

A retrospective cross-sectional study of delayed closure of anterior fontanelle in healthy infants and its associated factors

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Research

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Abstract

Background: Anterior fontanelle (AF) is a regular feature of developing infants, and its delayed closure (AFDC) is highly valued in clinical child healthcare.

Methods: A retrospective cross-sectional study was conducted with a 3-year follow-up to understand the occurrence of AFDC in healthy infants and its associated factors.

Results: 61 out of 792 infants examined had AFDC, resulting in an incidence rate of 7.71% of AFDC in healthy infants. 92.29% of infants were found to have experienced AF closure by the age of 24 months, while up to 99.87% of them achieved closure before 36 months. From the age of 1 month to 36 months, the median AF size of the AFDC group was significantly larger than that of the normal closure (AFNC) group. Between 6 and 36 months, the median weight as well as length/height of the AFDC infants were both lower than those of their counterparts. Additionally, there indicated no difference in head circumference between two groups. Several factors were associated with AFDC in healthy infants, which were heavier birth weight ($OR=1.001$), longer birth length ($OR=0.778$), larger AF size at 1 month ($OR=4.196$), and being male ($OR=1.851$).

Conclusion: AFDC in healthy infants was considered within a normal range for AF development and thus not pathological in this case. AF development was correlated to infant weight as well as length/height, but had no significant relationship with head circumference. Congenital factors such as birth weight, birth length, AF size at birth, and gender were found associated with AFDC in healthy infants.

Brief Points

1. What is already known on this topic?

- Delayed closure of anterior fontanelle (AFDC) may indicate some pathology, however, pediatricians found that some infants with AFDC had healthy growth and a normal developmental trajectory, which indicates that there may be a subset of AFDC infants who are normal variants of those children with healthy AF closure and who do not have any dysmorphic features and/or other pathological clinical signs. Currently, we have no understanding regarding the proportion of this subset of infants and the causes behind this subset.
- More than 90% of children have AF closure before 24 months, but most previous research stopped at the age of 24 months when observing AF development in children.
- AF development may be related with weight, height or length, head circumference development.

2. What this paper adds?

- The incidence rate of AFDC in healthy infants was 7.71%, which was determined to be within a normal range for AF development and not related to any diseases. And we determined that factors related to AFDC in healthy infants included the following congenital factors: AF size at birth, heavier weight, longer length, and being male.
- By the age of 24 months, 92.29% of infants had AF closure, with 99.87% achieving closure before 36 months old.
- AF development was significantly correlated to weight, length and height, but not to head circumference.

Introduction

Anterior fontanelle (AF) lies between the frontal and parietal bones of the skull and is normally described as “a curved rhomboid, nonmineralized fibrous membrane in the cranial vault at the convergence of the coronal, sagittal, and metopic sutures in the developing infant [1]”. AF palpation during a pediatric physical examination is necessary, as its size, shape, and state of closure may indicate underlying pathologies [2-5]. For instance, a relatively large AF in diameter may suggest diseases such as osteogenesis imperfecta, elevated intracranial pressure, achondroplasia, congenital hypothyroidism, or other skeletal- or growth-related anomalies [2,3]. Contrarily, a small AF in diameter or an early fontanel closure may indicate craniosynostosis, hyperthyroidism, microcephalia, or other aberrant cerebral development diseases [4]. Delayed closure of the anterior fontanelle (AFDC) are believed to reflect elevated intracranial pressure, congenital hypothyroidism, achondroplasia, Down syndrome, Apert’s syndrome, rickets, dermoid cyst, etc. [5].

Current pediatric textbooks have not agreed on a same definition for AFDC, most of which only state that AF should be closed at 1-1.5 years old and no later than 2 years of age [4]. There are few studies related to AFDC, resulting in a notable lack of epidemiological investigations and analysis of relevant factors. However, in the course of standard pediatric care, pediatricians have found that there exist some AFDC infants with healthy growth following a normal developmental trajectory [6]. This may indicate that a proportion of AFDC infants are simply variants within normal range of those with undelayed fontanel closure and therefore do not suffer from any dysmorphic features, nor are there any other pathological signs [7]. Due to the fact that there is no clear understanding regarding these healthy AFDC infants and the underlying factors of their proportion, a 3-year retrospective cross-sectional study was conducted to investigate the occurrence rate and explore associated factors of AFDC in healthy infants.

