Follow-up of isolated congenital complete atrioventricular block with longitudinal measurements of serum NT-proBNP and cardiothoracic ratio

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Abstract
There are a few children with isolated congenital complete atrioventricular block (ICCAVB) who do not require a pacemaker. We report a female infant born at 36 weeks by emergency cesarean section because of fetal heart rate abnormalities who was diagnosed as having ICCAVB. In accordance with the echocardiographic findings, we simultaneously measured the cardiothoracic ratio (CTR) by chest radiography and serum N-terminal pro-BNP (NT-proBNP) and have continued to follow her as an outpatient for about 8 years. CTR and NT-proBNP showed strong positive correlation ($r=0.894$, $p<0.05$). In such few children with ICCAVB as this patient, CTR measurement during their follow-up would be very useful to easily understand their cardiac load status.

Key words: cardiothoracic ratio, congenital complete atrioventricular block, follow up, heart failure, NT-proBNP

Introduction
The cardiac ventricles are the main site of brain natriuretic peptide (BNP) synthesis, and they release it in response to volume (increased wall stress) or pressure (ventricular filling pressure) loading. ProBNP, the inactive precursor, is cleaved into BNP, the active component, and N-terminal pro-BNP (NT-proBNP), an inactive by-product. Plasma concentrations of BNP correspond well with echocardiographic findings of ventricular strain. Plasma NT-proBNP is very high during the first few days of life in healthy neonates, decreases rapidly until the end of the first week of life, and then decreases slowly until the end of the neonatal period. Among patients with bradyarrhythmia, there are few reports of plasma NT-proBNP increasing in proportion to the aggravation of atrioventricular asynchrony. Congenital complete atrioventricular block (CCAVB) occurs in one out of 14,000 to 20,000 live births, most commonly after damage to the normal structure of the fetal heart by maternal autoantibodies against ribonucleoproteins (anti-Ro/SSA, anti-La/SSB). Although the characteristics of fetal and maternal antibody-associated AVB have largely been clarified, the clinical course of isolated, non-immune AVB (ICCAVB) diagnosed in utero, at birth or thereafter remains obscure.

To our knowledge, there are no reports on the natural course of ICCAVB accompanied by serial changes of plasma NT-proBNP. We present a female preterm infant with ICCAVB in whom changes of plasma NT-proBNP were measured serially along with the cardiothoracic ratio (CTR) soon after birth. This is the first report on combined use of CTR and NT-proBNP in the follow-up of ICCAVB.

Case Report
The healthy, asymptomatic 30-year-old mother...
was referred to a domestic gynecological clinic at 36 weeks of gestation for a regular pregnancy check. Fetal echocardiography revealed a structurally normal heart with a ventricular rate of 65-70 beats/min and no pericardial effusion. A female baby (weight, 2,300 g; length, 46.0 cm) was born by emergency cesarean section on the same day after the diagnosis of fetal distress. Electrocardiography revealed CCAVB with an atrial rate 150 beats/min and ventricular rate of 70-75 beats/min. Laboratory blood examinations of mother and baby were negative for antinuclear antibody. The baby was transferred to our NICU for evaluation of her arrhythmia and treatment. As a late preterm infant, she showed only mild respiratory distress and no signs of heart failure, and oral feeding progressed smoothly. She was ultimately discharged on day 62 with no serious complications (weight, 3,111 g; length, 52.1 cm). This girl has remained in CAVB with an atrial rate 115-125 beats/min and a ventricular rate of 50-55 beats/min up to the time of her last examination at the age of 8 years (Fig. 1). She has never complained of inconvenience in her elementary school life and participates in physical education classes as much as she can. Written informed consent was obtained from the patient’s parents to publish this case report.

In accordance with her echocardiographic findings, the transition of her CTR by chest radiography and serum NT-proBNP by blood examination has been followed from birth to her current age of 8 years. Her serum NT-proBNP was 6,285 pg/mL at birth but had sharply increased to a maximum of 45,146 pg/mL at 1 month of age. It then decreased, but not to within the reference interval, and its value has remained high at each measurement. Thus far, it has been observed at four time points that her CTR has characteristically increased once and then decreased: from the age of 8 months to 10 months, around 2 years old, from 3 to 5 years old, and from 6 to 7 years old. NT-proBNP also showed a trend almost parallel to that of CTR (Fig. 2a). As a result, it was confirmed that the two had a strong positive correlation ($r=0.894$, $p<0.05$) (Fig. 2b).

**Discussion**

To the best of our knowledge, studies of NT-proBNP in neonatal diseases have been reported as the serial changes of NT-proBNP in the pathologies of respiratory distress syndrome, transient tachypnea of the newborn, persistent ductus arteriosus, persistent pulmonary hypertension, bronchopulmonary dysplasia, and asphyxia. However, our patient had none of these diseases. The marked increase and subsequent decrease of NT-proBNP in the early postnatal period was considered to be due solely to her bradyarrhythmia. As a result, it has been possible to diagnose the status of this patient’s cardiac load induced by the ICCAVB on the basis of the temporal transition of NT-proBNP from the early postnatal age to her present age of 8 years.

Plasma NT-proBNP as a biochemical indicator and CTR as a physiological indicator were simultaneously measured, and their serial changes were followed to evaluate the degree of volume loading of the heart due to ICCAVB from the early postnatal period to the present. NT-proBNP was measured by electrochemiluminescence immunoassay and evaluated on a logarithmic scale. As a result, a strong positive correlation between these two factors was revealed throughout the observation period. Stroke volume in patients who develop solitary CCAVB will increase to compensate for a low heart rate. Volume loading of the left ventricle can occur in these patients, followed by heart failure, when the
Isolated CCAVB follow-up by NT-proBNP and CTR

Heart can no longer bear the volume load. Echocardiographic parameters such as left ventricular diastolic internal diameter and end-systolic wall stress are better physiological indicators, but they must be evaluated in comparison with reference intervals from healthy children because they gradually increase year by year. In contrast, CTR is a physical ratio unique to each child and has the advantage of being easy to evaluate. As one of the most basic and standard examinations, CTR on chest X-ray has been used as an index of cardiac enlargement. Unlike NT-proBNP, CTR is not influenced by renal function. CTR increases with cardiac hypertrophy, but it can also be influenced by other factors such as extracellular volume and pulmonary diseases such as pulmonary hypertension.

At the aforementioned four periods, the transition of this patient’s CTR showed a temporary increase and decrease. NT-proBNP also tended to show similar changes paralleling the changes in CTR. As a result, CTR and NT-proBNP have shown a strong positive correlation throughout the 8 years since her birth. Babies begin to stand from crawling at 8 to 10 months, and the movement from walking to a bit of running is complete at around 2 years old. Children attend kindergarten at age 3 to 5, at which point they leave the family and increase their amount of exercise through varied play with other young children in their age group. After entering elementary school at 6 to 7 years old, they increase their amount of exercise even further. What is common to each of these periods is that each is a time of progression in which children need to exceed their previous amount of exercise and adapt to it. Our patient’s parents frequently described these changes in living conditions at regular outpatient visits, and as a result, we confirmed that our patient could adapt to the amount of exercise required at each new period in her life.

This patient has had no other complications of cardiovascular disease, so her CTR has been influenced only by volume loading due to bradyarrhythmia. Although a few children with ICCAVB like her also do not require a pacemaker, CTR measurement during their follow-up would be very useful to easily understand their cardiac load status.

**Author contributions**

T.N. designed the report, drafted the initial manuscript and prepared the figures. S.N. reviewed and revised the manuscript. Both authors read and approved the final manuscript.
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