

Adducted thumb as an isolated morphologic finding: an early sonographic sign of impaired neurodevelopment

A STROBE compliant study

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Abstract

Fetal adducted thumbs have been described in association with hydrocephalus and other abnormalities, but in cases without other structural malformations the determination of prognosis and recurrence risk is challenging. The aim of our study is to analyze the characteristics, natural history, and postnatal outcome of such cases.

A retrospective study was conducted over a period of 4 years in a tertiary referral center. All fetuses diagnosed as adducted thumbs without other structural malformations comprised the study group. Prenatal sonographic features and neonatal outcome are documented.

There were 4 cases of fetal adducted thumbs diagnosed during the study period. No cases demonstrated other structural malformations throughout the gestation. A smaller head was noted in 2 cases during the follow-up, and all cases presented with polyhydramnios on the first or ensuing scans. Three cases died after birth due to swallowing or breathing difficulty, and the surviving 1 showed convulsion and mental retardation.

Fetal adducted thumb might be an early and specific sonographic marker of impaired neurodevelopment. Close follow-up and genetic investigation should be performed in these cases. Ultrasound examination plays an important role in the prenatal diagnosis and counseling of cases without detailed prenatal genetic analysis.

Abbreviations: CNV = copy number variation, CNS = central nervous system, MASA spectrum = mental retardation-aphasia-shuffling gait-adducted thumbs, MRI = magnetic resonance imaging.

Keywords: adducted thumb, fetal, isolated, neurodevelopment, ultrasonography

1. Introduction

Adducted thumb refers to persistent adduction and flexion of the thumb beyond 4 months after birth, which is an uncommon congenital malformation with heterogeneous etiology.^[1] A majority of postnatal cases occurred in association with other abnormalities.^[2] Prenatal adducted thumbs have been described in X-linked hydrocephalus, MASA spectrum (mental retardation-aphasia-shuffling gait-adducted thumbs) or in association with severe anomalies.^[3–6] Nevertheless, there has been scarce information on the prenatal identification and counseling of adducted thumbs without other structural abnormalities. In addition, 27 genetic syndromes were reported in which adducted

thumbs serve as a presenting symptom, but genetic investigation in the prenatal setting might not be comparable in the depth with that after birth. Therefore, our aim in this study was to describe the prenatal characteristics, natural history, and outcome of this unusual finding, and to analyze the sonographic signs related with the prognosis.

2. Materials and methods

This was a retrospective study performed at a tertiary referral center for prenatal diagnosis and management, approved by the local Medical Ethical Committee of Peking Union Medical College Hospital. The study period was February 2013–December 2017.

Fetal ultrasound examinations included a detailed extracardiac structural survey and a complete echocardiographic examination, which were done with Voluson E8 and E10 ultrasound machine (General Electric Kretztechnik, Zipf, Austria). Prenatal diagnosis of adducted thumbs was made on the basis that thumbs were folded under the other fingers in a persistent adduction and flexion posture, the tip of thumb stretched beyond the midline of the palm, but the remaining 4 fingers had spontaneous movement. During each examination, the hands were examined for at least 5 minutes. For each suspected case, information gathered includes: maternal age, reason for referral, family history, gestational age at diagnosis, fetal biometry, posture of hands and feet, and associated anomalies. All the parents received detailed counseling after ultrasound scans, and genetic analysis was offered with parental consent. Postnatal follow-up was available for all the surviving cases.

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3. Results

There were 4 cases of fetal adducted thumbs diagnosed during the study period, including 2 males and 2 females. The family and medical history were unremarkable except that 1 mother has delivered a boy with cleft lip and palate. All cases demonstrated fixed adduction of thumbs during the first scan (Fig. 1), but no other structural malformations were detected. A smaller head was noted in 2 cases (Table 1, cases 1 and 2) during the follow-up, and all the cases presented with polyhydramnios on the first or ensuing scans. After detailed counseling and explanation, all the parents declined cordocentesis, and chose to continue the pregnancy until delivery. Brain magnetic resonance imaging was performed in case 1 at 6 months and showed delayed myelination. Postnatal genome-wide copy number variation (CNV) analysis was performed in case 1 and case 2, and a duplication of 17.935 kb in 3p25.3 was revealed in the latter. Three patients (Table 1, cases 2–4) died after birth due to swallowing or breathing difficulty; intermittent convulsion and mental retardation were observed in the surviving patient (Table 1, case 1).