Methods

Study Design

This study was a retrospective cross-sectional study. All infants included were born between January 1, 2015 and December 31, 2015 and were followed for three years in the Child Health Department of the West China Second Hospital at Sichuan University. Exclusion criteria were as follows: (1) Imaging examination during maternal pregnancy indicating abnormal brain development, such as hydrocephalus; (2) Head injury or scalp hematoma at birth which

may affect the measurement of AF and head circumference; (3) Intracranial diseases such as pituitary tumors; (4) Skeletal metabolic disease such as rickets; (5) Endocrine disease affecting growth and development, such as congenital hypothyroidism; (6) Other serious diseases affecting growth and development, such as malignant tumors; (7) Missing or incomplete data.

In the study, infants of the AFDC group was defined as those with AF closure after 24 months in concordance to previous studies [7-9], while all others with AF closure earlier than 24 months were placed in the AFNC group.

Ultimately, a total of 792 infants were enrolled, including 731 with AFNC and 61 with AFDC. All information of the subjects were extracted from the Child Health Electronic Information System of West China Second Hospital at Sichuan University, including physical growth and development data, such as infants' weight, length (<36 months)/height (\geq 36 months), head circumference and AF size at various ages (0, 1, 6, 12, 18, 24, 30, and 36 months), as well as perinatal and nutritional information such as gender of infant, delivery mode, gestational age, fetus numbers, maternal gravidity and parity, VA and VD average supplement before 2 years old, and the time of introducing complementary food.

Analysis and Ethical Consideration

SPSS 22.0 statistical software was used to analyze statistical data. Numbers and percentages were used to describe the trend in AF closure across all infants. When comparing the AFNC and AFDC groups with regards to physical growth and development, a Shapiro-Wilk test was used for normal statistical analysis; a Mann-Whitney *U* test was used to detect the difference between two groups. Chi-Squared and Mann-Whitney *U* tests were both used for univariate analysis to explore significant variables associated with AFDC in healthy infants. A binary logistic regression was also conducted for multivariate analysis, where categorical variables were processed as dummy variables and continuous variables as original values. A *p*-value \leq 0.05 was considered statistically significant.

Ethical approval was obtained from the Ethics Committee of the West China Second Hospital at Sichuan University. All information used in the study will remain confidential and be used only for the purposes of the scientific work presented here.

Results

AFDC occurrence in healthy infants

The incidence rate of AFDC in healthy infants was calculated as 7.71% with 61 out of 792 infants having AFDC. Over 50% infants (420 out of 792) experienced AF closure from 12-18 months old (Table 1); by the age of 24 months, up to 92.29% of infants had achieved closure, and by 36 months, the percentage had reached 99.87% (Figure 1).

Difference in physical growth and development between AFNC and AFDC

Here, a significant difference in AF size was found between the AFNC group and their counterparts from the age of 1 to 36 months, as can be seen from Table 2 that Median AF size in the AFDC group was always notably larger than that in the AFNC group across all ages. Median weight and length of the AFDC infants were both significantly lower than those of the AFNC group beyond 6 months. However, no remarkable difference was discovered in head circumference between the two groups (Table 2).

Associated factors in AFDC in healthy infants

The univariate analysis revealed that birth weight ($\chi^2=21.218$, $p<0.001$) and gestational age ($\chi^2=5.262$, $p=0.022$) were both significantly associated with AFDC (Table 3). Results from the binary logistic regression suggested that heavier birth weight ($OR=1.001$, $p=0.002$), longer birth length ($OR=0.778$, $p=0.005$), larger AF size at the age of 1 month ($OR=4.196$, $p<0.001$), and being male ($OR=1.851$, $p=0.033$) were all associated with AFDC in normal infants (Table 4).

Discussion

A large majority of infants in this study (92.29%) achieved AF closure before the age of 24 months. Similar results were found in a study conducted by Liu *et al.* based on a cross-sectional survey of 104,147 children from 9 urban cities in China [10], who reported 94.2% with AF closure before 24 months. In another study by Kiesler *et al.* [3], the percentage was found to be approximately 96%. The differences may be explained by ethnic divergence. Unlike most of the previous relevant studies, our research extended the observation beyond 24 months, and showed that 99.87% of infants achieved AF closure before 36 months, which may help fill this gap in understanding AF development. The AFDC incidence rate of 7.71% in healthy infants is consistent with results from several other studies ranging from 4% to 7% [8,10,11], where the infants were reported to experience AF closure after 24 months, and some even beyond 36 months. As the AFDC infants in this study were considered healthy and within normal ranges for physical growth and development, it is concluded that this proportion of infants can be interpreted as normal variants within AF development and not related to any diseases.

