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Relevant researches on chronic viral myocarditis (CVMC) in children, complicated with arrhythmia and thyroid hormone level

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Abstract. – OBJECTIVE: To analyze the correlation between chronic viral myocarditis (CVMC) in children, complicated with arrhythmia and thyroid hormone level.

PATIENTS AND METHODS: 60 patients with CVMC complicated with arrhythmia were continuously selected (course of disease > 3 months) and they are were diagnosed with arrhythmia by the routine 18-lead electrocardiogram and 24-hour Holter; the average follow-up time is about 2 years, during which the left ventricular end-diastolic diameter (LVEDd), left ventricular ejection fraction (LVEF), the occurrence rate of malignant arrhythmia events, immune state of T cell and thyroid hormone level (FT3, FT4, TSH, TGAb and TPOAb) were compared.

RESULTS: Among the selected 60 patients, 18 patients (30.0%) who were suffering from malignant arrhythmia have been taken as the observation group. When compared with the control group, the standard deviation normal to normal intervals (SDNN), LVEF, CD4 and CD4/CD8 were reduced and LVEDd and CD8 were increased in the observation group; the difference has statistical significance ($p < 0.05$). When compared with the control group, FT3 and FT4 are significantly reduced and TSH, thyroglobulin antibody TGAB and thyroid peroxidase antibodies (TPOAb) are significantly increased; the difference has statistical significance ($p < 0.05$). According to the logistic regression analysis, we can conclude that: SDNN, FT3, FT4, TSH, TGAb and TPOAb are the independent risk factors of malignant arrhythmia ($p < 0.05$).

CONCLUSIONS: Thyroid hormones and antibody level are helpful to the prognosis of malignant arrhythmia resulting from children chronic VMC complicated with arrhythmia complications.

Key Words:

Chronic viral myocarditis, Arrhythmia, Thyroid hormone, 24-h holter, Left ventricular end-diastolic diameter, Left ventricular ejection fraction, T cell.

Introduction

The incidence of viral myocarditis (VMC) worldwide is about 1%-5%, which is the highest value among children and may be related to the high detection rate of Coxsackie virus-coxsackie and adenovirus receptor (CAR) among children[1]. The prevalence of children chronic VMC complicated with arrhythmia complications is about 10%-30%, and those children are the potential population who will suffer from adult dilated cardiomyopathy[2]; and the early detection and timely treatment conducted towards children is the important means to improve prognosis. However, the majority of VMC is a self-limited disease except those that have prominent clinical features of early acute disease or severe disease and poor prognosis; although with arrhythmia, for instance, ventricular premature beat or atrial premature beat, tachycardia or bradycardia, grade I or grade II atrioventricular block, etc., the majority of patients can usually get through within 1-10 years or it may have a little impact on cardiac function[3]. Therefore, at present, there is still a lack of a clinical means with higher sensitivity and specificity to screen high-risk children in the early period. 24-hour Holter is a good detection method to evaluate heart rate variability which is related to autonomic neural regulation disorders of the body, and has a better correlation on predicting major adverse cardiac events[4]. The pathogenesis of VMC not only includes the direct toxic effect of the virus on myocardial tissues but also includes the immune injury, and there are about 30-40% of sick children who have been misdiagnosed with congenital hypothyroidism[5]. We predict that, there is a certain degree of correlation between VMC and the abnormal thyroid hormone level, and such correlation may be the potential targets for diagnosis and therapy.

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The children with three years of chronic VMC complicated with arrhythmia were followed-up for 2-year. The correlation between VMC and thyroid hormone level was also analyzed, and the specific results are hereby concluded as below.

Patients and Methods

Information of Patients

60 patients who were admitted to our hospital and were diagnosed with children chronic VMC complicated with arrhythmia complications from January 2011 to January 2014 were continuously selected, and the inclusion criteria are as below: 1. Patients have not been cured when the course of VMC was longer than three months. Diagnosis criteria: the myocardial enzyme was 0.5 times higher than the myocardial enzyme within normal limits; the titer of serum virus antibody was persistently high, and patients were suffering from sustained arrhythmia (diagnosed by 18-lead electrocardiogram and 24-hour Holter) with or without cardiac dysfunction which includes ventricular enlargement, left ventricular ejection fraction (LVEF) decrease, etc. 2. Patients subjected to the regular VMC treatment, thus having good compliance and complete clinical data.

Exclusion criteria: (1) Patients with congenital heart disease, paraplasia?, autoimmune disease, metabolic disease and etc.; (2) Patients who were participating in other researches at the same time and wanted abandon the research and the follow-up observation. The informed consent has been obtained from the Ethics Committee of our hospital as well as the patients and their family members. The follow-up observation ended in 2016, being the average follow-up time about 2 years; then, after that period, the physicians kept on comparing the left ventricular end-diastolic diameter (LVEDd), left ventricular ejection fraction (LVEF), the occurrence rate of malignant arrhythmia events, immune state of T cell and thyroid hormone level (FT3, FT4, TSH, TGAb and TPOAb), and record corresponding data once every 3 months, and finally take an average.

