 0.2~12.7 years were taken. The resulting images were then statistically analyzed against a growth curve. We observed a remarkable increase in the size of the cerebellum in the first 2 years of life. Furthermore, the gray matter grew mainly between birth and 2 years of age in the postnatal stage. In contrast, the postnatal development of the brain mainly depended on the growth of white matter from birth through adolescence. This study presents basic data from a study of ethnic Chinese children's cerebellums using reconstructed 3D brain images. Based on the technique we introduce here, clinicians can more efficiently and precisely evaluate the growth of the brain.

Keywords: 3D neuroimaging, MRI reconstructed image, cerebellum growth, volume measurements

Abbreviations

3D, three-dimensional

MRI, magnetic resonance imaging

Brain development in early life is thought to be more susceptible to injury than in the latter stages. Any insult at this stage can cause permanent injury resulting in disability which is different from a mature cerebellum's injury that might be restored partially by rehabilitation. The previous literature of studies of the cerebellum clarified relationships between structural brain volume alterations and symptoms in various regions (1-4). Furthermore, based on a report by Krageloh-Mann et al (5), marked cerebellar atrophy in preterm babies was considered to be related to severe developmental delays. Thus cerebellar atrophy was shown to be a bad prognostic factor of motor and cognitive outcomes in children.

In our daily pediatric neurology practice, we need a convenient and efficient imaging tool to provide clinicians with the ability to trace developmental changes in the cerebellum of children and provide a reliable data reference base for healthy children. It would be helpful for interpreting information and communicating with the patient and his/her family.

Herein, we present a new daily practice method for three-dimensional (3D) image reconstruction using a conventional magnetic resonance imaging (MRI) scanner connected to a workstation. After carefully setting up the parameters for MRI scanning, the reconstruction process was managed by a software program that uses data from the MRI scanner. With this technique, we were able to study cerebellar growth in children with volume measurements from reconstructed 3D images of the brain. Few studies outside the US and European have systematically examined cerebellar development in childhood (6), and there are no detailed cerebellum development data for ethnic Chinese children. The purpose of this study was to establish such a database for further study.

METHODS

Patients

We collected data on subjects in a 3-year period at the Department of Pediatrics, Wan-Fang Hospital, Taipei, Taiwan. Data were obtained from subjects undergoing ordinary health examinations or other reasons for which neurologist had suggested an MRI brain imaging study, except those who had any form of cerebellar dysfunction. Brain MRI studies were applied to each of them followed by a 3D neuroimaging reconstruction processing study. If the subjects were later diagnosed as having cerebellar disease, then they were excluded from the study. In total, 50 cases were included during this period. All work carried out in this study was approved by the ethics committee of Wan-Fang Hospital. Informed consent was obtained from all patients or a parent prior to study participation.

Technique for 3D reconstruction

We carried out this process of 3D reconstruction according to Schierlitz et al (7) using 2D medical images and Avizo software (version 5.1, Mercury Computer Systems, Inc., France). The method for 3D image reconstruction began by setting up the indicator for MRI scanning to a mode suitable for large datasets that can work well on PCs using the Avizo software. A GE 1.5 Excite machine is used in this hospital. A subject's brain was scanned using transverse planes of ≤ 1.5 mm in order to obtain at least 80~120 slices. The conditions for MRI scanning were as follows: (1) Patient position:supine, (2) Coil: head, (3) T1W: 3D

SPGR, (4) TR: 33, (5) TE: 3.0, (6) Flip angle: 35°, (7)Bandwidth: 15.63, (8) Matrix: 256*192 Zip 512, (9) Fov (field of vision): 22 cm, (10) Cover range: whole brain. Scans were collected for algorithmic reconstruction and transmitted from the magnetic resonance unit database to an established workstation. The 3D Avizo software system was then used for image processing. The skull component of the brain was visually removed from the regions of interest using an arithmetic module in order to isolate the cerebellar hemisphere. We limited gray-scale values to 110~155 of 1024 (2^{10}) scales in order to approximate the boundary of the gray matter. The software's "threshold" and "edge detection" tools allowed the gray matter to be precisely delineated. Certain areas with fewer than 50 pixels (area < 0.1 cm^2) were removed to eliminate erroneously identified gray matter. We then repeated the procedure for the white matter with gray-scale values in the range of 75~95 of 1024. Subsequently, we computed volumetric measurements of the gray matter with the following formula: volume of cortex = (number of voxels within the cortex) × (volume per voxel), derived from Courchesne's et al.'s[8] formula, which can be modified to compute the white matter and entire cerebellar volumes. These procedures were done by a technician and a physician concurrently for three times in order to minimize the human operational errors and reconfirm the areas classified.