4. Discussion

Fetal adducted thumb refers to a thumb in a persistent adduction and flexion posture with its tip stretching beyond the midline of the palm. Under this circumstance, spontaneous movement could be observed in the remaining 4 fingers, which makes adducted thumb an unusual sonographic finding different from the clenched hand. Currently, the examination of fetal hands has been recommended in the 2nd and the 3rd trimesters, but the evaluation of fingers is not yet integrated into fetal anatomical survey. Adducted thumb is one of the finger anomalies which is clinically important, because it is not only indicating the upper motor neuron injury (cortex thumb)^[7] but also is related with a series of major malformations and genetic syndromes.^[1–3] In a review of 25 postnatal cases,^[2] only 3 (12%) presented as an isolated finding, and the remaining 22 (88%) displayed other abnormalities resulting in unfavorable prognosis, including developmental delay, epilepsy, aphasia, and spastic paraplegia. Therefore, when adducted thumbs are detected in utero, it is warranted that fetal neurodevelopment be evaluated and clinical signs indicating central nervous system (CNS) abnormalities be carefully searched. Since fetal neurodevelopment could not be evaluated as thoroughly as that after birth, and some central nervous system malformations might be progressive in utero, it seems to be a great challenge to decide the prognosis of fetal adducted thumbs when it is an isolated morphologic finding. Under this circumstance, our findings may have important clinical implications.

Our cohort of cases shared the ultrasound findings of fixed adduction of thumbs and polyhydramnios. When other conditions leading to polyhydramnios such as micrognathia and esophageal atresia were excluded, the excessive amniotic fluid could be a clue to fetal swallowing difficulty. In case 2, mild polyhydramnios appeared at 22 weeks and increased continuously during the following scans, and the baby manifested as a severe swallowing difficulty at birth and has been alive for 2 months. In case 3 and case 4, severe polyhydramnios was detected at 32 weeks, both babies showed swallowing or breathing difficulty at birth, and have lived not more than 1 month. On the contrary, in case 1, the fluid was normal at 22 weeks, mild polyhydramnios appeared at 28 weeks but resolved after 3 weeks, and this is the only surviving case in our cohort.



Figure 1. Case 1. (A) Two-dimensional ultrasound shows adducted thumb at 24 weeks. (B) Surface-rendered 3-dimensional ultrasound view shows adducted thumb. (C) Picture of the newborn infant shows adducted thumb.

Besides, we observed a decreased head circumference in case 1 and case 2, which might originate from the delayed neurodevelopment. In case 1, it was not apparent until 28 weeks, but in case 2, it presented as an early onset at 22 weeks, which was progressive throughout the gestation and showed a much worse prognosis. Taking all these clinical features into account, we postulate that in the cases of adducted thumbs, polyhydramnios, and decreased head circumference have an underlying association with the developmental defect or damage of CNS. Therefore,

