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Case series with review of the literature

Title:

Concomitant rheumatoid arthritis and amyotrophic lateral sclerosis. Report of two new cases and review of literature.

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Abstract

Objective. To describe a rare association between rheumatoid arthritis (RA) and amyotrophic lateral sclerosis (ALS). **Methods.** Two new case of patients with RA who developed amyotrophic lateral sclerosis (ALS), one reciving anti-TNFα agents, were reported. **Results.** Only other 5 cases of this rare association have been previously described in literature. The simultaneous presence of the two diseases represent a difficult diagnostic challenge because RA may mimic some musculoskeletal symptoms of ALS. There is no evidence in favor of a common pathophysiologic mechanism and thus the possibility of a fortuitous association must be raised. A neurotoxic side effect of various drugs for RA treatment could be considered. **Conclusions.** Casual or causal association remains a difficult choice. The possibility of a coincidental association must be raised but neurological side effects of TNF α blockers leads to discussion.

Key words:
Rheumatoid arthritis; amyotrophic lateral sclerosis (ALS); tumor necrosis factor alfa (TNF-α) blockers, motor neuron disease (MND).

Introduction

Rheumatoid arthritis (RA) is a systemic autoimmune disorder not confined to the joints. Neurological manifestations are detected in 40% of RA and include different form of peripheral neuropathy, such as mononeuritis multiplex or sensorimotor polyneuropathy, compressive cervical myelopathy and central or peripheral nervous system involvement mainly secondary to vasculitis. Different drugs commonly used for treatment may induce neurological complications. The development of anti-tumor necrosis factor alfa (TNFα) therapy is the most significant achievement in the treatment of the disease to date. Among the serious potential side effects the onset of neurologic disease, including demyelinating and multiple sclerosis (MS)-like syndrome, have been reported **(1-6)**.

Amyotrophic lateral sclerosis (ALS) is a degenerative motor neuron disease. Loss of pyramidal and anterior horn motor neurons leads to progressive limb weakness, disability, dysarthria, dysphagia and respiratory insufficiency with a progressive fatal course. The incidence of ALS ranges between 1.5 to 2.5 for 100,000 per year. Although there are familial cases of ALS, about 90% are sporadic and of unknown etiology. **(7).** Motor neuron involvement is unusual in rheumatoid arthritis. To our knowledge, only other 5 cases of this rare association have been previously described in literature, one of witch during anti-TNFα therapy **(8).** A potential role of TNF in the pathogenesis of neurodegenerative disease is still debated. TNFα is considered as a cytokine with both neuroprotective and neurotrophic effects. However, although TNFα-deficient animal models seems to be protected from motor neuron disease (MND), in trials with anti-TNFα therapy a worsening in the disease course has been observed in MS patients. This suggesting a causative relationship **(9).**

Here we report two new case of patients with RA who developed amyotrophic lateral sclerosis (ALS), both with bulbar syndrome, one during treatment with anti-TNα agent.

Case Reports

Case n. 1

A 65 years-old white female, affected by well controlled arterial hypertension, was first seen on July 2001 at our Rheumatology Unit. She had a 10 years history of seropositive and erosive rheumatoid arthritis treated overtime with corticosteroids, gold, cyclosporine A, hydroxycloroquine and methotrexate. A TC scan recently obtained did show an initial involvement of cervical tract with slight atlo-epistrophic anterior subluxation without medullar involvement. For the persistent activity of the disease (DAS 28 6.72) she was screened for

therapy with infliximab, administered at the dose of 3mg/kg every 8 week after initial induction regimen with closer infusions. A quick improvement was noted and sustained during the following 8 months. Then, due to a flare of RA, the dosage of infliximab was increased to 5 mg/kg and a new positive clinical response was obtained. Four months after, she developed first transient and then persistent giugular oppression, dysartria and dysphonia. The voice became weak and nasal. Thereafter, she reported worsening rhinolalia, dysphagia for solids and liquids and hyposthenia of lingual and respiratory muscles, especially after prolonged exercise. Anti-TNF-α therapy was stopped and a diagnostic procedure was started. Thyroid and laryngeal disease were excluded. On the physical examination, strength loss in both upper and lower limbs was evident. A complete neurologic examination did show hypotrophia of masseter and lower facial muscles deficit. Muscle enzyme and inflammatory indices were normal. Anti-acetilcholine receptor antibodies and Tensilon® test were negative. Additional investigations for malignancy, vasculitis and amyloidosis were negative. Brain magnetic resonance (MR) did prove negative apart from some subcortical and bilateral nonspecific small T2-hyperintense lesions. An elettromyogram of the four limbs revealed a pathological denervation and reinnervation pattern. Trascranial magnetic stimulation (TMS) confirmed the upper motor neuron dysfunction with neurogenic bulbar and segmental deficit. At the follow-up she developed additional weakness and atrophy of the forearms and tenar muscle regions. TMS showed progression of abnormalities including progressive inexcitability of central motor pathways and loss of the normal inhibitory cortical stimulation silent period. Fasciculations were also noted first in the tongue and then in the arms and thighs. A neurological treatment programme was started. Unfortunately, pharmacological therapy with riluzolo was not tolerated. Thereafter physical and speech therapeutical approach was started but the motor weakness worsened with exitus due to ab ingestis complications and respiratory failure 5 years from diagnosis.