Statistical analysis

We conducted statistical analyses of the data with Excel 2003 and SPSS version 11.5.

The total cerebellar volume, which was further differentiated into gray mater and white matter, was recorded by age and gender. The regression curves were individually graphed, and equations were determined. Our statistical probabilities and regression analyses used logarithmic functions.

RESULTS

During a 3-year period, we collected 50 cases which were enrolled in this study. Their age distribution and cerebellar volume are given in Table 1. Reconstructed 3D images of cerebellar growth of selected stages are shown in Fig. 1. As Fig. 2 shows, the regression curve of normal cerebellar growth at the ages of 0.2~12.7 years was $y = 12.743Ln(x) + 91.562$, $\mathrm{r}^2 = 0.313$, and the regression curve for the normal growth of gray matter of the cerebellum was $y = 7.3662Ln(x) + 79.583$, $r^2 = 0.1695$ and normal growth of white matter of the cerebellum was $y = 5.3797Ln(x) + 11.974$, $r^2 = 0.4166$ (Fig. 2). In the formula, y is the volume and χ the mean age. It is evident that the cerebellum volume substantially increased in the first 2 years of life. The majority of the cerebellar volume was accounted for by gray matter, which increased by almost 130% in the first 2 years; white matter volume also obviously increased in the first 2 years. The ratio of the volumes of gray matter to white matter after 2 years old was about four to one. When we considered the gender factor in the analysis, the volume of cerebellar growth differed between females and males, with girls always lagging behind; it is not until about 12 years of age that they had caught up to the volume of the male cerebellum (Fig. 3a). We also determined the male cerebellum growth equation to be $y = 6.6346Ln(x) + 104.66, \mathrm{r}^2 = 0.0866$ and the equation for females to be $y = 16.625Ln(x) + 79.581$, $r^2 = 0.6881$ (Fig. 3a). Furthermore, as Fig. 3b shows, it is evident that the volume of white matter increased with age, increasing more in females than in males, although the male cerebellar white matter volume was greater than that of females in the infant stage. The male cerebellum white matter growth equation was $y = 4.4506Ln(x) + 13.613, r^2 = 0.2485$ and that of females was $y = 6.0392Ln(x) + 10.881$, $r^2 = 0.6485$. On the other hand, the male cerebellar gray matter volume began to level off after 2 years old and was greater than that of females until around 11 years old, despite the rapidly increasing volume of females (Fig. 3c).

DISCUSSION

The advancement of digital image processing with algorithms makes it possible to practically, effectively, and efficiently demonstrate 3D images. Our study using a high-resolution gray-scale (1024) method to define gray-scale levels of different parts of the brain on a delicately sliced MRI scan (slice thickness of 1.5 mm, with approximately 80~120 slices in a normal brain). Then, we set up a level threshold and processed the images digitally. With this procedure, we can display each component of the brain using 3D images, including the cortex, white matter, ventricles, vessels, and pathological lesions. With delicately sliced MRI scans, this technology can become a new tool for more-precisely demonstrating both the normal anatomy and pathological lesions of the brain. This program can also be modified to perform volume arithmetic, which enables the evaluation of brain volume. Computation of volumetric measurements of the gray matter used the following formula: Volume of the cortex = (number of voxels within the cortex) × (volume per voxel). Modifications to this formula can allow computation of the volume of the white matter, ventricles, the whole brain, and even brain lesions (8).

Brain development in early childhood is extremely dynamic and is thought to be critical in neurodevelopmental disorders. Quantitative MRI has significantly advanced our understanding of brain development during growth. Several large-scale longitudinal studies have been published (6,9). However, none of those large-scale studies focused on the cerebellum or covered the age from infancy to adolescent. Filling in this serious gap in our current knowledge was one of the motivations to perform this study.

