

ORIGINAL ARTICLE

# Cardiac autonomic modulation in juvenile idiopathic arthritis with use of biological medication

Patrícia Merly Martinelli<sup>1,2,3</sup>, Ana Carolina Gonçalves de Abreu<sup>1</sup>, José Rener Cordeiro da Silva<sup>3</sup>, Asami Takahara Vasconcelos<sup>3</sup>, Adilson Monteiro<sup>1,4</sup>, Valdelias Xavier Pereira<sup>1</sup>, Rodrigo Daminello Raimundo<sup>1</sup>



<sup>1</sup>Laboratório de Delineamento de Estudos e Escrita do Centro Universitário Saúde ABC, Santo André, São Paulo, Brasil.

<sup>2</sup>Centro Universitário UniDomBosco, Curitiba – (PR), Brasil.

<sup>3</sup>Laboratório de Delineamento de Estudos e Escrita Científica do Centro Universitário UNINORTE – Rio Branco (AC), Brasil.

<sup>4</sup>Universidade Federal do Mato Grosso (UFMT) – Rondonópolis (MT), Brasil.

**Corresponding author**

martinelli\_patricia@hotmail.com

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**Abstract**

**Introduction:** The introduction of biological medication in Juvenile Idiopathic Arthritis (JIA) proposes better therapeutic results with decreased pain and inflammation and consequent reduction in joint damage. The autonomic state can be a predictor for verifying the response to immunomodulation therapy. Thus, measuring heart rate variability can express autonomous behavior and possibly accompany the response to therapy through the expression of the inflammatory condition.

**Objective:** Analysis of heart rate variability in a child with Juvenile Idiopathic Arthritis using the anti-Tumor Necrosis Factor.

**Methods:** This is a clinical case report of an 8-year-old male with a diagnosis of JIA - oligoarticular form, using etanercept, admitted to Clínica Escola de Fisioterapia UNINORTE, Acre, Brazil in 2017. We analyzed laboratory and imaging tests, kinetic-functional evaluation, examination of cardiac autonomic modulation and physiotherapeutic treatment for analgesic, anti-inflammatory purposes, gaining flexibility, strength and postural re-education, according to CARE guidelines, case report guidelines.

**Results:** After medication administration, there was a decrease in pain and normalization of serum creatinine (0.50 mg / dL) and CRP (less than 6 mg / dL) and an increase in erythrocyte sedimentation rate (17 mm3). In the examination of heart rate variability, the linear indices in the time domain showed a predominance of parasympathetic activity (RMSSD: 35ms), with decreased sympathetic control measured through the frequency domain (LF: 27.1 un). However, non-linear methods showed low variability with little dispersion of RR intervals.

**Conclusion:** In the present report, the linear indices showed parasympathetic predominance and in the non-linear analysis a low heart rate variability with abnormal and insufficient adaptation of the autonomic nervous system in a child with juvenile idiopathic arthritis using biological medication.

**Keywords:** juvenile arthritis, inflammation, etanercept, autonomic nervous system, heart rate variability.

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## Authors summary

### Why was this study done?

To describe cardiac autonomic behavior in a child using biological medication in order to understand the neurological influence of autoimmunity in this type of case.

### What did the researchers do and find?

The authors described a case report of an 8-year-old male child diagnosed with JIA - oligoarticular form, using etanercept (biological medication) through laboratory and imaging exams, kinetic-functional evaluation and cardiac autonomic modulation examination.

### What do these findings mean?

The description of childhood autonomic behavior of a boy undergoing biological drug treatment alerts the scientific community to a low-cost measurement test and mild discomfort such as HRV, which is an effective follow-up method.

## INTRODUCTION

Juvenile idiopathic arthritis (JIA) consists of a rheumatic disease characterized by chronic inflammation of the joints, lasting at least 6 weeks, unknown etiology, and onset before 16 years old<sup>1</sup>. It affects approximately 1 in every 1000 children in the world, with great variation of the prevalence by the different existing subtypes<sup>2</sup>. Rigante *et al.*<sup>3</sup> describe a frequency of 16 to 150 cases per 100,000 children.

The treatment of JIA has taken place in the last 10 years with the introduction of biological or immunobiological therapies aiming to inhibit Tumor Necrosis Factor alpha (TNF $\alpha$ ) and cytosine. This change brought improvements in therapeutic outcomes and quality of life. However, it restrains a discussion on the safety of the use of biological drugs<sup>4,5</sup>.

