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Head-up tilt test results in child twins with nervous mediated syncope

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ABSTRACT

Objective: To investigate the familial genetic characteristics of syncope in children.
Methods: A detailed medical history was taken from four twin pairs of children complaining of dizziness, headache, chest tightness, chest pain, prodromal symptoms of syncope or syncope, meanwhile, these patients were given routine physical examination, 12-lead ECG, echocardiography, Holter ECG, EEG, MRI of the head and other tests to exclude cardio-cerebrovascular and pulmonary diseases, with those with unknown origin for syncope undergoing head-up tilt test (HUTT) and inquiry of detailed family history.
Results: The four pairs of twins with syncope beginning at 7–12 years and induced mostly by standing position (4/5), and positive family history was noted in two pairs. Vasovagal syncope (VVS)-vasoinhibitory response pattern was predominant in HUTT (4/5). The results and the response pattern in HUTT might diversify between two members within same twin pair: one appeared as vasoinhibitory response pattern and one postural orthostatic tachycardia syndrome (POTS) pattern in the first pair, one vasoinhibitory response pattern and one negative response pattern in the second pair, vasoinhibitory response pattern in the third pair and negative response pattern in the fourth pair.
Conclusions: The hereditary factors may play a more important role in younger children with syncope. Environment and psychological factors may induced syncope attack. The results and the response pattern in HUTT are diversified and which might different between two members within twin pair.

1. Introduction

Syncope is defined as transient loss of consciousness and postural tone resulting from an insufficient supply of oxygen to the brain. Wieling reported that 15% of the children and adolescents under 18 years experienced syncope for at least 1 time [1]. Hu reported that 19.83% of the Chinese students in Changsha of Hunan province of China had experienced syncope of unknown origin [n = 4215, age (5–18 years old)] [2]. The syncope in 70.5% of the children manifested as the autonomic nervous mediated syncope (NMS) [3]. NMS is classified as vasovagal syncope (VVS), postural orthostatic tachycardia syndrome (POTS), orthostatic hypotension (OH) and orthostatic hypertension (OHT), with VVS the most common. Head-up tilt test (HUTT) is a reliable method for the diagnosis of NMS.

Syncope is likely to recur repeatedly, thus causing psychological fear in children and their parents, affecting their learning and quality of life, and in severe cases it can lead to syncope-related somatic injuries, therefore, it is important to understand its causes. Clinically, we found that there is some familial aggregation tendency in children with syncope and studies suggest that a positive family history is a risk factor for recurrence of VVS in children [4]. To elucidate the pathogenesis of syncope, it is necessary to study its genetic characteristics. Child twins share 50–100% of the genes and early familial influence, therefore, the study on child twins contributes to the clarification of the familial genetic characteristics of syncope in children. In recent years, a lot of research at the molecular level has been done regarding genetic characteristics of syncope, such as positive family history of syncope [5,6], the risk of syncope in children whose parents had syncope [7–9], the possible genetic mechanisms of syncope [10–12], and gene polymorphism analysis [13–15]. However, the reports on the HUTT results in child twins with syncope are rare. We retrospectively analyzed the clinical manifestation and HUTT results of four pairs of child twins of the same sex in order to deepen our understanding on the genetic characteristics of syncope in children.

2. Methods

The study group contained children who were referred to our children syncope clinic of the Second Xiangya Hospital of Central South University because of unexplained dizziness, headache, chest pain, syncope and prodromal symptoms of syncope between September 2000 and April 2014 prospectively included in the study. All patients with syncope and prodromal symptoms of syncope underwent history taking, physical examination, 12-lead ECG, echocardiography, Holter ECG, EEG, head MRI and other tests to rule out cardio-cerebrovascular diseases and lung diseases. HUTT was performed for 4401 episodes among those with syncope of unknown cause, with four pairs of twins undergoing data analysis regarding age, gender, family history, clinical manifestation, hemodynamic changes and other information, and recently receiving follow-up by telephone. The consent form for HUTT was taken from the subjects or their guardians. HUTT is noninvasive

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and it is performed in line with the ethical standards stated by Second Xiangya Hospital, Central South University and has gained approval from the ethics committee.

HUTT consisted of baseline head-up tilt test (BHUT) and/or sublingual nitroglycerin head-up tilt test (SNHUT). The test methods and assessment of results and reaction type were in line with the methods previously reported by our group [16]. The detailed family history for each case was obtained and the family relatives were divided into first-degree relatives (father, mother, and siblings), and second-degree relatives (paternal relatives, maternal relatives).

3. Results

3.1. General data

Of the total four pairs of twins, three pairs were males and one pair females with mean age of 10–14 years and onset age of 7–12 years. Two pairs were identified as monozygotic twins (MZ) (the first and third pairs), however, whether dizygotic or monozygotic for the other two pairs remains unclear. Clinically, these patients presented with syncope, prodromal symptoms of syncope, chest pain, blackouts, headache, dizziness, pale and other symptoms, and four cases presented with syncope for 1–4 times with duration ranging from a few seconds to 3–5 min and time span ranging from several months to several years. The recurrent cases had the same precipitating factors such as standing position (three cases), position change (one case), severe loss of consciousness (two cases) and accompanied convulsions (one case). Telephone follow-up at 3 years showed no recurrent clinical symptoms such as syncope and prodromal symptoms. Five cases had identified precipitating factors, with four cases precipitated by standing position. One male pair and one female pair (MZ) showed positive family history of syncope in their male family members. None of the four twin pairs showed family history of sudden cardiac death. Past history revealed type A preexcitation syndrome in one case treated with radiofrequency ablation (Table 1).