Cerebellar growth in our study possessed a similar trend to that of the cerebrum, which was reported previously (10-16). We observed a dramatic increase in the size of the cerebellum in the first 2 years of life, in which overall gray matter volumes rapidly increased to a lifetime maximum at around age 2 years (Fig. 3c), and white matter and continually increased beyond childhood (Fig. 3b).

Giedd et al had reported that volume changes of cerebrum cortical gray matter were nonlinear and regionally specific (9), but grew with the similar pattern that they increased during pre-adolescence with a maximum size; followed by a decline during post-adolescence. This phenomenon was not seen in our result of cerebellar gray matter growth. The volume of cerebellar gray matter increased as a sharply parabolic curve with age, increasing less in females than in males, and became leveling beyond about 12 years old.

Another recent report using quantitative diffusion tensor imaging to evaluate cerebellar white matter development also demonstrated that myelination of the cerebellar white matter continued to sharply increase for up to 36 months after birth, which was then followed by a gradual increase into childhood and adolescence (17). As myelination and synapse formation account for brain and white matter growth during the postnatal stage, these also support our finding of continual increases in the cerebellar white matter volume.

Interestingly when we analyzed the data differentiated by gender, female children seemed to lag behind males in development. We do not know whether this result is due to the limited study number or not. We believe in the future, after more data become available, this condition will be elucidated.

Accumulating evidence reveals that cerebellar growth may underpin motor and cognitive development in infancy (18-20). Many cerebellar disorders are frequently reported to be related to structural brain volume alterations and/or morphological changes (1-4). Our quantitative information on cerebellar development may play a pivotal role in clarifying brain neurodevelopmental abnormalities, and this 3D neuroimaging method can also serve clinicians as an efficient and cost-effective method to visually map and study brain development in actual patients. The methodology introduced in this study can help clinicians map their patients' brain development and is helpful to us for interpreting and communicating information to the patient and his/her family.

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Figure Legends

Fig 1. 3D reconstructed neuroimages of the cerebellum at different ages: (1a) anterior view, (1b) vertical view of a 1-year-old child (volume: 79.12 cm^3); (2a) anterior view, (2b) vertical view of a 2-year-old child (volume: 91.44 cm^3); (3a) anterior view, (3b) vertical view of a 4-year-old child (volume: 92.27 cm^3); (4a) anterior view, (4b) vertical view of an 8-year-old child (volume: 102.52 cm^3).

Fig 2. Growth curves of the total cerebellum, gray matter, and white matter value (cm^3) from 3 months to 12.7 years of per age group. —◆— means of grey matter, —■— means of white matter, —▲— means of cerebellum. The regression curve of normal cerebellar growth at the ages of 0.2~12.7 years was $y = 12.743Ln(x) + 91.562$, $r^2 = 0.313$, and the regression curve for the normal growth of gray matter of the cerebellum was $y = 7.3662Ln(x) + 79.583$, $r^2 = 0.1695$ and normal growth of white matter of the cerebellum was $y = 5.3797Ln(x) + 11.974$, $r^2 = 0.4166$. In the formula, In the formula, y represents volume, and χ represents age.

Fig 3. Growth curves of the cerebellum of male and female children from 3 months to 12.7 years of age. —◆— means of female, —■— means of male. (A) Growth curves of the cerebellum of male was $y = 6.6346Ln(x) + 104.66$, $r^2 = 0.0866$; female was $y = 16.625Ln(x) + 79.581$, $r^2 = 0.6881$. (B) Growth curves of the cerebellar white matter of male was $y = 4.4506Ln(x) + 13.613$, $r^2 = 0.2485$; female was

$y = 6.0392Ln(x) + 10.881$, $r^2 = 0.6485$. (C) Growth curves of the cerebellar gray matter of male was $y = 2.1892Ln(x) + 91.032$, $r^2 = 0.0136$; female was $y = 10.587Ln(x) + 68.696$, $r^2 = 0.5731$. In the formula, y represents volume, and χ represents age.

Table(s)

Table 1. The grey matter volume, white matter volume and cerebellum volume of 50 patients.