Table 1**Clinical features and follow-up in 4 cases of fetal adducted thumbs.**

Case no.	1	2	3	4
Family history	Cleft lip and palate, male	–	–	–
Gender	Female	Male	Male	Female
Gestational age (wk) at referral	21	22	32	32
US findings during referral	Adducted thumbs	Adducted thumbs; BPD = 5.8%, HC < 2.3%; polyhydramnios (DP 8.0 cm)	Adducted thumbs; polyhydramnios (DP 12.7 cm)	Adducted thumbs; polyhydramnios (DP 13.7 cm)
Other signs during follow-up	28 wk: BPD = 19.1%, HC = 2.3%; polyhydramnios (DP 8.1 cm) 31 wk: BPD = 11.8%, HC < 2.3%	25 wk: BPD < 2.3%, HC < 2.3%; polyhydramnios (DP 8.5 cm) 31 wk: BPD/HC: 2 SD below the mean polyhydramnios (DP 13.2 cm)	–	–
Brain imaging	Delayed myelinization on MRI (6 mo)	–	–	–
Genetic analysis	Negative	A duplication of 17.935 kb in 3p25.3	–	–
Outcome	Mental retardation, intermittent convulsion (3 y, 5 mo)	swallowing difficulty, intermittent convulsion, death at 2 mo	Swallowing difficulty, death at 22 d	Breathing difficulty, death at birth

BPD = biparietal diameter, d = days, DP = deepest pocket, HC = head circumference, mo = months, MRI = magnetic resonance imaging, wk = week, y = years.

these signs need to be carefully searched and followed up, especially when they are not apparent in an earlier gestation.

According to the literature, a majority of fetal adducted thumbs (8/11) were diagnosed in concomitant with hydrocephalus or other anomalies such as duodenal atresia, dysplastic corpus callosum, and ductus venosus agenesis,^[3–6] and it was claimed by some authors that isolated cases seemed to have a favorable prognosis.^[6] On the contrary, our cases did not present other structural malformations but showed CNS abnormalities and unfavorable prognosis after birth. Therefore, we tend to regard prenatal adducted thumbs as a specific pathologic sign indicating intrauterine damage or delayed neurodevelopment, and we recommend a close follow-up in cases of persistent adducted thumbs to determine if there are other sonographic signs related with CNS involvement. If excessive amniotic fluid or decreased head circumference exists, the chance of unfavorable prognosis should be considered. In addition, since some malformations are not easy to detect in utero, a detailed evaluation of CNS after birth should be considered in the isolated cases.

Genetic causes of adducted thumb include single gene defects, cytogenetic abnormalities, and a number of neuromuscular and metabolic disorders,^[2] and it could be a clinical clue to different genetic syndromes, for example, distal arthrogyriposis type I, whistling-face syndrome, ulnar drift syndrome, X-linked hydrocephalus, and MASA syndrome.^[1,8–11] In postnatal cases of adducted thumbs, various cytogenetic abnormalities have been observed, and it was recommended that mutational analysis of *LICAM* gene be performed in cases with hydrocephalus, and genome-wide CNV analysis be performed in every patient without directly recognized syndromes.^[2] Among the 11 cases of fetal adducted thumbs, genetic evaluation was performed in 10 cases, revealing *LICAM* mutations in 2 cases with severe hydrocephalus.^[3] As for our cases, genetic analysis was only approved in case 1 and case 2, and a duplication of 17.935 kb in 3p25.3 was detected in the latter. Although no further cytogenetic

and molecular analyses were assigned to the baby and its parents, we speculate that this duplication might cause a positional effect on the *CALL* gene on 3p26 and a *CALL* gene defect might lead to adducted thumbs, intellectual disability, relative microcephaly, and seizures. In our opinion, genetic analysis such as karyotyping, chromosomal microarray, and whole exome sequencing should be recommended in each prenatal case, not only for an extensive genetic counseling for the family, but also for an accurate definition of this disorder at the molecular level. In addition, female carriers of *LICAM* gene mutation may manifest as mild features like isolated adducted thumbs, thus mutation analysis of this gene should be performed in all female fetuses. The limitation of our study is that it was conducted on a time interval of 4 years and molecular genetic investigation has not been widely applied in China until recently.

In summary, our study demonstrates that adducted thumbs might indicate the maldevelopment of fetal CNS and therefore examination of the fetal hands and fingers should be integrated into fetal anomaly scans. All prenatal cases should be followed closely by ultrasound to rule out the signs related with CNS involvement, especially in the cases without genetic investigation.

Author contributions

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