Cardiology in the Young

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Fingolimod-related atrioventricular block in paediatric age group with multiple sclerosis: two case reports

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Brief Report

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Abstract

Multiple sclerosis is a chronic inflammatory and demyelinating disease of the central nervous system, usually seen in young adults. Early onset of multiple sclerosis at age younger than 18 years is called paediatric multiple sclerosis. Unlike adult multiple sclerosis, paediatric multiple sclerosis causes morbidity at earlier ages and often progresses in a relapsing–remitting form. Although fingolimod is an effective drug used as a disease-modifiying therapy agent in relapsing–remitting paediatric multiple sclerosis patients, it can cause dysryhthmia in the early period after first dose. Our first case is a 14-year-old girl with relapsing–remitting paediatric multiple sclerosis patients who was started to take fingolimod treatment. In the fifth hour of the follow-up, asymptomatic bradycardia was seen and the electrocardiogram was consistent with first-degree atrioventricular block. Her rhythm got spontaneously normal after 12 hours. Second case was 13 years old girl. Steroid treatment was started after her first paediatric multiple sclerosis attack. Despite treatment, she had a second attack 2 weeks after the first attack. Therefore, the neurologist switched to fingolimod therapy. Second-degree atrioventriculer block developed after 4 hours from the initiation of therapy. After 8 hours, rhythm regressed to first-degree atrioventricular block then returned to normal up to 13th hours of follow up. The aim of this article is to draw attention to dysrhythmia side effect of fingolimod which can be fatal. Therefore, the clinician must take precautions. Close cardiac rhythm monitoring is mandatory after the initiation fingolimod theraphy.

Multiple sclerosis is chronic inflammatory and demyelinating disease of the central nervous system. Early onset of multiple sclerosis, at age younger than 18 years is called paediatric multiple sclerosis. Paediatric multiple sclerosis often progresses in a relapsing–remitting form. Fingolimod is a reliable agent with proven efficacy in relapsing–remitting paediatric multiple sclerosis disease. However, it can lead bradycardia or atrioventricular conduction disorders especially at the beginning of the treatment. In this article, we reported two cases with this predictable side effect of fingolimod.

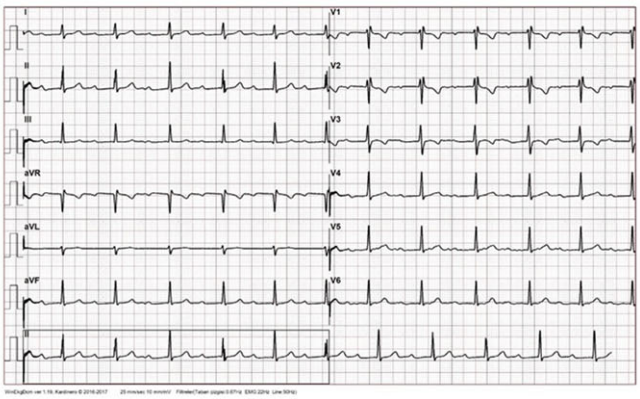
Cases

First case is a 14-year-old female patient who was diagnosed with multiple sclerosis in November 2021. In the first attack, pulse methylprednisolone was given to the patient, and than as a maintenance therapy interferone-beta 1a was started. In April 2022, patient had a new attack. During acute period, patients general condition was improved by administration of pulse methylprednisolone therapy. Then interferone-beta 1a treatment was requested to be replaced with fingolimod. Paediatric cardiology evaluation was performed in terms of possible cardiac side effects. ECG was normal. In echocardiographic examination, silent PDA with no haemodynamic significance was detected. Paediatric cardiology consented to start fingolimod and recommended a 6-hour cardiac rhythm monitorisation after the first dose of drug. The patient hospitalised after 1 month for the initiation of oral fingolimod treatment as 0.5 mg dose daily. Cardiac rhythm monitorisation was provided for possible arrhythmias after the first dose. First-degree AV block developed in the 5th hour of the follow-up.(Fig 1a)

Monitored follow-up of the patient was continued. Fingolimod treatment was ceasaed. At the 12th hour of the follow-up, the rhythm completely returned to normal. (Fig 1b)

Second case is a 13-year-old female who admitted to our hospital in March 2022 with the complaint of blurred vision. Optic neuritis was detected by ophthalmology department and paediatric neurology consultation was requested. She was diagnosed with multiple sclerosis by the evaluation of paediatric neurology. Pulse methylprednisolone was given during the attack period. Pulse methylprednisolone treatment was given 7 days for ongoing optic neuritis and therapy continued with oral prednisolone following 2 weeks. Paediatric neurology outpatient control was recommended 2 weeks later. While taking oral prednisolone treatment patient

(*a*) ECG of 14 years old girl after initiation of oral fingolimod treatment. First degree AV block developed in the 5th hour of the follow-up.