The autonomic system is related to the inflammatory disease's expression, consisting of a therapeutic or cofactor target that influences the treatment. This can be seen by examining the HRV<sup>6,7</sup>. Autonomic status may be a predictor to verify response to anti-TNF therapy<sup>4,6</sup>.

Thus, understanding the neurological influence of autoimmunity comprises current and important thematic for the outcome of this condition<sup>4,8</sup>. In this study, we attempted to describe the HRV in a child with JIA using the anti-tumor necrosis factor (etanercept).

## METHODS

This is a case report of an 8 year-old, male, with a diagnosis of JIA - oligoarticular form, using etanercept, admitted to the Physiotherapy's Clinic School UNINORTE, Acre, Brazil, in 2017. Laboratory and imaging exams were evaluated and kinetic-functional evaluation, cardiac autonomic modulation examination and physiotherapeutic treatment with analgesic, anti-inflammatory, flexibility gain, strength and postural reeducation were performed. The manuscript was approved by the Ethics and Research Committee under the number of opinion 2,766,017/2018 and followed the CARE guidelines, case report guidelines.

## CASE REPORT

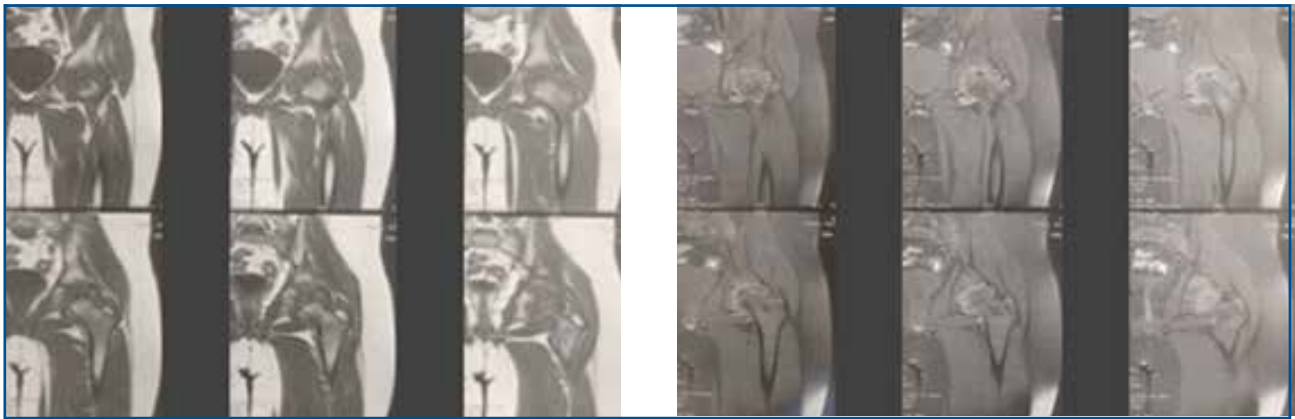
Patient's identification: T. A. F., 8 years old, male, dark skinned, public student of the basic level, native from Rio Branco – AC/Brasil, living with parents and two siblings.

Main complaint and duration: Forwarded to the Physiotherapy Service of the Physiotherapy's Clinic School UNINORTE in April 2017, with pain complaints in lower limbs (LMI) and claudication.

Previous History of the present disease: Clinical diagnosis of Juvenile Idiopathic Arthritis, oligoarticular form. The patient presented tonsillitis and sporadic colds, pain in the lower limbs (hip, knee and ankle) and lumbosacral spine, left hip discrepancy (1 cm) with antalgic gait. The previous history reveals the onset of pain at the age of four, in 2015, followed by pain and inflammation in the joints of the hip, knee, ankle, lumbar and sacral spine, between acute and remission status, Nuclear Magnetic Resonance (NMR) of the left hip (2015.08.08) presented avascular necrosis of the femoral head. The clinical diagnosis of JIA was confirmed at the age of seven, with hemossedimentation rate: 14 mm in the first hour, reference values (RV): 0 to 20 in the first hour and normal C - reactive protein (less than 6 mg/dL, RV: negative - lower than 6.0 mg/dL) and decreased serum creatinine (0.43 mg/dL, RV: 0.70 to 1.20 mg/dL) with a positive response to drug treatment with metotroxane (10 mg) and prednisolone 5 ml 12/12h (1mg/ml). In August 2016, there was an increase in C-reactive protein (0.50 mg/dL, RV: 0 to 5 mm<sup>3</sup>) and hemossedimentation rate (11 mm<sup>3</sup> in the first hour, RV: 0 to 5 mm<sup>3</sup>), serum creatinine (0.49 mg/dL). X-ray (2016.05.06) showed impaction, sclerosis, irregularity and deformity of the femoral head's epiphysis (Figure A.1). The NMR examination, on 2017.08.06, identified avascular necrosis of the femoral head, characterized by fragmentation, collapse and sclerosis of the femur's proximal epiphyseal ossification center, associated with moderate stroke/synovial thickening in the hip (Figure A.2) .