Case n. 2

The second case was a 74 year-old white woman with long-standing seropositive and erosive RA (30 years) and a secondary pulmonary fibrosis, who had failed many DMARDs approach with cyclosporine, gold and methotrexate, this one for 10 years at least. She developed rapidly severe dysphagia and then dysphonia, weakness and weigth loss. The physical examination showed fasciculations in the tongue, paralysis of XII bilateral cranic nerve, hypotrophia of masseter and lower facial muscles deficit. Also in this case, following the indications of the neurologist, the patients was underwent to a long series of clinical and instrumental analysis. The morphological study of brain and cervical tract did not show abnormalities. The elettromyogram and TMS revealed neurogenic abnormalities of central motor conduction and the diagnosis of MND was

done. Actually the patient is still alive. Her major problems are feeding, due to severe dysphagia, and respiratory complications, related to concomitant pulmonary fibrosis and muscles weakness.

Discussion

The association between RA and ALS is very unusual. To date, only 5 other cases of RA and ALS occurring in the same patient have been reported **(8,10,11)(Table 1).** In all cases, RA was erosive and symmetrical with severe functional impairment. All patients, except one, were positive for rheumatoid factor. Five case out seven, including our two, suffered from a long-standing RA and ALS occurred in the middle-late age**,** ALS started independently from the introduction of a new therapy except in two patients, our case n.1 and the case reported by Dziadzio M. et al.**(8**), where neurological symptoms appeared after initiation and/or increase in dosage of infliximab. In the literature another case of ALS occurred during treatment with infliximab for ankylosing spondylitis has been reported **(12**). Others reports concern ALS occurring in combination with other autoimmune disease: 2 cases of systemic lupus erithematosus (SLE) **(13,14)** , 1 case of scleroderma **(15)** , 3 case of bollous pemphigoid **(16)** and 2 case with concomitant MS **(17)** . Other additional cases show ALS mimicking autoimmune diseases, e.g. ,Sjogren's syndrome or RA**,** and autoimmune disease mimicking ALS, e.g. neuropsychiatric SLE **(18-20)** .

The simultaneous presence of the two diseases represent a diagnostic challenge because RA may mimic some musculosckeletal symptoms of ALS and vice versa. At presentation, four of seven patients had neurologic symptoms confined to the lower limbs, foot drop, that might be confused with a peripheral neuropathy complicating RA.. At onset, ALS may produces a deficit of abductor pollicis brevis and atrophy of interosseous muscles giving an aspect which can mimic the hand joint deformities of RA **(20-22)** . On the follow-up, a more suspected bulbar syndrome developed in all patients.

The rarity of the association do not represent an evidence in favor of a shared pathophysiologic mechanism. Rather it seems to be a random association. However, a therapeutic neurotoxic side effect could be considered. There are reports of subacute reversible polyneuropathies with predominant motor symptoms resulting from gold therapy **(24)**. Neuromuscular symptoms has been described following chloroquine therapy, but without anterior horn cell involvement **(25,26)** . Methotrexate has been associated with a variety of neurologic central nervous system (CNS) sequelae such as demyelination and necrosis **(27-32)**. Althought our patients did not show pertinent lesions of MTX neurotoxicity, both are taking methotrexate for long period and ongoing when ALS onset. TNFα blockers has been associated with demyelinating syndromes, also, and other forms of white matter injury (e.g. leucoencefalopathy) **(1-6)**