Detection Methods

Holter detection: TLC3000A 12-lead Holter analyzer produced by Contec Medical Systems Co., Ltd. (Melbourne, FL, USA) was adopted, and computer-assisted analysis and manual editor and corrector were adopted as recording modes to eliminate all ectopic beats and artifacts and to detect the heart rate variability (HRV) of sinus beats, and the population standard deviation (SDNN) < 110 ms was chosen as the diagnostic criteria for abnormity. The malignant arrhythmia events refer to the unexplained syncope, severe bradycardia or grade-II and grade-III atrioventricular block, sustained sinus tachycardia, sustained ventricular tachycardia, continuous (≥ 6) ventricular premature beat, ventricular fibrillation and sudden death.

Measurement of LVEDd and LVEF: GE logo5-type color ultrasonic apparatus (Waltham, MA, USA) was adopted with transducer frequency of 3.0 MHz, and M-type sampling was conducted on the section plane of left ventricular short axis mitral valve chordae tendineae near the standard sternum under the guidance of two-dimensional echocardiogram, and physicians tried their best to ensure that the sampling line went perpendicular to the posterior wall of interventricular septum, and then measured the left ventricular end-diastolic diameter and left ventricular end systolic diameter, and finally LVEF was automatically output according to the Teichholz corrector formula.

Detection of T cell immune state and thyroid hormone level: the bridge-linked enzyme assay was adopted to measure peripheral blood T lymphocyte subsets including CD4, CD8 and CD4/CD8, and the kit was provided by Shanghai Kelong Company; the radio-immunity assay was adopted for FT3, FT4 and TSH, and the kit was provided by Beijing Institute of Atomic Energy, and the measuring instrument was the SN-682 γ-calculating instrument produced by Rihuan Factory of Beijing Institute of Atomic Energy, and the reference range of FT3 is 3.2-9.2 pmol/ L and the reference range of FT4 is 8.6-25.6 pmol/L, and enzyme-linked immunoadsorbent assay (ELISA) was adopted to detect TGAb and TPOb, and the kit is provided by Beijing Origene Biological Technology Co., Ltd., and the reference range of TGAb is < 30%, and the reference range of TPOAb is < 20U/L; all of the above-mentioned procedures shall be carried out according to the specification.

Table I. Occurrence of malignant arrhythmia events according to follow-up observation.

Groups	Number of cases	Male/ Female	Age	SDNN (ms)	LVEDd (mm)	LVEF (%)	CD4 (%)	CD8 (%)	CD4/CD8 (%)
Observation group	18	8/10	10.5 ± 3.3	75.6 ± 10.9	42.5 ± 3.4	38.7 ± 3.3	37.6 ± 6.4	30.6 ± 5.2	1.1 ± 0.5
Control group	42	20/22	11.2 ± 3.5	92.4 ± 12.4	38.6 ± 3.7	46.9 ± 2.7	45.5 ± 6.5	21.4 ± 5.3	1.9 ± 0.4
t (χ^2)		0.051	0.624	6.329	5.428	5.946	6.103	6.647	6.326
p		0.821	0.427	0.025	0.037	0.033	0.029	0.021	0.026

Statistical Analysis

SPSS19.0 software (SPSS Inc., Chicago, IL, USA) was adopted to carry out data input and analysis, the quantitative data are expressed by the mean±standard deviation, the inter-group comparison was tested by *t*-test, the qualitative data are expressed by the number of cases or the percentage (%), and inter-group comparison was tested by χ^2-test; the logistic model was adopted to carry out multi-factor regression analysis; $p<0.05$ means the difference has statistical significance.

Results

Occurrence of Malignant Arrhythmia Events According to Follow-Up Observation

18 patients (30.0%) among 60 patients who were suffering from malignant arrhythmia are taken as the observation group, in which there are 2 patients who have died, 2 patients who have suffered from syncope, 4 patients who have suffered from severe bradycardia or atrioventricular block and 10 patients who have suffered from tachycardia, ventricular premature beat, ventricular tachycardia, ventricular fibrillation, etc.; the patients who have not suffered from malignant arrhythmia are taken as the control group. According to the comparison on the gender and age between the two groups, the difference has no statistical significance ($p > 0.05$); when compared with control group, SDNN in observation group is reduced together with LVEF, CD4, CD4/CD8, LVEDd and CD8 in observation group is increased, and the difference has statistical significance ($p < 0.05$) (Table I).