Figure A. 1: Left hip x-ray - AP / OBLIQUA.



**Figure A. 2:** Nuclear magnetic resonance. The. Cross section, T1 weighting. B. Cross section, T2 weighting, bone window.

Interrogation about devices: deny.  
Personal and family history: deny.

**Clinical Findings**

General and specific clinical examination: in August/2016 presented good general condition, ruddy, hydrated, afebrile (axillary temperature: 36.6°C), normal heart rate variability: 76 beats per minute (bpm), normotensive (100/60 mmHg), eupneic (respiratory rate 23 irp/m), heart and lung auscultation without relevant findings, weight: 28,400 kg, height: 124 cm, normal body mass index (BMI): 18.21 kg/m<sup>2</sup>. Distended and flaccid abdomen, with no pain complaint in palpation, positive Fabere test to the left, pain while performing the test and a lot of resistance.

Kinetic-functional evaluation: presented a pain

complaint during hip and left knee movements and to prolonged orthostatism, with irradiation to the anterior region of the left lower limb. Decreased muscle strength (MS), Impaired flexibility in left hip flexion (100°) and preserved reflexes. Asymmetry in lower limbs with right-sided scoliosis, lumbar hyperlordosis, abdominal protrusion, bilateral internal femoral rotation, plantar arch collapse, with global static postural alteration (Figure A.3).

Diagnostic: Juvenile idiopathic arthritis - oligoarticular.

Prognostic: With appropriate treatment, joint prognosis is often good in patients whose disease is limited to a few joints. With the introduction of the biological agent we sought remission or low disease activity and prevention of irreversible joint damage.



**Figure A. 3:** anterior view (a), posterior (b) and lateral (c), discrepancy in MMII (d).

## Therapeutic Intervention

**Medical conduct:** Laboratory and complementary exams were requested and an active phase of the disease was verified with refractory response to conventional therapy. The rheumatologist prescribed etanercept (25 mg) through monthly assisted infusions (August/2016).

**Physiotherapeutic conduct:** minimization of the pain and inflammation, maintenance of muscle trofism and range of motion.

**Adverse and unforeseen events:** the patient presented recurrent pharyngotonsillitis.

**Laboratory tests:** In February 2017, serum creatinine values of 0.50 mg/dL (RV: <0.50) and hemosedimentation rate of 17.00 mm<sup>3</sup> in the 1st hour (RV: 0 to 5 mm<sup>3</sup>) and C-reactive protein (less than 6 mg/dL, VR: negative - less than 6.0 mg/dL).

## Complementary examinations

In February/2017, the HRV test was performed by the Polar Rs800cx heart rate monitors, with beat-to-beat recording, and only those series with more than 95% of sinus beats were used for analysis. The capture was subjected to digital filtering in Polar Precision Performance SW software (version 4.01.029) and Kubios<sup>9</sup> software. HRV was analyzed in time and frequency domains.

When comparing the linear indexes, time domain, with findings in the literature of healthy children, in the same age group, an increase (35.8 ms) in the RMSSD is observed (square root of the square mean of the differences between successive normal RR intervals, found from the analysis of adjacent RR intervals, in a time interval), which expresses the behavior of the parasympathetic activity. In the frequency domain it is observed that the variable low frequency (LF-0.04-0.15) was decreased (27.1 un), this reveals the sympathetic and parasympathetic behavior through the baroreflex activity, with sympathetic predominance. The high frequency peak (HF-0.15-0.4 Hz) representing the parasympathetic (vagal) activity, influenced by breathing, was elevated (78.2 un). Thus, it was observed a predominance of the parasympathetic ANS on the cardiac autonomic modulation with HRV increase both in the frequency domain and in the time domain.

## DISCUSSION

The influence of the autonomic nervous system on the inflammatory disease's response, through its interaction with the immune system, has been the aim of researches<sup>4,5</sup>. Studies show that autoimmune disease can affect autonomic homeostasis<sup>6,8,10</sup>. Research performed in patients with Sjogren's Syndrome showed an increase in the parasympathetic response, with a reduction in LF and an increase in HF, corroborating with the findings of this report<sup>11</sup>.