The role of TNF in the pathogenesis of MND and in the immune-mediated demyelination is still unexplained. Several TNF/TNFreceptor actions may independently contribute or, in concert, initiate, promote or down-regulate some pathogenetic pathways of the disease **(9)**. Data from the literature suggest that TNF may have at least two distinct roles: neuroprotective and neurotoxic. It has been hypothesized that a perturbation of the TNF/TNF receptor system can potentially precipitate or worsen an underlying demyelination progress **(33,34)** . A pro-inflammatory effect of TNFα in the initiation of experimental autoimmune encephalomyelitis (EAE) has been described. TNFα has been considered as an important mediator in MS pathogenesis and its role has been strongly supported in several animals models of MS. The role of TNFα in neurodegenerative disease could also be related to its ability in inducing cell death by necrosis or apoptosis **(35,36)**. High circulating levels of TNFα and its soluble receptor are recognized in the blood of ALS patients, such as in RA patients **(37)** . However, dosing TNFα levels in the brain and spinal cord of MND mice, some authors suggested that elevated TNFα may be not the primary event in the development of MND. TNFα, also, inhibits glutamate uptake. Considering the excitotoxic hypothesis of ALS, it could be speculated that the high CNS glutamate concentration induced by TNFα might contribuite to motor neuron degeneration **(38)** . TNFα production may also be secondary to oxidative stress which is another pathogenetic mechanism proposed in ALS, as well as microglia activation **(39, 40).** Alternatively, potential neuroprotective role for TNFα cannot really be excluded **(9).** TNFα also leads to the activation of NFkB, which triggers the production of anti-apoptotic and neurotrophic factors. Anti-TNFα antibodies seems to be protective in animal models of MS, cerebral ischemia, brain trauma, bacterial meningitis and cerebral malaria in which inflammation could play a role. In animal models, the neutralization of endogenous TNFα by means of over-expression of soluble receptor can reduce the death of injured motor neurons. This suggest that TNFα may play an important role in neuronal degeneration in the CNS after lesion. On other hand, it seems to be not essential for the induction of disease but may limits the evolution in a second time of its history. These two contradictory effects can perhaps be explained by the activation of two different receptors, TNFR1 for neurotoxic effect and TNFR2 for neuroprophic **(41-45)**. Surprisingly, when these concepts were transfered on clinical point of view and anti-TNFα antibodies were finally tested in MS-patients, any clinically significant changes was noted, instead the number of magnetic resonance lesions increased after each treatment and the disease worsened **(46)** . A possibile explanation deriving from the fact that the animals models, used to reproduce the acute fase of the disease and to search the target-therapy molecules, providing only a partial presentation of the human chronic pathogenetic mechanism. Some studies suggest that deficiency of this cytochine prolongs and intensifies myelin-directed autoimmunity as a possible explanation for the immune

activating effect of anti-TNFα treatment of MS **(45)** . Clinical trials are ongoing about the therapeutic use other anti-TNFα agents and thalidomide, the older agent with anti-TNFα effect **(47-49).**

What to think of the cases of ALS occurred during treatment with TNFα blockers, 2 for RA and 1 for ankylosing spondylitis ? Casual or causal association? It remains a difficult choice. Actually, we are unable to reach a final conclusion like the others authors. However, it's reasonable to insert the ALS onset during anti-TNFα therapy in the larger chapter of neurological side effects of this drug class **(50).** It's possible that the interference on the balance between TNFα neuroprotective and neurotoxic effects can determine the develop or progress of ASL.

In conclusion, there are very few reports of concurrent ALS and RA and the possibility of a coincidental association must be raised. The major point is represented by the diagnostic difficulties in the identification of ALS in patients with another chronic disease with musculo-skeletal symptoms as RA. A potential neurotoxic side effect must be kept into consideration. The unclear pathophysiologic role of TNFα in ALS and the possibility of neurologic side effects during drugs exposure leads to caution in the clinical pratice.

Key message

Concomitant RA and ALS is rare and may be casual. A potential neurotoxicity of TNF α blockers must be considered.

References

1. Jarand J, Zochodne DW, Martin LO, Voll C. Neurological complication of infliximab. J Rheumatol 2006;33:1018-1020

2. Scheinfels N. Adalimumab: a review of side effects. Expert Opinion Drug Saf 2005;4:637-641

3. Hamon MA, Nicolas G, Deviere F, Letournel F, Doubas F. Demyelinating neuropathy during anti-TNF alpha treatment with a review of the literature. Rev neurol 2007;163:1232-1235

4. Thomas CW Jr, Weinshenker BG, Sandborn WJ. Demyelination during anti-tumor necrosis factor alpha therapy with infliximab for crohn's disease. Inflamm Bowel dis 2004;10:28-31.

5. Vadikolias K, Kouklakis G, Heliopoulos I et al. Acute paraplegia after the initiation of anti-tumor necrosis factor-alpha therapy for Crohn's disease. Eur J Gastroenterol Hepatol 2007;19:159-162.

