Case Report

DOI: 10.5582/irdr.2019.01060

Heart rate variability in a patient with alternating hemiplegia

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Summary **Alternating hemiplegia of childhood (AHC) is a rare disorder characterized by repetitive episodes of transient hemiplegia. Although autonomic nervous system dysfunction is believed to be associated with AHC, there are no reports of heart rate variability (HRV) in patients with AHC. In the current study, we analyzed HRV in a 20-year-old female with this disorder. The frequency of paralytic attacks have decreased since the patient was a teenager, compared to when she was < ten years old; however, as a 20-year-old, she still experiences paralytic attacks several times per month to more than ten times per month. Thus far, she has only suffered paralytic attacks and no epileptic seizures. Using Sanger sequencing, Gly947Arg (2839G>A) in the sodium-potassium (Na^+/K^+)-ATPaseα3 subunit gene (*ATP1A3*) was confirmed from her blood sample. An elevated heart rate lasting one to two minutes and sometimes longer, was primarily observed at night while the patient was sleeping. Large fluctuations in HRV, including low- and high- frequency components, were primarily observed while the patient was sleeping but suppressed during paralytic attacks. These results confirm the presence of an autonomic nervous system disorder in AHC. Because large variation of the autonomic nervous function was observed at night, the pathophysiological function should be investigated for 24 hours.**

Keywords: Transient hemiplegia, paralytic attack, autonomic nervous dysfunction, abnormal eye position

1. Introduction

Alternating hemiplegia of childhood (AHC) associated with mutations of the sodium-potassium (Na^+/K^+)-ATPaseα3 subunit gene (*ATP1A3*) is a rare disorder characterized by repetitive episodes of transient hemiplegia (*1-3*). It is characterized by repeated attacks of uni- or bilateral hemiplegia with abnormal eye movements (*4,5*).

AHC is considered to be associated with autonomic nervous dysfunction because of symptoms of heart rate fluctuations, sweating, conjunctival injection, lacrimation and so on (*6,7*). However, frequency analysis of heart rate variability (HRV) widely used to evaluate autonomic nervous function has not yet been reported in patients with this disorder. In the current study, we analyzed HRV to assess autonomic nervous system function in patients with AHC including during periods of paralytic attack.

2. Case Report

Upward movement of the eyes and transient paralysis of the right or left upper limbs were noted at five months of age. Head control was possible at six months and sitting was possible at ten months. The paralytic attacks occurred at a frequency of once every day to once every three days. The patient was clinically diagnosed with AHC at a university hospital. The frequency of attacks have decreased since the patient

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was a teenager, compared to when she was < ten years old; however, as a 20-year-old, the patient still experiences paralytic attacks several times per month to more than ten times per month. The patient was once able to stand with support and cruise, but can now only sit and bear crawl and not cruise. Owing to intellectual disabilities, verbal communication is near impossible, but she can raise her hands when shown to do so. Complete assistance is required during mealtime, and she is unable to eat when attacks occur during this period. Thus far, she has only suffered paralytic attacks and no epileptic seizures. Anticonvulsant drugs such as sodium valproate, clonazepam and clobazam, have been administered. Flunarizine, which was privately bought by her mother, had been administered to her since the age of four. After coming to our institution at the age of 18, flunarizine administration was discontinued due to a lack of government insurance coverage, however, the frequency of attacks did not change after its cessation.

Using Sanger sequencing, Gly947Arg (2839G>A) in *ATP1A3* gene was confirmed from her blood sample but her mother had no mutation in ATP1A3 gene. Approval of this case report with the gene analysis was indicated by her mother's signature on the documents accepted by the ethics committee of our institutions.

Based on a 24-hour Holter electrocardiogram (ECG), the patient's HRV was analyzed using software (MemCalc/Chiram 3 version 2.1.10, GMS) sixteen times for two years of her stay at our institution. This examination was completed during a paralytic attack three times out of sixteen examinations. Changes in RR intervals, heart rate, coefficients of variance of RR intervals (CVRR), low frequency (LF) [0.04-0.15Hz] and high frequency (HF) [0.15-0.4Hz] components of HRV and the compressed waveform of ECG, were analyzed.