(*b*) ECG of 14 years old girl after cessation of fingolimod treatment. The rhythm completely returned to normal.

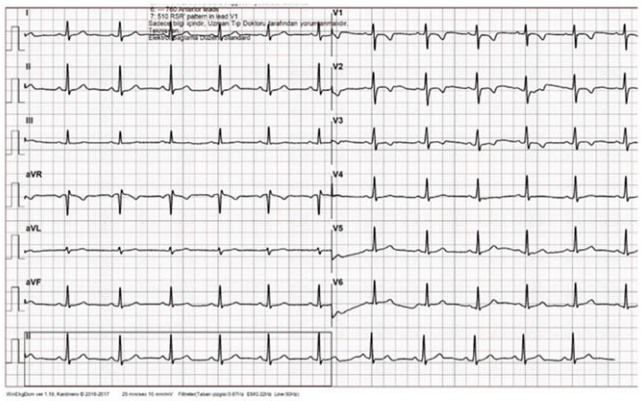
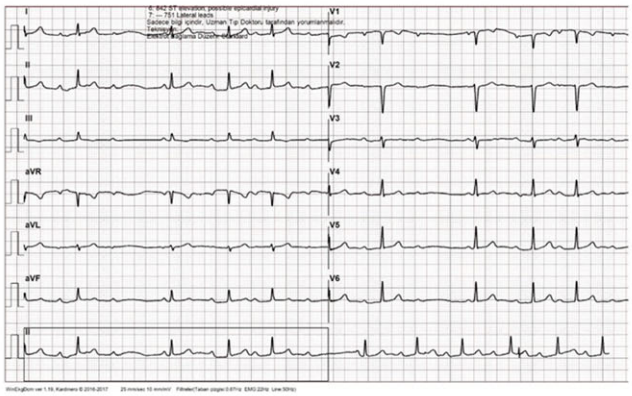
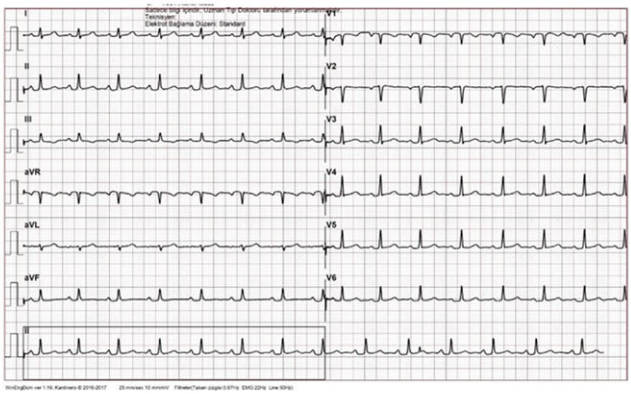


Figure 1. ECG changes of 14 years old patient after first dose of drug.

(*a*) ECG of 13 years old girl after initiation of oral fingolimod treatment. Second degree AV block developed after four hours .



(*b*) ECG of 13 years old girl after cessation of fingolimod treatment. After an average of 8 hours the rhythm regressed to 1st degree AV block.



(*c*) ECG of 13 years old girl after cessation of fingolimod treatment. After 13 hours rhythm got normal sinus

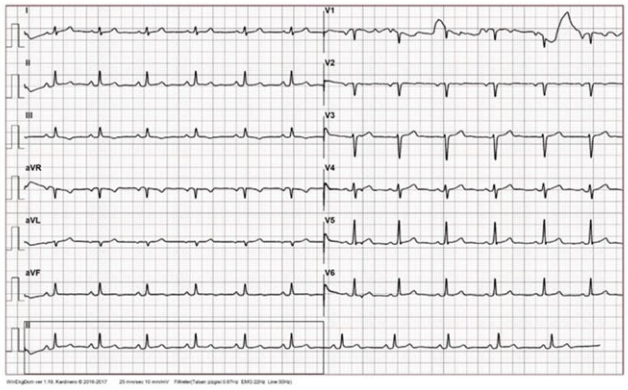


Figure 2. ECG changes of 13 years old patient after first dose of drug.