The significantly larger AF size of AFDC infants found in our study indicated that AFDC in normal infants was related to congenital AF enlargement. Larger birth AF size, given normal brain development and skull osteogenesis, suggested longer time needed for full AF closure. Infants' AF development is possibly correlated to weight and length/height development but not related to head circumference, which is in agreement with conclusions from Liu *et al.* [10], who also found no correlation between the time of AF closure and head circumference. However, Kumar *et al.* [12] and Oumer *et al.* [13] reported that AF size was only significantly related to newborn weight, and according to Wu Ting *et al.* [9] none of height, weight or head circumference has any relationship with AF size. As for the lack of a correlation between AF development and head circumference, it was probably due to the existence of the bone seams in the infant

skull, which are connected by elastic, membranous fiber tissue. With the continuous ossification and maturation of the skull, the AF gradually closes, but the bone seams are still able to expand to provide the space for brain development, which leads to a continually increasing head circumference regardless of when the AF closes[4,10].

Finally, our results showed that heavier birth weight, longer birth length, larger congenital AF size, and being male were associated with AFDC. Previous studies by Roy *et al.* confirmed that AF size at birth was correlated to birth weight [14]. Additionally, Perera *et al.* also reported significant relationship between AF size and birth length [15], which is suggested to be related to maternal nutritional status during pregnancy. If the mother was able to provide sufficient nutrition in the late period of pregnancy, which means sufficient reserves of minerals and trace elements (e.g., calcium and phosphorus) for the developing fetus, the likelihood for AFDC will be lowered. As for the influence of gender, results in our study is in line with Oumer *et al.*, who found that AF size of male infants was larger than that of their female counterparts [13]. Interestingly, we found both Vitamin A and D supplements, as well as the time of introducing complementary food were not associated with AFDC. The hypothesis for this is that our research was conducted in an economically developed city in China, where parents hardly had any financial problems providing their infants with enough vitamin supplements and balanced diets. Given the conclusion here that there was no significant difference between AFDC group and AFNC group in terms of nutrition and diets, it's also highly suggested that a diagnosis of AFDC should also be combined with an assessment of clinical symptoms and a biochemical examination, and large doses of vitamin D should not be blindly preferred in the treatment since AFDC is not necessarily caused by nutritious factors.

Admittedly, there are some limitations to this study. Being a single-center study as it is, the study was likely not to be sufficiently representative and may have introduced certain selection bias. Besides, as this was also a retrospective study, it is limited in both sample size and data types; given this, it would be advisable that a case-control study of AFDC should be conducted in the future.

Conclusion

This study presented a retrospective cross-sectional analysis of delayed closure of the anterior fontanelle (AFDC) in healthy infants with a 3-year follow-up. The results showed the incidence rate of AFDC in healthy infants was 7.71%, which was considered to be within a normal range for AF development and thus not related to any diseases. AF development was significantly related to infants' weight and length/height, but not to head circumference. Heavier birth weight, longer birth length, larger AF size at birth, and being male were all significantly associated with AFDC in healthy infants.

Abbreviations

AF: Anterior Fontanelle

AFDC: Anterior Fontanelle Delayed Closure

AFNC: Anterior Fontanelle Normal Closure

Declarations

1. Ethical Approval and Consent to participate

Ethical approval was obtained from the Ethics Committee of the West China Second Hospital at Sichuan University. All information used in the study will remain confidential and be used only for the purposes of the scientific work presented here.

2. Consent for publication

All authors gave final approval of the version to be published, and agree to be accountable for all aspects of the work.

3. Availability of data and materials

Not applicable

4. Competing interests

We declare that we have no competing interests.