An example showing changes in heart rate, CVRR, LF and HF components of HRV during a paralytic attack is depicted (Figure 1). Upward rotation of the eyes with conjunctival injection and lacrimation were noted at 14:40. The paralytic attack appeared at 14:50. When the examination began at 15:22, she was unresponsive to her name. At 20:10, she became responsive to her name, but her upper and lower limb paralysis continued. At 20:30, her eye position returned to normal and at 23:00 she could move her right hand but not her left. The paralytic

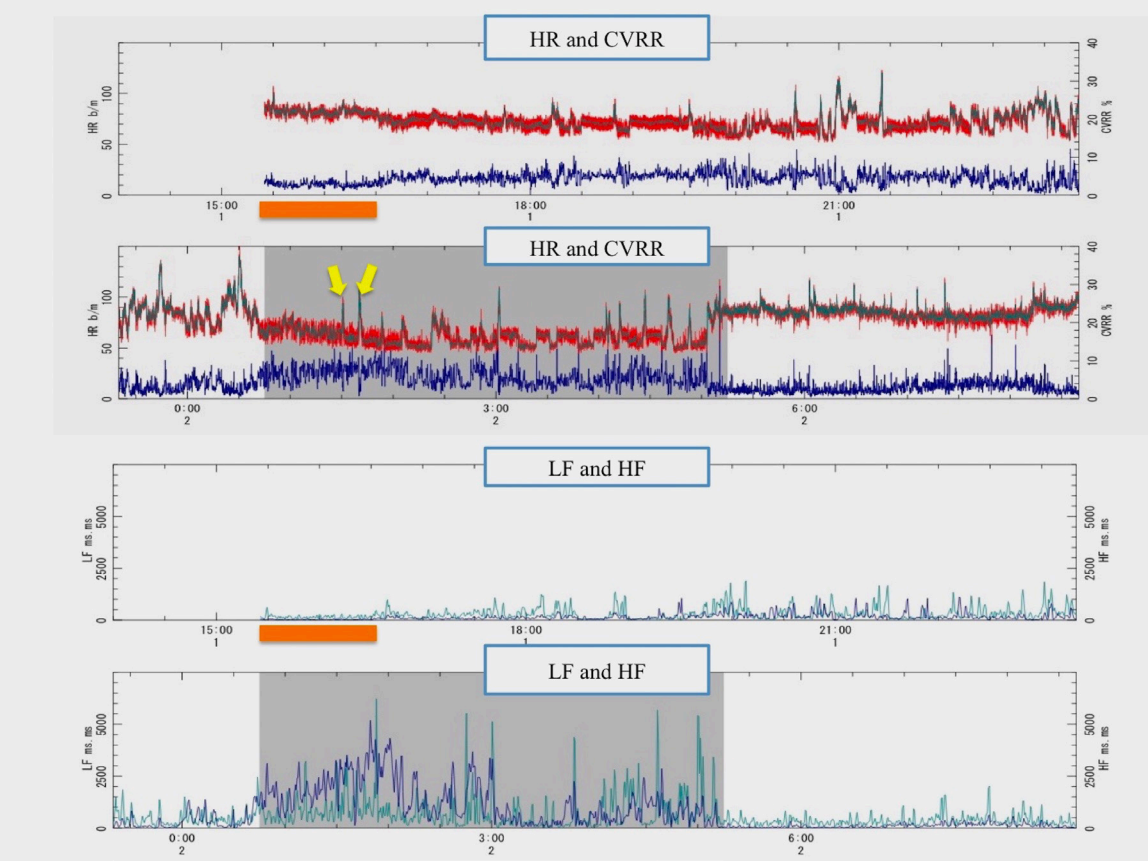

Figure 1. Changes in heart rate (HR), coefficient of variation of RR intervals (CVRR), low-frequency (LF) and high-frequency (HF) components. When this recording began at 15:22, she had paralytic attack as explained in the text. The upper two graphs show the changes that occur in eight beats of HR, averaged (beat/minute) and CVRR %. The red and blue graphs show HR and CVRR, respectively. The lower two graphs show the changes of the power components of LF and HF in heart rate variability (HRV). The light blue and dark blue graphs show LF and HF, respectively. X axis shows time from 15:22 to next day 8:40. CVRR, LF and HF were suppressed especially during the initial period of the paralytic attack from 15:22 to 16:30 (orange bar). Yellow arrows indicate HR elevation that continued for about one minute at 1:30 and 1:40. This is further demonstrated in Figure 2. Note the large amplitude fluctuations that occur in both LF and HF during sleep (shaded area from 0:45 to 5:15).