Group	Age	Number	Grey matter volume (cm^3)		White matter volume (cm^3)		Cerebellum volume (cm^3)	
			range	mean±SD	range	mean±SD	range	mean±SD
1	3m~11m	5	35.4~107.3	67.8±25.9	5.3~17.6	9.7±4.9	40.6~124.9	77.5±30.3
2	1~1.9y	5	78.4~109.3	91.5±16.1	9.9~17.6	13.2±3.1	91.7~126.6	104.7±17.2
3	2~3.9y	4	81.3~114.1	96.8±13.9	10.4~23.3	17.1±5.2	91.7~131.7	113.9±17.6
4	4-5.9y	18	74.4~113.0	93.9±10.3	12.8~28.7	19.6±4.9	91.8~139.7	113.6±12.2
5	6~8.9y	9	52.9~105.5	89.3±15.2	13.7~40.9	26.8±8.9	66.7~139.8	16.1±21.2
6	9~12y	9	70.1~109.1	92.4±16.8	16.1~34.1	23.4±6.1	86.2~138.1	115.8±19.9

m: month

SD: standard deviation

y: years old

Figure 1

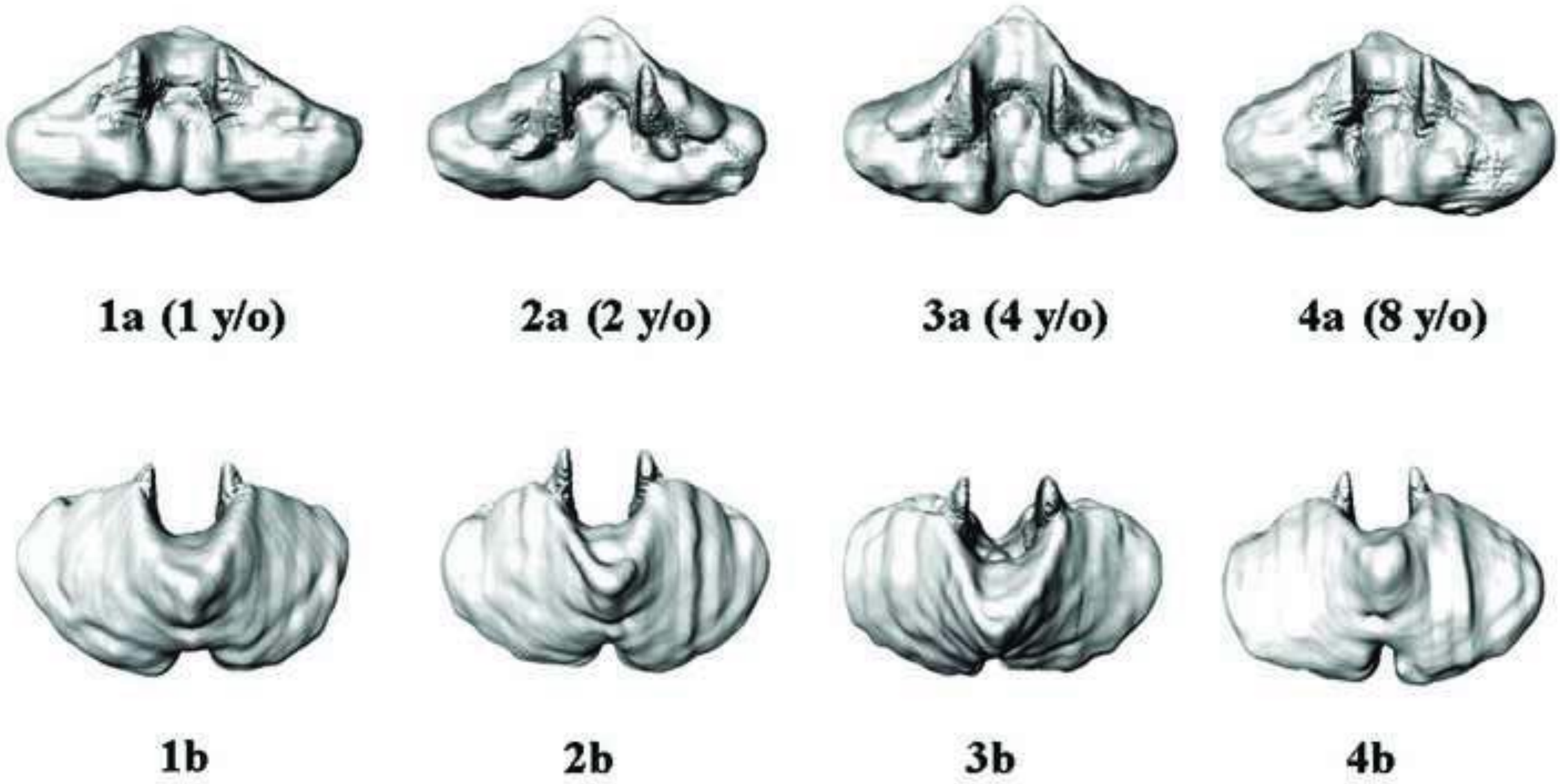

Figure 2
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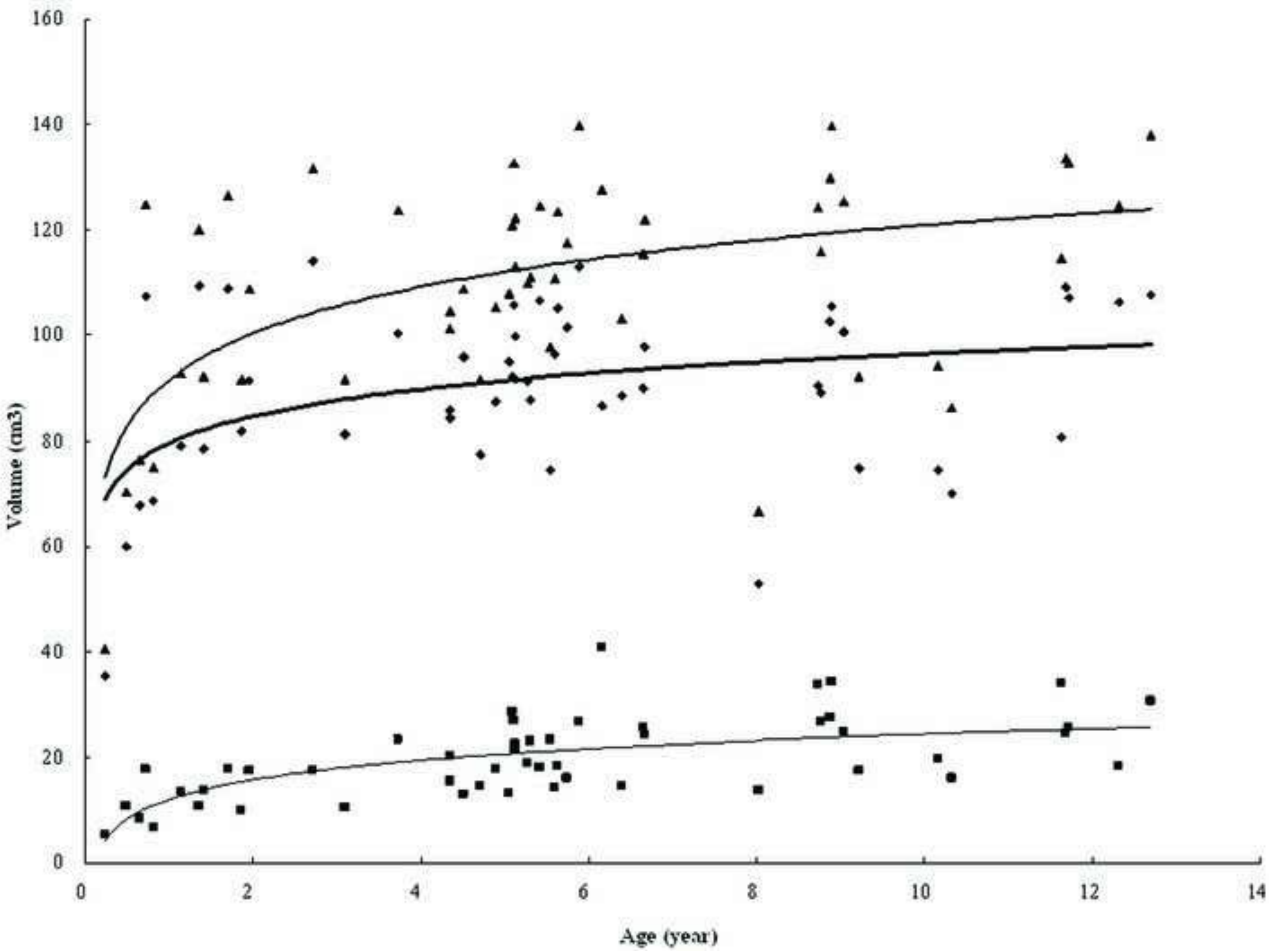