5. Funding

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6. Authors' contributions

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Tables

Table 1
the closure time of AF(N = 792)

Month	Numbers of closed	Closed	Unclosed	Percentage of AF closure
0-6	2	2	790	0.25%
6-12	105	107	685	13.51%
12-18	420	527	265	66.54%
18-24	204	731	61	92.29%
24-30	56	787	5	99.49%
30-36	4	791	1	99.87%
AF, anterior fontanelle				

Table 2
The comparison of physical growth and development in AFNC and AFDC infants(N = 792)

Month	Anterior Fontanelle			Weight			Height			Head Circumfe
	AFNC (n = 731) M(min,max)	AFDC (n = 61) M(min,max)	Z	AFNC (n = 731) M(min,max)	AFDC (n = 61) M(min,max)	Z	AFNC (n = 731) M(min,max)	AFDC (n = 61) M(min,max)	Z	
0				3.19 (1.16, 5.25)	3.14 (1.59, 4.67)	-0.617	49.36 (32.00, 55.00)	48.53 (36.00, 54.00)	-2.149*	
1	1.45 (0.50, 3.50)	1.73 (1.00, 3.50)	-5.711*	4.25 (1.50, 6.50)	4.04 (1.82, 5.40)	-1.385	54.34 (41.00, 61.00)	53.37 (45.00, 58.50)	-1.671	37.11(30.20,40)
6	1.42 (0.00, 3.50)	1.58 (0.20, 3.50)	-3.988*	7.96 (3.20, 11.30)	7.69 (6.30, 10.10)	-2.039*	67.44 (53.00, 74.50)	66.20 (61.50, 73.00)	-2.896*	43.49 (35.80, 47.20)
12	0.53 (0.00, 3.00)	1.10 (0.20, 3.00)	-6.945*	9.58 (4.10, 13.43)	9.33 (7.20, 11.10)	-2.083*	75.59 (60.00, 84.00)	74.68 (69.00, 80.00)	-2.541*	46.31 (38.00, 52.70)
18	0.04 (0.00, 2.50)	0.55 (0.20, 2.50)	-12.470*	10.82 (4.95, 15.20)	10.20 (8.40, 13.00)	-2.894*	82.38 (65.00, 91.50)	81.00 (74.50, 88.00)	-3.314*	47.67 (39.30, 53.30)
24	0.00 (0.00, 0.00)	0.44 (0.10, 1.30)	-28.097*	12.01 (5.70, 16.90)	11.35 (9.60, 13.65)	-3.145*	88.11 (70.50, 97.50)	86.75 (79.80, 93.00)	-3.473*	48.60 (40.50, 53.60)
30	0.00 (0.00, 0.00)	0.01 (0.00, 1.00)	-7.760*	13.12 (6.40, 18.50)	12.50 (10.40, 15.10)	-3.218*	93.00 (73.00, 102.90)	91.34 (83.00, 99.00)	-3.430*	49.19 (40.70, 54.40)
36	0.00 (0.00, 0.00)	0.01 (0.00, 0.80)	-3.462*	14.23 (6.90, 21.10)	13.60 (11.10, 16.20)	-3.809*	96.20 (78.00, 107.60)	94.20 (85.70, 102.30)	-4.237*	49.79 (41.80, 54.70)

AFNC, anterior fontanelle normal closure /AFDC, anterior fontanelle delayed closure;Mann-Whitney U test; *,P<0.05

Table 3
The univariate analysis of perinatal and nutritional information(N = 792)

item	category		χ^2/Z	P
	AFNC (n = 731) %	AFDC (n = 61)		
birth weight (g)				
<2500 (%)	95(13.0)	16(26.2)	21.218 ^a	<0.001*
2500 ~ 4000 (%)	608(83.2)	37(60.7)		
>4000 (%)	28(3.8)	8(13.1)		
birth length (cm)				
<48 (%)	158(21.6)	21(34.3)	5.289 ^a	0.071
48 ~ 52 (%)	546(74.7)	38(62.3)		
>52 (%)	27(3.7)	2(3.3)		
gender				
Male (%)	422(57.7)	28(45.9)	3.210 ^a	0.081
Female (%)	309(42.3)	33(54.1)		
delivery				
vaginal delivery (%)	154(21.1)	14(23.0)	0.120 ^a	0.745
cesarean delivery (%)	577(78.9)	47(77.0)		
gestational age				
premature (%)	110(15.0)	16(26.2)	5.262 ^a	0.022*
Mature (%)	621(85.0)	45(73.8)		
fetus numbers				
1 (%)	690(94.4)	56(91.8)	0.689 ^a	0.390
≥ 1 (%)	41(5.6)	5(8.2)		
gravidity				
≤ 3 (%)	700(95.8)	60(98.4)	0.983 ^a	0.504
>3 (%)	31(4.2)	1(1.6)		
parity				
1 (%)	654(89.5)	54(88.5)	0.053 ^a	0.828
>1 (%)	77(10.5)	7(11.5)		
VA average before 2y (IU)	1602.3	1501.7	-1.604 ^b	0.109
VD average before 2y (IU)	545.3	538.1	-1.177 ^b	0.239
The time of introducing complementary food (months)	8.02	6.40	-0.384 ^b	0.701
AFNC, anterior fontanelle normal closure /AFDC, anterior fontanelle delayed closure				
VA-Vitamin A, VD-Vitamin				
^a , χ^2 test; ^b , Mann-Whitney U test; *, P<0.05				

