CASE STUDIES

Tumor necrosis factor-alpha blockade with etanercept improves autonomic dysfunction in rheumatoid arthritis

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Abstract

Rheumatoid arthritis (RA) is an autoimmune and chronic inflammatory disease associated with autonomic neuropathy. There is no specific treatment recommendation for autonomic neuropathy (AN) in rheumatic diseases. In addition, there is no study demonstrating therapeutic efficacy of TNF-inhibitor (TNFi) etanercept on autonomic neuropathy in RA. This is the first reported observation of improvement in AN with blockade of TNFi-etanercept in RA. We report a case of a 46-year-old female with severe disease activity treated with subcutaneous etanercept 50mg once a week along with methotrexate 15 mg/week. A significant improvement in cardiovascular autonomic neuropathy and sudomotor function was noted after 6 weeks of treatment.

Keywords: Rheumatoid arthritis, etanercept, autonomic dysfunction, cardiovascular autonomic neuropathy, sudomotor dysfunction.

Introduction

Autonomic neuropathy, a well-recognized extra-articular manifestation of rheumatoid arthritis (RA), is first reported by Bennett and Scott in 1965.[1] It has been shown to be one of the most important predictors of cardiovascular risk.[2] However, despite the completion of half a century after the first reporting of the condition, there is no specific therapeutic strategy for autonomic dysfunction in rheumatic diseases. Therapeutic effect of disease-modifying anti-rheumatic drugs (DMARDs) and biologic DMARDs (infliximab, tociluzimab, rituximab) on autonomic neuropathy has been demonstrated in RA and ankylosing spondylitis (AS) patients.[3-5] However, there is no specific treatment recommendation for autonomic neuropathy in RA. Treatment with TNF-inhibitor (TNFi) etanercept has revolutionized the treatment of RA, however, its impact on autonomic neuropathy has not been reported. The present case study describes the improvement of autonomic neuropathy with etanercept in RA.

Case report

A 46-year-old normotensive, non-diabetic female with 20 years of seropositive RA with inadequate response to combination of synthetic DMARDs (methotrexate 15 mg/week, hydrochloroquine 400 mg/day and sulphasalazine 3 gm/day) was initiated with subcutaneous etanercept 50 mg once a week along with methotrexate 15 mg/week.

In addition to active RA, the patient had light headedness and bloating after eating a small meal. These symptoms were suggestive of autonomic dysfunction. High erythrocyte sedimentation rate (ESR) of 35 mm/1st hr and high c-reactive protein (CRP) of 21 mg/dl were noted, and DAS-28 (Disease Activity Score in 28 joints) score was 8.35 (Table 1). Cardiovascular autonomic function tests were assessed using a battery of non-invasive tests and sudomotor function- peripheral sympathetic autonomic function (Sudoscan-Impeto Medical Device, EZS 01750010193, Paris-France). Autonomic function tests showed marked abnormalities of sympathetic, parasympathetic and sudomotor function (Table 1 and Fig. 1). No other cause for neuropathy was apparent from clinical history, physical examination and biochemical screening.

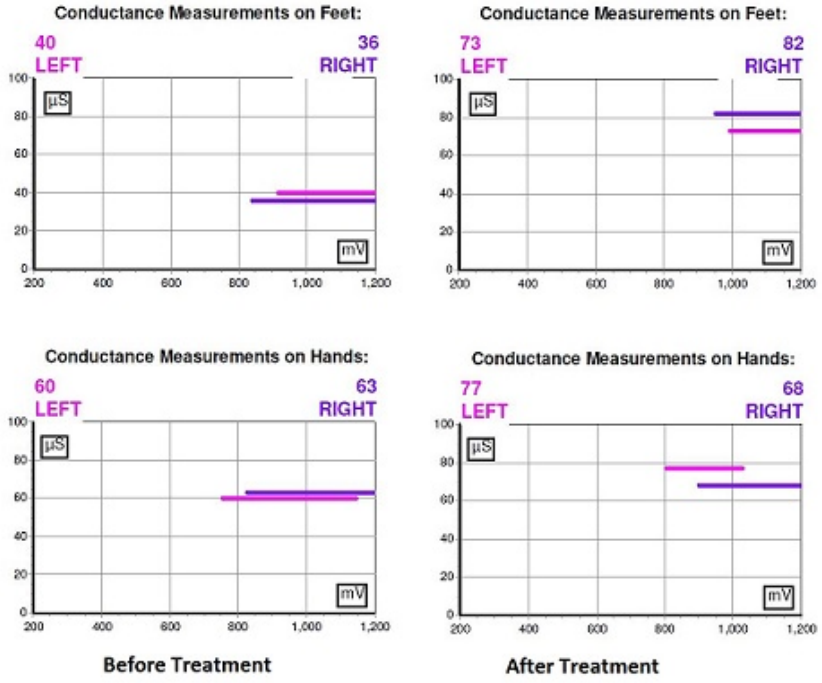
Vitamin D, vitamin B12, and thyroid, renal and liver