6. Simsek I, Erdem H, Pay S, Sobaci G, Dinc A. Optic neuritis occurring with anti-Tumor Necrosis Factor-{alpha} therapy. Ann Rheum Dis. 2007; 66:1255-1258

7. Soriani MH, Desnuelle C. Rev Neurol (Paris). 2009;165:627-40.

8. Dziadzio M, Reddy V, Rahman S, Mummery C, Keat A. Is TNFα a good therapeutic target in motoneuronal degeneration ? A case of amyotrophic lateral sclerosis in a patient with RA receiving infliximab. Rheumatology 2006;45:1445-1446

8. Ghezzi P, Mennini T. Tumor necrosis factor and motorneuronal degeneration: an open problem. Neuroimmunomodulation 2001;9:178-182.

10. Schady BW, Metcalfe RA, Holt PJL. Rheumatoid arthritis and motor neurone disease – an association ? Br J Rheumatol 1989;28:70-73

11. M'Bappè, Moguilevski A, Arnal C, Cocheton JJ, Roullet E. Concomitant rheumatoid arthritis and amyotrophic lateral sclerosis. A puzzle illustrated by a new case. Joint Bone Spine 2000;67:242-244.

12. Loustau V, Foltz V, poulain C, Rozenberg S. Diagnosis of amyotrophic lateral sclerosis in a patient treated with TNFα blockers for ankylosing spondylitis: fortuitous association or new side effects of TNFα blockers? Joint Bone Spine 2009;76:213-214

13. Forns X, Bosch X, Graus F, Navarro M, Font J. Development of amyotrophic lateral sclerosis in the course of systemic lupus erythematosus. Clin Rheumatol 1992;11:578-579.

14. Forns X, Bosch X, Graus F, Navarro M, Font J. Amyotrophic lateral sclerosis in a patient with systemic lupus erythematosus. Lupus 1993;2:133-134.

15. Priori R, Buonopane A, Francia A, Valesini G. Scleroderma and motor neuron disease: an unusual association. Clin Rheumatol 1993;12:428-429.

16. Chosidow O, Doppler V, Bensimon G et al. Bollous pemphigoid and amyotrophic lateral sclerosis. A new clue for understanding the bollous disease ? Arch Dermatol 2000;136:521-524.

17. Attout H, Toussirot E, Auge B, Chavot D, Wending D. Rheumatoid arthritis and multiple sclerosis in the same patient. Two case-reports. Rev Rhum Engl Ed. 1999 Mar;66:169-72

18. Attout H, Rahmeh F, Ziegler F. Syndrome de Gougerot-Sjogren simulant une sclérose latérale amyotrophique. Rev Méd Intern 2000;21:706-708.

19. Aiello I, Cavallari A, Colamussi V. Amyotrophic lateral pseudosclerosis during rheumatoid arthritis disease. Description of a case. Minerva Medica 1980;71:3669-3674.

20. Maldonado M, Williams R, Adair J, Hart B, Gregg L, Sibbit W. Neuropsychiatric systemic lupus erythematosus presenting as amyotrohic lateral sclerosis. J Rheumatol 2002;29:633-635.

21. Traynor BJ, Codd MB, Corr B, Forde C, Frost E, Hardiman O. Amyotrophic lateral sclerosis mimic syndromes: a population based study. Arch Neurol 2000;57:109-113.

22. Belsh JM, Schiffman PL. Misdiagnosis in patients with amyotrophic lateral sclerosis. Arch Intern Med 1990;150:2301-2305.

23. O'Reilly DF, Brazis PW, Rubino FA. The misdiagnosis of unilateral presentation of amyotrophic lateral sclerosis. Muscle nerve 1982;6:724-726.

24. Doyle JB, Cannon EF. Severe polyneuritis following gold therapy for rheumatoid arthritis. Ann Intern Med 1950;33:1468-1472.

25. Whisnant JP, Espinosa RE, Kierland RR, Lambert EH. Chloroquine neuromyopathy. Proc Mayo Clinic 1963;38:501-513.

26. Hicklin JA. Chloroquine neuromyopathy. Ann Phys Med 1968;9:189-192.

27. Sandoval C, Kutscher M, Jayabase S, Tenner M. neurotoxicity of intrathecal methotrexate: MR imaging findings. Am J Neuroradiol 2003;24:1887-1890.

28. Rollins N, Winick N, Bash R, Booth T. Acute methotrexate neurotoxicity: findings on diffusione-weighted imanging and correlation with clinical outcome. Am J neuroradiol 2004;25:1688-1695.

29. Vezmar S, Becker A, Bode U, Jaehde U. Biochemical and clinical aspects of methotrexate neurotoxicity. Chemotherapy. 2003 May;49:92-104.