3.2. HUTT results

Five of the total eight patients (four pairs) were positive in HUTT (three were male and two female), with four appearing as VVS-vasoinhibitory pattern and one POTS pattern. The results and the response pattern in HUTT might diversify between two members within same twin pair or between twin pairs: with one member appearing as vasoinhibitory response pattern and one POTS pattern in the first pair, one vasoinhibitory response pattern and one negative response pattern in the second pair, and two appearing as vasoinhibitory response pattern in the third pair and two negative response pattern in the fourth pair. HUTT test-induced symptoms include chest tightness, precordial discomfort, dizziness, blackouts, blurred vision, irritability, changes in complexion, abdominal pain, fainting-like symptoms and other fainting-like symptoms. In the two MZ pairs, similar HUTT results and reaction types were noted for No. three pair, but HUTT results and reaction types differed between two members in the first pair (Table 2).

4. Discussion

Clinically, a positive family history was noted in some children with syncope, with VVS syncope showing the highest proportion. Newton et al. conducted a questionnaire survey among patients with a definitive diagnosis of VVS ($n = 603$) and the results showed that 19% had family history for blackouts or faints [5]. Vlahos and Kolettis reported that positive family history was noted in 68 of the 76 children with syncope (89.4%) [6]. Neqrusz-Kawecka et al. conducted a questionnaire survey consisting of questions regarding syncopal history among 392 undergraduates (consisting of 281 women and 111 men, aged 18–32 years; 47 % of the population had one brother or sister, and the mean number of individuals per family was 4.4 ± 1.0) and in which syncope was reported in 32.1% of the patients studied (36.7% in women vs. 20.7% in men; $P < 0.05$), 29.1% of mothers, 16.8% of fathers, 30.9% of sisters and 14.2% of brothers. Its logistic regression analysis showed that the inheritance mode of VVS might be regulated by multiple genes [7]. Márquez et al. reported that among the patients with a positive family history of VVS, the first-degree relatives accounted for 73% and second-degree relatives accounted for 27%, thus an autosomal dominant inheritance was postulated [17]. Zheng et al. reported 36 of the 383 patients (9.4%) with unexplained syncope (UPS) had positive family history, with 12% (23/191) positive in both HUTT and family history, and they claimed that there is hereditary tendency for VVS, much as in the offsprings who are more likely to faint if their first-degree relatives have positive history of syncope, and the external stimulus may accelerate the occurrence of syncope [8]. Klein et al. conducted a questionnaire survey among 51 pairs of same-sex twins (at least one member in each pair had history of syncopal episode) meanwhile recording their family history of first- and second-degree relatives, the typical precipitating factors of VVS (in response to blood or injury or medically-related situations, long standing, pain or fear) and found that the symptoms of syncope in MZ are more consistent than in dizygotic twins (DZ) (0.75 vs 0.5, $P > 0.05$); at least 2 episodes were independent of the external environment (0.71 vs 0.27; $P < 0.05$); the typical contributing factors of VVS can induce syncope attack (0.62 vs 0.00, $P < 0.01$). These data of the twins provided strong evidence supporting close association between heredity and VVS; and family history analysis reveals complex inheritance mode (polygenic inheritance and environmental factors) normally and the possibility of major autosomal dominant gene identified in rare cases [10]. In our study on four twin pairs with syncope, two pairs were positive in family history, five cases have definite predisposing factors and four cases were associated with standing position, which is consistent with the literature. In our study, there were two pairs of MZ twins, of which, the third pair showed positive family history and in whom similar HUTT results and response were noted between the two members, yet

Table 1
Clinical characteristics of syncope in four twin pairs.

No.	Relationship between the twins	Age (years)	Gender	Clinical manifestation	Precipitating factor	Onset age (years)	Past history	Family history
1a	Elder brother	14	Male	Rapid heart rate, chest pain, blackouts, pale	Standing position	12	Preexcitation syndrome treated with radiofrequency ablation	Negative
1b	Younger brother	14	Male	Sighing	Negative	11	Negative	Negative
2a	Elder brother	14	Male	Syncope	Standing position	11	Negative	Father with syncope
2b	Younger brother	14	Male	Syncope	Position change	9	Negative	Father with syncope
3a	Elder sister	11	Female	Syncope	Standing position	11	Negative	Syncope in father and elder brother
3b	Younger sister	11	Female	Syncope	Standing position	9	Negative	Syncope in father and elder brother
4a	Elder brother	10	Male	Dizzy and headache	Negative	7	Negative	Negative
4b	Younger brother	10	Male	Dizzy and headache	Negative	7	Negative	Negative