Table 4
The logistic regression of associated factors of AFDC(N = 792)

variables	BETA	SE	Wald χ^2	P	OR(95% CI)
birth weight	0.001	0.000	10.006	0.002*	1.001(1.001, 1.002)
birth length	-0.251	0.090	7.811	0.005*	0.778(0.653, 0.928)
AF size in 1 m	1.434	0.247	33.692	<0.001*	4.196(2.585, 6.810)
gender	0.616	0.288	4.571	0.033*	1.851(1.053, 3.255)
delivery	-0.094	0.342	0.076	0.783	0.910(0.466, 1.779)
gestational age	-0.588	0.525	1.256	0.262	0.555(0.198, 1.779)
fetus numbers	0.464	0.576	0.648	0.421	1.590(0.514, 4.921)
gravity	-1.160	1.071	1.174	0.279	0.313(0.038, 2.556)
parity	0.528	0.451	1.367	0.242	1.695(0.700, 4.106)
VA average before 2y	-0.001	0.001	1.870	0.172	0.999(0.998, 1.000)
VD average before 2y	-0.001	0.002	0.006	0.936	1.000(0.996, 1.004)
the time of introducing complementary food	-0.071	0.113	0.397	0.529	0.931(0.747, 1.162)
Regression Equation	$\chi^2 = 7.884$, df = 8, $R^2 = 0.171$				
AFDC, anterior fontanelle delayed closure;VA-Vitamin A,VD-Vitamin D binary logistic regression; *,P<0.05					

Figures

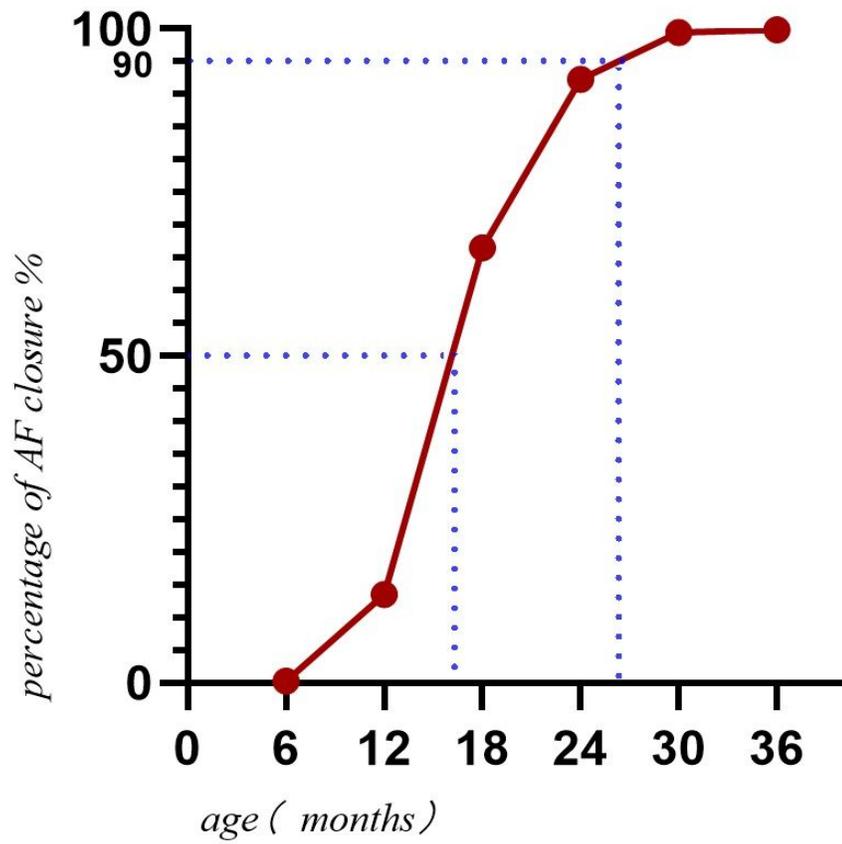


Fig.1 the trend of AF clousure ($N=792$)

Figure 1

Figure 1