CASE STUDIES

Tumor necrosis factor inhibition may improve autonomic dysfunction in rheumatoid arthritis

Ashit Syngle[1]*, Inderjeet Verma[2], Pawan Krishan[2], Nidhi Garg[2]

[1]Director Cardio Rheuma & Healing Touch City Clinic, Chandigarh & Senior Consultant Physician & Rheumatologist Fortis Multi Speciality Hospital, Mohali, India

[2]Department of Pharmaceutical Sciences & Drug Research, Punjabi University, Patiala, India

Abstract

Autonomic nervous system (ANS) involvement in rheumatoid arthritis (RA) has been well recognized. Symptoms of autonomic dysfunction are absent and not specific, but diagnosis of ANS dysfunction by non-invasive means is warranted to prevent severe consequences. However, there is no study demonstrating therapeutic efficacy on autonomic neuropathy (AN) in RA. This is the first reported observation of improvement in AN with the TNF-α inhibitor (TNFi), infliximab in RA.

We report here a case of a 57-year-old, seropositive RA female with severe disease activity, investigated for AN. Non-invasive tests based on peripheral sympathetic and cardiovascular autonomic neuropathy (CAN) function were used for accurate assessment of autonomic function. The patient was treated with infliximab 3 mg/kg intravenous infusion at weeks 0, 2, and 6. An improvement in autonomic dysfunction was noted after 6 weeks of therapy in both sympathetic and parasympathetic CAN.

Introduction

Rheumatoid arthritis (RA), a chronic inflammatory disease affecting the synovial tissue, causes irreversible joint damage, chronic pain, stiffness, functional impairment and premature mortality. It affects about 1% of the general population. The extra-articular manifestations of RA are diverse involving many organ systems.[1] The involvement of autonomic nervous system (ANS) has been reported to occur in 24-100% of the patients with RA.[2] Autonomic neuropathy in RA was first reported by Bennett and Scott in 1965.[3] The study conducted by Toussirot *et al.* demonstrated that among 50 RA patients, 60% had ANS dysfunction, defined by abnormal results of two of the three cardiovascular reflex tests.[4] However, autonomic dysfunction is now well documented in RA.[2-5] Evaluation of sympathetic and parasympathetic nervous system involvement has been done employing sweat response, orthostatic test and combination of cardiovascular reflex tests. Recently, autonomic dysfunction has also been reported in psoriatic arthritis.[6] Although the symptoms of autonomic dysfunction may be absent, non-specific and extremely varied; diagnosis of ANS dysfunction is non-invasive and is warranted in patients to prevent severe consequences including sudden death.

Infliximab, a TNF-inhibitor (TNFi), is now widely used in the treatment of RA and other autoimmune diseases due to its efficacy. Infliximab has also been shown to improve the endothelial dysfunction associated with the chronic inflammation in RA and ankylosing spondylitis.[7-8] We report here a case of RA with autonomic dysfunction treated with infliximab and its effect on AN. To the best of our knowledge this is the first reported observation of improvement in AN with infliximab in RA.

Methods

We here in report a case of 57-year-old woman with 9 months history of severe RA, who was treated with combination of methotrexate 15 mg/week, leflunomide 10 mg/day and hydroxychlorquine 400 mg/day. The patient was investigated for AN. Autonomic function was assessed by a battery of non-invasive tests. Cardiovascular autonomic dysfunction was diagnosed by applying cardiovascular reflex tests according to Ewing, and was considered to exist if at least two tests were positive.[6, 9] Peripheral sympathetic autonomic

function was assessed by Sudoscan (Sudoscan - Impeto Medical Device, EZS 01750010193, Paris, France).[9, 10] All tests were performed under standardized conditions, in climate-controlled rooms (temperature=23°C), in the morning. Symptoms of ANS were assessed by administering the questionnaire survey of autonomic symptoms. Infliximab 3 mg/kg/dose intravenous infusion at weeks 0, 2, and 6 was added to her treatment regimen.

Results and Discussion

The patient was a 57-year-old female diagnosed with seropositive RA around 9 months before. She was normotensive and non-diabetic with a history of synthetic disease modifying anti-rheumatic drug (DMARD) failure.

Table 1:Results of autonomic profile and clinical tests

Parameters	Time intervals			
	0 week	2 week	6 week	Normal values
HR response to Valsalva (PS)	1.28	1.27	1.29	≥ 1.21
HR response to deep breath (PS)	08*	08	17	≥ 15
HR response to standing (PS)	0.96*	1.0	1.04	≥ 1.04
BP response to standing (S)	08	06	02	SBP ≤10
BP response to handgrip (S)	06*	14	18	DBP ≥16
Sudoscan (S)	65	69	76	> 60 µs
ESR mm/hr	37	28	20	0-10
CRP mg/dl	11	1.35	6.0	< 6
DAS-28	7.17	6.34	4.0	< 2.5

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. * Indicates autonomic dysfunction

She had high erythrocyte sedimentation rate of (37 mm/1st hr), C-reactive protein level (4.90 mg/dl), and Disease Activity Score in 28 joints (DAS-28) (Table 1). The patient is a teetotaler. No other cause for neuropathy was found on biochemical screening. Thyroid, renal, and liver functioning and the level of vitamin B12 were normal.

Cardiovascular autonomic function tests showed marked abnormalities in both parasympathetic and sympathetic functions (Table 1). There was no sudomotor dysfunction in hands and feet. The patient did not have any symptom of AN. Autonomic function tests were repeated before every infusion of infliximab till 6 weeks. After 3 doses of infliximab, all autonomic function became normal (Table 1).

Despite its massive prevalence, the pathogenesis of the autonomic neuropathy in RA is not clearly understood. It could result from vasculitis, amyloidosis or therapeutic side effect. The presence of circulating autoantibodies against nerve growth factor and the vagus nerve has been demonstrated in RA patients who had cardiovascular ANS dysfunction.[12] In a recent study, it was found that the autonomic dysfunction in RA is related to elevated intrathecal proinflammatory cytokine interleukin-1β, which reduces the vagus activity and interferes with the cholinergic neurotransmission.[13] Increasing evidence has demonstrated that TNF-alpha is a crucial cytokine in the pathogenesis of RA. The pathogenic role of TNF-alpha has been also shown in the development of AN in type 1 diabetes.[14] Recent studies in type 2 diabetes and heart failure patients have showed that TNF-alpha is an independent predictor of depressed heart rate variability, a representative marker of cardiovascular autonomic neuropathy.[15, 16] However, we have not been able to find any published literature demonstrating the impact of infliximab or any drug on AN in RA. Given the deleterious effect of AN on morbidity and mortality, it is important to study the effect of at least the existing therapeutic modalities on the autonomic dysfunction. In the present study, improvement in inflammatory disease activity as well as autonomic function is noticed in RA patient treated with the TNFi.

Conclusion

The study finding suggests that the improvement in both sympathetic and parasympathetic autonomic functions may be due to inhibition of TNF-alpha or disease remission. Further studies are warranted to confirm these observations and explore the role of infliximab and other therapeutic molecules on autonomic dysfunction in RA.

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Competing interests

The authors declare that they have no competing interests.

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* Correspondence: Dr. Ashit Syngle, Director Cardio Rheuma & Healing Touch City Clinic, Chandigarh & Senior Consultant Physician & Rheumatologist, Fortis Multi Speciality Hospital, Mohali, India
ashitsyngle@yahoo.com

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