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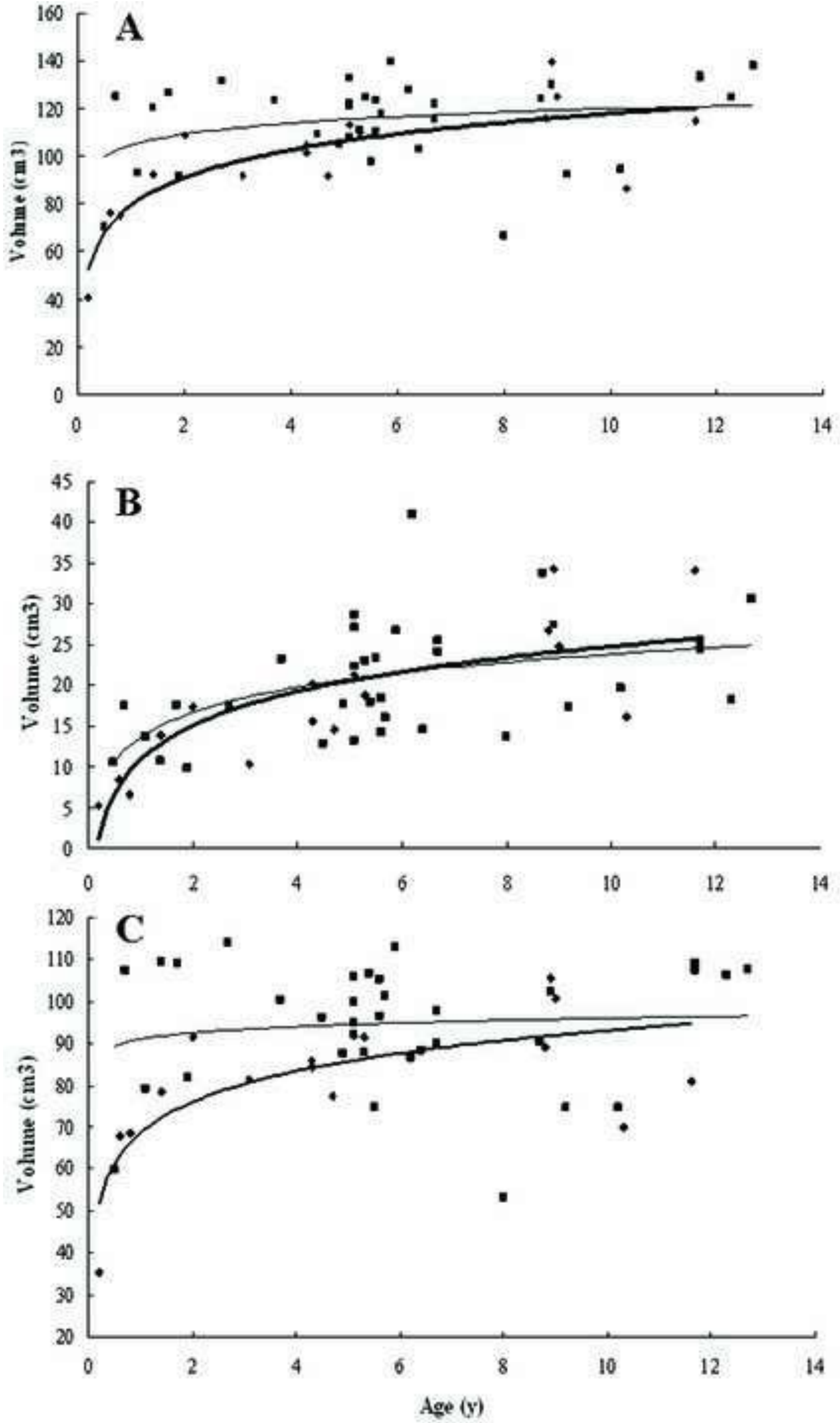

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