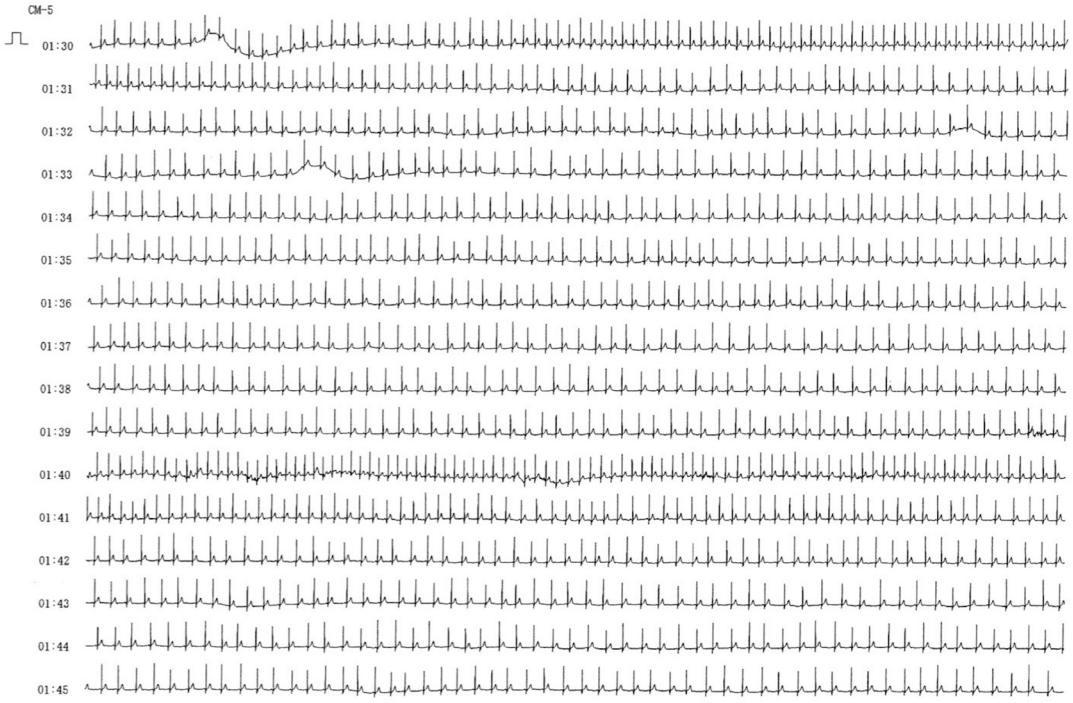

Figure 2. A compressed electrocardiogram (ECG) waveform. Note that transient tachycardia lasted for about one minute at 1:30 am and 1:40 am. This corresponds to yellow arrows shown in Figure 1.