Comparison on Thyroid Hormone Level

FT3 and FT4 in observation group are significantly reduced than those in control group, but TSH, TGAb and TPOAb in observation group are significantly increased, and the difference has statistical significance ($p < 0.05$) (Table II).

Multi-Factor Regression Analysis

The gender, age, SDNN, LVEDd, LVEF, CD4, CD8, CD4/CD8, FT3, FT4, TSH, TGAb and TPOAb are taken as the independent variable, and malignant arrhythmia events are taken as the dependent variable, and independent and dependent variables are included into the logistic regression model, and the step-back technique is adopted to screen data, from which we conclude that: SDNN, FT3, FT4, TSH, TGAb and TPOAb are the independent risk factors of malignant arrhythmia ($p < 0.05$) (Table III).

Discussion

Chronic VMC, complicated with arrhythmia, is often confused with thyroid hypofunction, whose early clinical symptoms are atypical; in addition, FT3 and FT4 are slightly reduced according to the thyroid hormone detection, and TSH level is normal, all of which suggest

Table II. Comparison on thyroid hormone level.

Groups	FT3 (pmol/ L)	FT4 (pmol/ L)	TSH (μIU/ ml)	TGAb (%)	TPOAb (U/L)
Observation group	1.5 ± 0.6	6.7 ± 2.1	14.4 ± 2.9	36.6 ± 4.2	27.6 ± 4.1
Control group	5.9 ± 1.2	15.3 ± 3.4	7.2 ± 2.3	25.2 ± 4.7	13.2 ± 3.3
t 7.628	7.421	8.332	7.635	9.329	
p < 0.001	< 0.001	< 0.001	< 0.001	< 0.001	

Table III. Multi-factor regression analysis.

Factors	β	Wald	*p*	OR	95% CI
SDNN	0.324	4.627	0.035	1.204	0.063-2.304
FT3	0.126	5.203	0.031	1.247	0.075-2.656
FT4	0.247	5.327	0.030	1.326	0.083-2.315
TSH	0.203	5.120	0.032	1.524	0.066-2.847
TGAb	0.106	5.629	0.027	1.867	1.003-2.769
TPOAb	0.032	5.547	0.029	1.659	0.099-2.302

that the patients suffer from normal thyroidal sick syndrome of non-thyroid disease[6]. In this circumstance, the physicians do not recommend to apply thyroid hormone replacement therapy to patients; what the physicians shall do is just to conduct follow-up observation[7]. For the sick children who have not had their sustained arrhythmia relieved and even suffer from malignant arrhythmia events, we can conclude from the follow-up detection of thyroid hormone that, FT3 and FT4 are significantly reduced, but TSH, TGAb and TPOAb are significantly increased. The lower FT3 may show the protective adaptive mechanism that the body produces when the patients suffer from critical disease so that the metabolism of liver, kidney, heart, skeletal muscles and other tissues mainly relying on circulating T3 are reduced, the energy is saved and consumption is reduced[8]. In addition, fewer T4 are transformed to T3 due to the inhibition of pathological factors and decrease of deiodinase activity. However, some authors think that the lower FT3 may be the "predicting signal" for the progress of critical disease, and the prognosis of FT3 is often poor[9]. Chopra et al[10] think that, the inhibitor of thyroid hormone exists in the tissues outside of thyroid hormone under the normal circumstance, and it can inhibit the combination of serum T3, T4 and thyroid binding protein. Upon the occurrence of CVMC, the myocardial tissues are directly damaged by virus or induced by the cellular immunity and auto-antibody, thus producing some antibodies or inhibitors which can penetrate into the blood circulation, and then stimulate the secretion and the release of TGAb and TPOAb. According to these authors[10], the specific expression of α-hydroxybutyrate dehydrogenase in myocardial tissues is increased, which is closely related to the decrease of FT3 and FT4 as myocardial injury. However, they also point out that[10] the human body can promote the deposition of T3 in the nucleus by increasing the quantity of T3 receptors in the cell nucleus so that the thyroid hormone in cells can reach the normal level as necessary, thus the metabolic status of thyroid function can be like that of normal thyroid function. Given this, the physicians do not advise the patients to supplement exogenous thyroid hormone prematurely.

