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The Diagnostic Significance of Comorbidities of Congenital Heart Diseases, Low-Set Ears, and Intrauterine Growth Restriction in Neonates With Trisomies 13 and 18

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Abstract

Background: Trisomies 13 and 18 (T13/18) are autosomal trisomy syndromes with dismal prognoses. Deciding whether to perform a chromosomal analysis for the definitive diagnosis is often difficult (even for experienced pediatricians) because representative clinical signs may not be found in all T13/18 neonates.
Objectives: This study aimed to investigate any clinical signs that could be useful for screening for T13/18 in participants without the representative clinical signs traditionally found in odd-looking neonates with malformation syndromes.
Patients and Methods: We retrospectively analyzed 15 T13/18 patients, 33 trisomy 21 patients, and 48 controls with other malformation syndromes, for apparent clinical signs during the neonatal period. All participants had been admitted to the neonatal intensive care unit of Kansai Medical University over a nine-year period.
Results: The three leading clinical signs in patients with T13/18 were congenital heart diseases (CHD; 100%), low-set ears (LSE; 80%), and intrauterine growth restriction (IUGR; 73.3%). A comorbidity of these two leading non-specific clinical signs was CHD with LSE, which showed the highest diagnostic accuracy between T13/18 and controls with a sensitivity of 80.0% and a negative predictive value of 92.5%. The chi-square test among these three groups ($P < 0.01$) and multiple comparison tests of proportional differences showed that the comorbidity of CHD with LSE was specific for autosomal trisomy syndromes. A comorbidity of CHD with IUGR also revealed a similar diagnostic accuracy with a sensitivity of 73.3% and a negative predictive value of 90.9% as well as a specificity for T13/18.
Conclusions: The comorbidities of either CHD with LSE or CHD with IUGR should be suspected in neonates with autosomal trisomy syndromes, particularly T13/18 without the expected representative clinical signs.

Keywords: Comorbidity, Congenital Heart Diseases, Intrauterine Growth Restriction, Low-Set Ears, Neonate, Trisomy 13, Trisomy 18

1. Background

Trisomy 13 (T13), trisomy 18 (T18), and trisomy 21 (T21) are common autosomal trisomy syndromes (1). It is important to distinguish T13 and T18 (T13/18) from T21 and other malformation syndromes as soon as possible because T13/18 has a dismal prognosis; therefore, the option to terminate life-sustaining treatment should be offered. Chromosomal analysis is used to obtain a definitive diagnosis for autosomal trisomy syndromes. Because representative and specific clinical signs, such as overlapping fingers (OLF) or rocker-bottom foot (RBF), may not be present in all neonates with T13/18 (1), recognition of the need for chromosomal analysis in patients suspected of having T13/18 is often difficult, even for experienced pediatricians. In contrast, T21 can usually be distinguished from T13/18 and other malformation syndromes due to its characteristic clinical signs, such as upslanting palpebral fissures or a low nasal bridge.

2. Objectives

This study aimed to investigate any clinical signs that were useful for recommending a chromosomal analysis to screen for T13/18 when the representative and specific clinical signs were not present in odd-looking neonates, including T21 and other malformation syndromes.

3. Patients and Methods

3.1. Patients

The target population of our study included 15 patients with T13/18, 4 with T13, and 11 with T18, as well

as 33 with T21 and 48 controls with malformation syndromes excluding autosomal trisomy syndromes. The control group contained 4 patients with Prader-Willi syndrome, 4 with VATER association, 3 with hemifacial microsomia, 2 with Kabuki syndrome, 2 with Waardenburg syndrome, 4 with chromosomal aberrations, 9 with known malformation syndromes (Goldenhar syndrome, EEC syndrome, Pierre-Robin syndrome, tuberous sclerosis, Herlyn-Werner-Wunderlich syndrome, 5p- syndrome, 22q11.2 deletion syndrome, Jacobsen syndrome, and Beckwith-Wiedemann syndrome), and 20 with unclassified malformations.

All patients hospitalized in the neonatal intensive care unit of Kansai medical university from January 2006 to January 2015 were included in this study.

3.2. Statistical Analysis

The statistical analysis was retrospective. Clinical signs that had been described in the patients' medical records within 28 days of their birth were extracted. All clinical signs proved to be important clinical findings, which have been described in the literature (2).