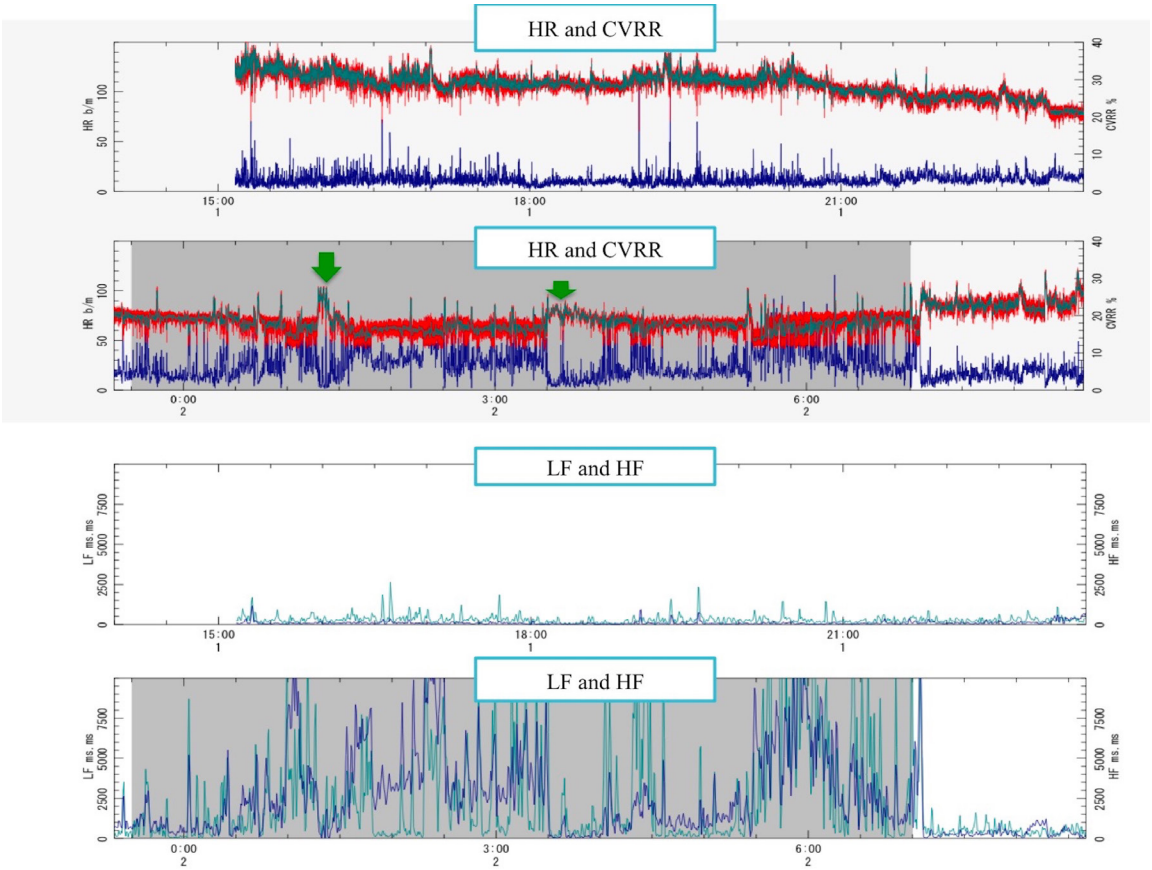

Figure 3. Changes in HR, CVRR, LF and HF components recorded when there was no paralytic attack. Green arrows indicate HR elevation lasting ten minutes and thirty minutes with CVRR reduction during sleep (shaded area). Although LF and HF variations were large at night as in Figure 1, they were relatively weak during the HR elevations. Compared to reduction of CVRR, LF and HF recognized in the initial period of paralytic attack in Figure 1, such reduction was not observed in the same time period.

attack had completely ceased by 0:00 of the next day. One hour after the beginning of the examination, CVRR, LF and HF components of the HRV were greatly suppressed (Figure 1).

The suppression of CVRR, LF and HF components of the HRV that occurred during the initial period of the attack was confirmed in the other two examinations. An elevated heart rate lasting one to two minutes and sometimes longer, was primarily observed at night while the patient was sleeping. The elevated heart rates that lasted roughly one minute were demonstrated using the Holter ECG (Figure 2). The amplitude and variation of LF and HF components were also higher while the patient slept (Figure 1 and Figure 3). Except for the heart rate elevation lasting one or two minutes, heart rate elevation with reduced CVRR lasting five to forty minutes were observed two or three times during sleep in most recordings. An example of the recording is shown with green arrows in Figure 3.

3. Discussion

After the first description of AHC (*8*), the characteristic clinical manifestations have been the mainstay of diagnostic criteria for AHC (*9*). The current case has consistently shown these clinical manifestations from the first paralytic attack to the present day. AHC has been associated with an increased risk of sudden death that may be caused by lethal cardiac arrhythmias (*10*). Cardiac dysfunction may account for some of the unexplained premature mortality of patients with AHC (*6*).

HRV may be used to assess autonomic imbalances, diseases, and mortality. HF power primarily reflects a parasympathetic influence, while LF power has been shown to reflect both sympathetic and parasympathetic influences (*11*). Epilepsy is associated with reduced HRV (*12*). In the present study, both LF and HF components were low during the initial period of the paralytic attacks. It has been reported that sleep relieves paralytic attacks in patients with AHC, however, the present study revealed a large amplitude and variation of LF and HF components, or autonomic dysfunction, during sleep. Recently sleep dysfunction with abnormal apnea-hypopnea index and mean arousal index was reported in patients with AHC (*13*). Sleep disturbance related to AHC should be studied further.

In conclusion, analysis of HRV revealed autonomic nervous dysfunction in a patient with AHC. Because large variation of the autonomic nervous function was observed at night, the biological rhythm should be investigated for 24 hours.

Acknowledgements

This study was supported by research grants from the Ministry of Education, Culture, Sports, Science and Technology of Japan (15H02548, 19K17381, 25670481), the Ministry of Health, Labor and Welfare of Japan (H26-Nanji-Ippan-051 and 049, H30- Nanji-Ippan-007) and Japan Agency for Medical Research and Development (AMED 18dk0207041h001, 15ek0109038a).

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(Received May 14, 2019; Revised May 22, 2019; Accepted May 27, 2019)