According to Witton and Feuer[11], IL-1, TNF-α and some other high-expression cytokines can be detected in the body of VMC patients, thus stimulating the production of auto-antibody including anti-myocardial antibody (anti-mitochondrial antibody, anti-cardiac myosin antibody, etc.), thus resulting in the decrease of myocardial contraction, increase of LVEDd and reduction of LVEF. In addition, the said high-expression cytokines can induce the combination of perforin and granzyme or induce the cell apoptosis by the way of Fas-FasL[12]; the matrix metalloproteinases and balance disorders of inhibiting factors lead to the abnormal reconstruction of cardiac collagen[13]. All of these are related to the reduction of cardiac function and the occurrence of malignant arrhythmia. Besides, the immune dysfunction induced by T cell, for instance, the decrease of CD4, increase of CD8, a decrease of CD4/CD8, also plays an important role in the pathological and physiological processes[14]. Through multi-factor regression analysis, we can further conclude from this research that SDNN, FT3, FT4, TSH, TGAb and TPOAb are the independent risk factors of malignant arrhythmia. It is suggested that the malignant arrhythmia events resulting from VMC complicated with arrhythmia may be closed related with the abnormity of thyroid hormone level. TGAb is the antibody produced after the thyroglobulin in thyroid follicular colloid enters the blood, and the detection rate of TGAb is higher among various kinds of thyroid diseases, especially the autoimmune diseases[15]. TPOAb is the primary antibody chosen for high-specificity and high-sensitivity diagnosis and treatment of autoimmune thyroid diseases[16]. The correlation

between LVEDd, LVEF, T cell level and malignant arrhythmia events have not been assessed, because VMC arrhythmia may not result from the reduction of cardiac function, and the level of T cell is more prominent in the acute stage of VMC. Of course, the sample size and follow-up time are also the influencing factors, which shall be further proved by the animal experiment.

Conclusions

The thyroid hormones and antibody level are helpful to the prognosis of malignant arrhythmia resulting from children chronic VMC complicated with arrhythmia complications.

Conflict of Interest

The Authors declare that they have no conflict of interests.

References

1) Liao Y, Chen KH, Dong XM, Fang Y, Li WG, Huang GY, Song W. A role of pre-mir-10a coding region variant in host susceptibility to coxsackie virus-induced myocarditis. Eur Rev Med Pharmacol Sci 2015; 19: 3500-3507.
2) Huber SA. Viral myocarditis and dilated cardiomyopathy: etiology and pathogenesis. Curr Pharm Des 2016; 22: 408-426.
3) Han FL, Liang F, Jiang TC, Liu M. Increased expression of CXCR5 and CXCL13 in mice with experimental autoimmune myocarditis. Eur Rev Med Pharmacol Sci 2017; 21: 1860-1867.
4) Czosek RJ, Jefferies JL, Khoury PR, Anderson JB, Wilmot I, Knilans TK, Spar DS. Arrhythmic burden and ambulatory monitoring of pediatric patients with cardiomyopathy. Pacing Clin Electrophysiol 2016; 39: 443-451.
5) Brokhin M, Klein I. Low T3 syndrome in a patient with acute myocarditis. Clin Cornerstone 2005; 7 Suppl 2: S28-29.
6) Cihákova D, Sharma RB, Fairweather D, Afanasyeva M, Rose NR. Animal models for autoimmune myocarditis and autoimmune thyroiditis. Methods Mol Med 2004; 102: 175-193.
7) Fung G, Luo H, Qiu Y, Yang D, McManus B. Myocarditis. Circ Res 2016; 118: 496-514.
8) Mishra P, Samanta L. Oxidative stress and heart failure in altered thyroid States. ScientificWorldJournal 2012; 2012: 741861.
9) Lee YM, Ki YJ, Choi DH, Kim BB, Shin BC, Song H, Kim DM. Value of low triiodothyronine and subclinical myocardial injury for clinical outcomes in chest pain. Am J Med Sci 2015; 350: 393-397.
10) Chopra IJ, Hershman JM, Pararidge WM, Nicoloff JT. Thyroid function in nonthyroidal illnesses. Ann Intern Med 1983; 98: 946-957.
11) Whitton JL, Feuer R. Myocarditis microbes and autoimmunity. Autoimmunity 2004; 37: 375-386.
12) Bennett MR. Apoptosis in the cardiovascular system. Heart 2002; 87: 480-487.
13) Ruiz-Ortega M, Lorenzo O, Ruperez M, Suzuki Y, Egido J. Angiotensin II actives nuclear transcription factor-Kappa B in aorta of normal rats and in vascular smooth muscle cells of ATI knockout mice. Nephrol Dial Transplant 2001; 16 (Suppl 1): 27-33.
14) Huber SA, Graveline D, Newell MK, Born WK, O'Brien RL. V γ1+T suppress andV γ4+ cell promote susceptibility to coxsackievirus B3-induced myocarditis in mice. J Immunol 2000; 165: 4174-4181.
15) Wang XM, Chen C, Dong GP, Huang K, Fu JF, Liang L. Detection of thyroid antibodies in children with type 1 diabetes mellitus. Zhongguo Dang Dai Er Ke Za Zhi 2012; 14: 38-41.
16) Chen X, Jin B, Xia J, Tao X, Huang X, Sun L, Yuan Q. Effects of thyroid peroxidase antibody on maternal and neonatal outcomes in pregnant women in an iodine-sufficient area in China. Int J Endocrinol 2016; 2016: 6461380.