30. Eichker AF, Batchelor TT, Henson JW. Diffusione and perfusion imaging in subacute neurotoxicity following high-dose intravenous methotrexate. Neuro Oncol 2007;9:373-377.

31. Raghavendra S, Nair MD, Chemmanam T, Krishnamoorthy T, Radhakrishnan VV, Kuruvilla A. Disseminated necrotizing leukoencephalopathy following low-dose oral methotrexate. Eur J Neurol. 2007 Mar;14:309-14.

32. Catsman-Berrevoets CE, van Dongen HR, Kros JM. Development of the anterior cingulate syndrome in a child due to delayed necrotising methotrexate leukoencephalopathy. J Neurol Neurosurg Psychiatry. 1997 Mar;62:301-2.

33. Liu J, Marino MW, Wong G et al. TNF is a potent anti-inflammatory cytochine in autoimmune-mediated demyelination. Nat Med 1998;4:78-83.

34. Ikeda k, Ieasaki Y, Shiojima T, Kinoshita M. Neuroprotective effect of various cytochines on developing spnal motorneurons following axotomy. J Neurol Sci 1996;135:109-113.

35. Hovelmeyer N, Hao Z, Kranidioti K et al. Apoptosis of oligodendrocytes via Fas and TNF-R1 is a key event in the induction of experimental autoimmune encephalomyelitis. J Immunol. 2005;175:5875-84.

36. Cleveland DW:From Charcot to SOD1:Mechanism of selective motor neuron death in ALS. Neuron 1999;24:515-520.

37. Poloni M, Facchetti D, Mai R et al. Circulating levels of tumor necrosis factor-alpha and its soluble receptors are increased in the blood of patients with amyotrophic lateral sclerosis. Neurosci lett 2000;287:211-213.

38. Chao CC, Hu S. Tumor necrosis factor-alpha potentiates glutamate neurotoxicity in human fetal brain cell cultures. Dev Neurosci 1994;16:172-179.

39. Jonsson PA, Ernhill K, Andersen PM et al. Minute quantities of misfolded mutant superoxide dismutase-1 cause amyotrophic lateral sclerosis. Brain. 2004;127:73-88.

40. Borchelt D. Amyotrophic lateral sclerosis – Are microglia killing motor neuron ? N Engl J Med 2006;355:1611-1613.

41. Terrado J, Monnier D, Perrelet D et al. Soluble TNF receptors partially protect injured motorneurons in the postnatal CNS. Eur J Neurosci 2000;12:3443-3447.

42. Suvannavejh GC, Lee HO, Padilla J, Dal Canto MC, Barret TA, Miller SD. Divergent roles for p55 and p75 tumor necrosis factor receptors in the pathogenesis of MOG (35-55)-induced experimental autoimmune encephalomyelitis. Cell Immunol 2000;205:24-33.

43. Kassiotis G, Kollias G. Uncoupling the proinflammatory from the immunosuppressive properties of tumor necrosis factor (TNF) at the p55 receptor level: implication for pathogenesis and therapy of autoimmune demyelination. J Exp Med 2001;193:427-434.

44. Kassiotis G, Pasparakis M, Kollias G, Probert L. TNF accelerates the onset but does not alter the incidence and severity of myelin basic protein-induced experimental autoimmune encephalomyelitis.Eur J Immunol. 1999;29:774-80.

45. Kollias G, Kontoyiannis D, Douni E, Kassiotis G. The role of TNF/TNFR in organ-specific and systemic autoimmunity: implications for the design of optimized anti-TNF therapies. Curr Dir Autoimmun. 2002;5:30-50.

46. Van Oosten BW, Barkhof F, Truyen L et al. Increased MRI activity and immune activation in two multiple sclerosis patients treated with the monoclonal anti-tumor necrosis factor antibody cA2. Neurology 1996;47:1531-1534.

47. Neymotin A, Petri S, Calingasan NY et al. Lenalidomide (Revlimid) administration at symptom onset is neuroprotective in a mouse model of amyotrophic lateral sclerosis. Exp Neurol. 2009;220:191-7.

48. Kiaei M, Petri S, Kipiani K et al. Thalidomide and lenalidomide extend survival in a transgenic mouse model of amyotrophic lateral sclerosis. J Neurosci. 2006;26:2467-2473.

49. Stommel EW, Cohen JA, Fadul CE, et al. Efficacy of thalidomide for the treatment of amyotrophic lateral sclerosis: a phase II open label clinical trial. Amyotroph Lateral Scler. 2009;10:393-404.

50. Bernatsky S, Renoux C, Suissa S.Demyelinating events in rheumatoid arthritis after drug exposures. Ann Rheum Dis 2010 ; 69:1691-1693