The incidences of each clinical sign in patients with T13/18 and T21 were compared with those of controls using the chi-square test, the Kruskal-Wallis (Scheffe) test, and multiple comparison tests of proportional differences: Tukey's wholly significant difference (WSD) test (3). The results were considered significant when a P value was found to be less than 0.05. To determine the diagnostic accuracy of the comorbidities of the common clinical signs, the sensitivity, specificity, the positive predictive value (PPV), the negative predictive value (NPV), and the 95% confidence interval were calculated. All statistical calculations were performed using Excel statistical software (Excel-Toukei, Ver. 2012, SSRI Co., Japan).

3.3. Ethical Considerations

This study was approved by the ethical committee of Kansai Medical University during the data collection period. All authors and contributors had been trained in research ethics. No neglected responses from the target population or their families were found after the announcement of this study.

4. Results

The clinical profiles of infants with T13/18, patients with T21, and healthy controls are shown in Table 1. No significant differences were observed in the sex ratio or gestational age among the groups. Infants with T13/18 had a lower birth weight than those with T21 and controls ($P < 0.01$).

Clinical signs to the fifth frequency in infants with T13/18 and T21 are shown in Table 2. Among them, congenital heart disease (CHD), low-set ears (LSE), and intrauterine growth restriction (IUGR) were the three leading clinical signs in infants with T13/18, occurring in 100%, 80%, and 73.3% of the patients, respectively. CHD and LSE were also the two most prevalent clinical signs in infants with T21 and were observed in 72.7% of patients, respectively. The chi-square test showed a significant difference among the groups for CHD ($P < 0.01$). A significant difference in LSE or IUGR by chi-square test was also observed ($P < 0.01$). The OLF or RBF were almost specific for T13/18, while upslanting palpebral fissures, a low nasal bridge, and epicanthus were specific for T21.

Because CHD, LSE, and IUGR are frequently found in other malformation syndromes, multiple comorbidities among clinical signs were analyzed (Table 3). The chi-square test showed a significant difference in the proportion of the coexistences of the CHD with LSE, the CHD with IUGR, and the LSE with IUGR among the three groups ($P < 0.01$). Tukey's WSD test revealed a significant difference in the proportion of the coexistence of CHD and LSE between T13/18 and the controls and also between T21 and the controls; however, no difference was observed for the T13/18 and T21 participants. The comorbidity of CHD with IUGR and that of LSE with IUGR showed significant differences between T13/18 and T21 and also between the T13/18 patients and controls according to Tukey's WSD test.

The diagnostic accuracy of the comorbidities of these three clinical signs (CHD, LSE, and IUGR) in infants with T13/18 and that in controls is shown in Table 4, which also presents the diagnostic accuracy of OLF and RBF. The comorbidity of CHD with LSE had the highest sensitivity of 80%, the highest NPV of 92.5%, and a high odds ratio of 13.5 with a reliable 95% confidence interval. The comorbidity of CHD with IUGR had similar results as those of CHD with LSE. In contrast, the comorbidity of LSE with IUGR showed a lower sensitivity of 53.3% and a higher specificity of 89.6%, which were similar to those of OLF or RBF.

Based on these findings, it was suggested that the comorbidity of CHD with LSE was useful for discriminating T13/18 or T21 from other malformation syndromes, while that of CHD with IUGR was helpful to distinguish T13/18 from T21 or other malformation syndromes.

5. Discussion

This study aimed to investigate any useful clinical signs to screen for T13/18 in patients without the representative and specific clinical signs frequently observed in odd-

Table 1. Clinical Profiles of Trisomy 13 or 18, Trisomy 21, and Other Malformation Syndromes[a,b]

Clinical Profiles	T13/18 (n = 15)	T21 (n = 33)	Controls (n = 48)	P Value
Sex (male: female)	6: 9	23: 10	17: 14	0.1
Gestational weeks	37.1 (32.5 - 41.2)	37.6 (33.2 - 41.0)	38.4 (32.3 - 41.5)	0.07
Birth weight, g	1796 (1120 - 2958)	2822 (2142 - 3684)	2456 (1546 - 4185)	< 0.01

Abbreviations: T13/18, trisomy 13 or trisomy 18; T21, trisomy 21; Controls, malformation syndromes excluding autosomal trisomy syndromes.
[a]Gestational weeks and birth weight are shown as the median (minimum-maximum).
[b]Statistical analysis: The sex ratio was analyzed by the chi-square test; gestational weeks and birth weight were assessed using the Kruskal-Wallis test (multiple comparison procedure; Scheffe).