had an early second attack. Therefore, fingolimod therapy planned. The ECG was normal in the paediatric cardiology pre-treatment evaluation. Echocardiographic evaluation revealed mild mitral valve prolapse with a trace-minimal regurgitation. Paediatric cardiology consented to start fingolimod and recommended 6 hours cardiac rhythm monitorisation after initial dose.

Second-degree AV block developed after 4 hours of the initial therapy and fingolimod was stopped. (Fig 2a) After an average of 8

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hours, the heart rhythm first regressed to first-degree AV block. (Fig 2b) After 13 hours, rhythm got normal sinus (Fig 2c). Next day the patient underwent a holter ECG and no pathology was determined.

Discussion

Multiple sclerosis is a chronic inflammatory and demyelinating disease of the central nervous system that usually occurs in young adults in the 3rd and 4th decades. Sometimes, the first symptoms appear before the age of 18. The form of disease appears before age of 18 is called paediatric multiple sclerosis. In the review of Brola and Steinborn in 2020, it was reported that 3–5 % of multiple sclerosis patients started in childhood.[1] In 2009 Gorman et al., in their comparative study, stated the features that distinguish paediatric multiple sclerosis from adult multiple sclerosis. It is typical that the course of the disease is in the form of relapsing–remitting. The primary progressive form is very rare. The interval between disease onset and subsequent recurrences is shorter. It has a higher recurrence rate compared to adult multiple sclerosis.[2] The disease is relatively difficult to treat. The effectiveness of disease-modifying therapy drugs in children and adolescents is generally based on observational studies. Therefore, the number of drugs accepted for disease-modifying therapy is limited. In a multicentre study conducted in 2006, it was recommended to start the first-line treatment in pulse methylprednisolone with interferon beta or glatiramer acetate which is more safe.[3]Transition to second-line therapy should be considered in the presence of rapidly progressing severe multiple sclerosis or when the first-line therapy is not effective. Fingolimod is a second-line disease-modifying therapy agent approved by the FDA in 2008 for the treatment of children aged 10 years and older with relapsing–remitting form of disease. In a clinical study conducted in 2018, it was observed that fingolimod significantly reduced annual MRI activity and brain volume loss compared to interferon beta-Ia. However, it has been stated that the frequency of serious side effects can be seen.[4] While fingolimod pharmacologically exerts a non-selective agonistic effect on sphingosine-1 receptors, it shows functional antagonism to the sphingosine-1 receptors-1 subtype by inducing receptor down-regulation.[5] Fingolimod has been approved by the FDA and EMA in patients with relapsing–remitting paediatric multiple sclerosis. However; in a small patient population, transient asymptomatic bradycardia has been reported upon initiation of therapy. Asymptomatic bradycardia with or without atrioventricular block is usually self-limited. Petruzzo et al. reported that arrhythmia developed in the first 6 hours after the administration of the first oral dose of fingolimod in their case report in 2021. Therefore, they recommended that patients starting treatment should be monitored during this initial period to identify any changes in their electrocardiogram and heart rate which may require further treatment.[6] In addition, fingolimod is contraindicated in patients with cardiac diseases ranging from cardiac conduction defects to ischaemic heart disease and heart failure.[7]

In the report of two cases by Zanetta et al. in 2021, it was stated that Fingolimod is an effective disease-modifying therapy agent especially in the control of relapsing–remitting paediatric multiple sclerosis disease. Fingolimod has an important place in clinical treatment, especially in paediatric age group, due to the lack of drugs with proven efficacy in resistant remitting–relapsing type multiple sclerosis disease. Close rhythm monitorisation is required, especially at the beginning of the first dose, to avoid complications related to rhythm disorders such as bradycardia with or without atrioventricular block, which is one of the predictable side effects of the drug and to give treatment when necessary.[8]

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Competing interest. None.

Ethical standards. The study protocol conforms to the ethical guidelines of the 1975 Declaration of Helsinki as reflected in a priori approval by the institution's human research committee.

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