Table 1: Clinical and autonomic function characteristics

Categorical variables	Baseline	After 6 weeks	Normal
HR response to deep breath (PS)	19	20	≥15
HR response to standing (PS)	0.96	1.16	≥1.04
HR response to valsalva (PS)	1.04	1.12	≥1.21
BP response to standing (S)	15	07	≤10
BP response to handgrip (S)	05	18	≥16
Sudoscan (µs)	49.5	75	>60
ESR (mm/1st hr)	35	27	0-10
CRP (mg/dl)	35.4	3.50	<6
DAS-28	8.35	4.68	<2.5
HAQ-DI	2.1	1.1	----

Abbreviations: PS parasympathetic damage; S sympathetic damage; HR heart rate; SBP systolic blood pressure; DBP diastolic blood pressure; ESR erythrocyte sedimentation rate, CRP C-reactive protein, DAS-28 diseases activity score in 28 joints. The values of sudoscan expressed the mean of both hands and feet.

Fig. 1: Sudomotor function before and after 6 weeks of treatment with etanercept



functions were normal. No abnormalities were reported in detailed neurological examination. Autonomic function tests were repeated after 6 weeks of etanercept exposure. After 6 weeks of therapeutic etanercept, there was a rapid improvement in heart rate response to standing and valsalva reflecting parasympathetic autonomic activity, and blood pressure response to handgrip reflecting sympathetic autonomic activity (Table 1). There was also a significant improvement in sudomotor function after 6 weeks of therapy (Table 1). ESR, CRP and DAS-28 scores were reduced (Table 1) and autonomic symptoms disappeared after 6 weeks of etanercept administration.

Discussion

This is the first case study to demonstrate the therapeutic impact of TNFi etanercept on autonomic neuropathy in RA. The early diagnosis and appropriate treatment of autonomic neuropathy is important because of patients being at higher risk of cardiovascular morbidity and mortality.[6] Cardiovascular autonomic neuropathy is a significant risk predictor for sudden cardiac death in autoimmune rheumatic diseases.[7]

The improvement of autonomic dysfunction by TNFi etanercept therapy could be explained by the following theoretical evidence. Primarily, it has been proposed that the drug action might be through the inhibition of inflammatory cytokines. In a recent study it has been suggested that increased disease severity, ESR, TNF-α and IL-6 predicts the autonomic dysfunction in RA, and TNF-α and IL-6 blockade could potentially be beneficial for the treatment of autonomic dysfunction.[8] This hypothesis is supported by the observation that RR interval variability (heart rate variability) is a marker of vagus nerve tone and is inversely related to levels of inflammatory markers (IL-6 and CRP) in the Coronary Artery Risk Development in Young Adults(CARDIA) study.[9] A study by Malave and colleagues has demonstrated that circulating level of TNF has been described as an independent predictor of depressed heart rate variability.[10] Furthermore, a similar study has shown that heart rate variability predicts anti-TNF therapy response in RA patients.[11] Secondly, the patients with increased ESR, CRP and disease activity also have disturbances in the balance of the autonomic nervous system. Finally, there is numerous evidence for the contribution of the nervous system to inflammation. A review (2008) of thirteen studies on heart rate variability, inflammation, and cardiovascular function by Haensel *et al.* has stated a strong relationship between heart rate variability and inflammatory markers in cardiovascular diseases.[12]

Conclusion

To the best of our knowledge this is first reported observation of improvement in autonomic neuropathy with etanercept, in RA. In conclusion, the present case highlights that abnormal cardiovascular autonomic function and peripheral sympathetic neuropathy appeared to be rapidly improved after treatment with etanercept. Further clinical studies are warranted to confirm these observations and explore the role of etanercept in large population.

Competing interests

The authors declare that they have no competing interests.

Citation

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