Table 2. Incidence of Clinical Signs in Trisomy 13 or 18, Trisomy 21, and Other Malformation Syndromes[a,b]

Clinical Signs	T13/18, (N = 15)	T21, (N = 33)	Controls, (N = 48)	P Value	Tukey's WSD Test Results[c]		
					T13/18 and T21	T21 and Controls	T13/18 and Controls
CHD	15 (100)	24 (72.7)	25 (52.1)	< 0.01	0.273[d] (0.261)	0.207 (0.243)	0.480[d] (0.343)
LSE	12 (80.0)	24 (72.7)	17 (35.4)	< 0.01	0.073 (0.290)	0.373[d](0.243)	0.446[d](0.329)
IUGR	11 (73.3)	2 (6.1)	14 (29.2)	< 0.01	0.672[d] (0.328)	0.231[d] (0.193)	0.441[d] (0.311)
OLF	10 (66.7)	0 (0)	3 (6.3)	< 0.01	0.667[d] (0.249)	0.063 (0.092)	0.604[d] (0.242)
RBF	8 (53.3)	0 (0)	2 (4.2)	< 0.01	0.533[d] (0.223)	0.042 (0.075)	0.492d (0.232)
UPF	0 (0)	23 (69.7)	0 (0)	< 0.01	0.697[d] (0.364)	0.697[d] (0.239)	0 (0)
LNB	0 (0)	21 (63.6)	3 (6.3)	< 0.01	0.636[d] (0.316)	0.574[d] (0.222)	0.063 (0.135)
Epicanthus	0 (0)	19 (57.6)	0 (0)	< 0.01	0.576[d] (0.350)	0.576[d] (0.153)	0 (0)

Abbreviations: CHD, congenital heart disease; IUGR, intrauterine growth retardation; LSE, low-set ears; LNB, low nasal bridge; OLF, overlapping finger; RBF, rocker-bottom foot; T13/18, trisomy 13 or trisomy 18; T21, trisomy 21; Controls, malformation syndromes excluding autosomal trisomy syndromes; UPF, upslanting palpebral fissures; WSD, wholly significant difference (multiple comparison tests of proportional differences, Tukey).
[a]Values are expressed as No. (%).
[b]The WSD values are shown in parentheses in the columns for the Tukey's WSD test.
[c]Proportional Differences Between the Two Groups by Tukey's WSD Test.
[d]Indicates a significant difference.

Table 3. Incidence of the Comorbidity of Three Leading Clinical Signs in Trisomy 13 or 18[a,b]

Comorbidity of Clinical Signs	T13/18 (n = 15)	T21 (n = 33)	Controls (n = 48)	P Value	Tukey's WSD Test Results[c]		
					T13/18 and T21	T21 and Controls	T13/18 and Controls
CHD-LSE	12 (80.0)	20 (60.6)	11 (22.9)	< 0.01	0.194 (0.316)	0.377[d] (0.236)	0.571[d] (0.344)
CHD-IUGR	11 (73.3)	2 (6.1)	8 (16.7)	< 0.01	0.672[d] (0.301)	0.106 (0.160)	0.566[d] (0.291)
LSE-IUGR	8 (53.3)	1 (3.0)	5 (10.4)	< 0.01	0.530[d] (0.257)	0.101 (0.257)	0.429[d] (0.127)

Abbreviations: CHD, congenital heart disease; IUGR, intrauterine growth retardation; LSE, low-set ears; LNB, low nasal bridge; OLF, overlapping finger; RBF, rocker-bottom foot; T13/18, trisomy 13 or trisomy 18; T21, trisomy 21; Controls, malformation syndromes excluding autosomal trisomy syndromes; UPF, upslanting palpebral fissures; WSD, wholly significant difference (multiple comparison tests of proportional differences, Tukey).
[a]Values are expressed as No. (%).
[b]The WSD values are shown in parentheses in the columns for the Tukey's WSD test.
[c]Proportional Differences Between the Two Groups by Tukey's WSD Test.
[d]Indicates a significant difference.

looking neonates. To the best of our knowledge, this study is the first to show that either the comorbidity of CHD with LSE or CHD with IUGR was significantly useful in distinguishing autosomal trisomy syndromes (especially atypical T13/18) from other malformation syndromes.