Holman *et al.*<sup>4</sup> described the HRV as a predictor exam of response to anti-TNF therapy in patients with inflammatory arthritis and emphasizes the importance of autonomic influence on the expression of autoimmune diseases. Boettger *et al.*<sup>12</sup> verified changes in rats' HRV and observed that initially there was a predominance of sympathetic ANS, followed by a reduction of this tone after the administration of etanercept. The authors suggest

that the neutralization of TNF alpha reduces sympathetic tone due to the reduction of the peripheral inflammatory response caused by the medication.

A prospective analysis of the HRV in psoriatic patients demonstrated a significant decrease in sympathetic oscillatory (LF%) and low/high frequency (LF/HF) components after treatment with etanercept. Thus, it was evidenced that the use of the medication can affect the cardiac autonomic modulation and reduce the cardiovascular risk<sup>13</sup>.

The use of anti tumor necrosis factors has shown a decrease in inflammatory response, with delayed bone degeneration and improvement in patients' quality of life<sup>4,12</sup>.

The novelty of the study is the description of the autonomic behavior in the boy's childhood in biological drug treatment, alerting the scientific community to a low-cost measurement and mild discomfort examination such as HRV, consisting of an effective method of follow-up.

The case report is related in the scientific literature as the type of initial study design to develop new possibilities of study design, being limited in bringing results of causality and reproducibility. Perceptions of the patient involved were not reported because they were not appropriate in this case report.

Studies have sought to describe the mechanisms of neuroendocrine regulation and its influence on inflammatory diseases<sup>4,8,10,14-16</sup>. The investigations are based on the effect of inflammatory cytokines on sympathetic activity and feedback cycles; existence of correlation between inflammation and HRV markers; an interaction of sympathetic predominance with inflammatory processes or even TNF itself as a direct depressant of HRV, causing an attenuation of beta adrenergic signaling<sup>4,8,17</sup>.

In this case's report a parasympathetic predominance and insufficient adaptation of the autonomic nervous system was observed. Thus, there is a need for greater discussion about the topic for understanding and standardization of autonomic behavior in immunomodulators<sup>18</sup>.

## CONCLUSION

In the present report linear indexes presented a parasympathetic predominance with an increase in HRV, evidencing a good adaptation of the autonomic modulation before the treatment.

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## Resumo

**Introdução:** A introdução de medicamentos biológicos na Artrite Idiopática Juvenil (AIJ) propõe melhores resultados terapêuticos com diminuição da dor e inflamação e consequente redução no dano articular. O estado autonômico pode ser um preditor para verificar a resposta à terapia de imunomodulação. Assim, medir a variabilidade da frequência cardíaca pode expressar um comportamento autônomo e possivelmente acompanhar a resposta à terapia através da expressão da condição inflamatória.

**Objetivo:** Análise da variabilidade da frequência cardíaca em uma criança com artrite idiopática juvenil utilizando o Fator de Necrose Tumoral.

**Método:** Este é um relato de caso clínico de um homem de 8 anos com diagnóstico de AIJ - forma oligoarticular, usando etanercept, admitido na Clínica Escola de Fisioterapia UNINORTE, Acre, Brasil em 2017. Analisamos testes laboratoriais e de imagem, cinéticos - avaliação funcional, exame da modulação autonômica cardíaca e tratamento fisioterapêutico para fins analgésicos e anti-inflamatórios, ganhando flexibilidade, força e reeducação postural, de acordo com as diretrizes da CARE, diretrizes de relato de caso.

**Resultados:** Após a administração da medicação, houve diminuição da dor e normalização da creatinina sérica (0,50 mg/dL) e PCR (menos de 6 mg/dL) e aumento da taxa de sedimentação de eritrócitos (17 mm<sup>3</sup>). No exame da variabilidade da frequência cardíaca, os índices lineares no domínio do tempo mostraram predominância da atividade parassimpática (RMSSD: 35ms), com diminuição do controle simpático medido pelo domínio da frequência (LF: 27,1 un). Entretanto, métodos não lineares apresentaram baixa variabilidade com pouca dispersão dos intervalos RR.

**Conclusão:** No presente relatório, os índices lineares mostraram predominância parassimpática e, na análise não linear, baixa variabilidade da frequência cardíaca com adaptação anormal e insuficiente do sistema nervoso autônomo em criança com artrite idiopática juvenil em uso de medicação biológica.

**Palavras-chave:** artrite juvenil, inflamação, etanercepte, sistema nervoso autônomo, variabilidade de frequência cardíaca.

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