A high sensitivity (80% and 73.3% in the present study, respectively) and NPV (92.5% and 90.9%, respectively, in the present study) are required for the first neonatal screening to determine whether to perform more specific genetic examinations rather than a high specificity and PPV. There-

Table 4. The Diagnostic Accuracy of Clinical Signs for Discriminating Trisomy 13 or 18 From Other Malformation Syndromes[a]

Clinical Signs	Sensitivity	Specificity	PPV	NPV	Odds Ratio
Comorbidity					
CHD-LSE	80.0 (60.0 - 100.0)	77.1 (65.2 - 89.0)	52.2 (31.8 - 72.6)	92.5 (84.3 -100.0)	13.5 (3.2- 56.4)
CHD-IUGR	73.3 (50.9 -95.7)	83.3 (72.7 - 93.9)	57.9 (35.7 - 80.1)	90.9 (82.4 -99.4)	13.8 (3.5 -54.3)
LSE-IUGR	53.3 (28.1 -78.5)	89.6 (81.0 - 98.1)	61.5 (35.0 -88.0)	86.0 (76.4 -95.6)	9.8 (2.5 - 38.8)
Overlapping Finger	66.7 (42.8 -90.6)	93.8 (87.0 - 100.0)	76.9 (54.0 -99.8)	90.0 (81.7 - 98.3)	30.0 (6.1 -146.7)
Rocker-bottom Foot	53.3(28.1 -78.5)	95.8 (90.1 - 100.0)	80.0 (55.2 -100.0)	86.8 (77.7 - 95.9)	26.3 (4.6 - 150.0)

Abbreviations: CHD, Congenital heart disease; IUGR, intrauterine growth retardation; LSE, low-set ears; NPV, negative predictive value; PPV, positive predictive value.
[a]The 95% confidence interval is shown in parentheses.

fore, these comorbidities of CHD with LSE or CHD with IUGR can lead to efficient chromosomal analysis because these clinical signs can be easily recognized even by inexperienced pediatricians. The comorbidities have the potential to suggest T13/18 due to their high diagnostic accuracy: a specificity of 77.1% - 83.3% and an odds ratio of 13.5 - 13.8 with a reliable 95% confidence interval above 3.0. It has been suggested that the comorbidities should be comparable to the representative and specific clinical signs of T13/18, ORF, or RBF. However, one weak point of ORF or RBF is the low incidence rate. T13/18 cases without OLF or RBF may not be diagnosed accurately during the neonatal period, and the patient may therefore receive inappropriate or unwanted medical services. Our results in Table 2 also indicated that only 73.3% of cases showed the representative and specific clinical signs of T13/18, OLF, or RBF. However, the comorbidities of CHD with LSE or CHD with IUGR elevated the first screening ratio to 100.0%.

The genetic relationship of CHD and LSE has not been clarified, although the comorbidity of CHD with LSE has been reported in several case series (4, 5). Otopharyngeal and cardiovascular disorders are embryologically closely related to each other, and several common genes are associated with cardiac neural crest cells at the otic vesicle toward the second heart field (6, 7). In fact, low expression in some transcription factors for otic and cardiovascular development, such as GATA6, has been postulated to cause CHD (8). The GATA6 gene is present on chromosome 18, and a mutation of this GATA6 gene is found in T18 patients with CHD (9). The comorbidity of CHD along with IUGR has been reported in some cases and in etiological studies (10). However, the embryological mechanisms associated with T13/18 remain unknown. At the same time, a similar mechanism, such as GATA6 in T18, has not been shown for chromosomes 13 and 21.

A limitation of this study was the small number of infants with T13/18 who were included. Additionally, there was an imbalance in the number of patients between those with T13 and those with T18, which may have affected the incidence of clinical signs in patients with T13/18. However, we still suggest that the comorbidity of CHD with LSE or CHD with IUGR has clinical significance for screening infants with T13/18 from infants with other malformation syndromes because their NPVs can be as high as 90%. Another limitation was that genetic tests of the target population were not carried out because of the retrospective analyses in this study. In the future, it would therefore be worthwhile to examine the expression and mutation of the GATA6 gene in cases with a comorbidity of CHD with LSE or CHD with IUGR.

5.1. Conclusion

The comorbidities of either CHD with LSE or CHD with IUGR are useful for neonates with suspected autosomal trisomy syndromes (particularly T13/18) who present without any representative and specific clinical signs for implementing a chromosomal analysis.

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Footnotes

Authors' Contribution Yoshimitsu Fujii conceptualized and designed the study and drafted the initial manuscript; Eriko Kanda, Masato Hirabayashi, Kenji Mine, and Atsushi Ohashi were in charge of the data collection. Shoji Tsuji and Kazunari Kaneko coordinated and supervised the study.

Conflict of Interests None of the authors has any conflicts of interest relevant to this article to disclose.

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