CASE REPORT

Parkinsonism as a side effect of infliximab

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SUMMARY

We present a case of a 64-year-old man with Crohn's disease who developed parkinsonism after starting treatment with infliximab (Remicade). The patient had a 30-year history of Crohn's disease with previous surgical procedures and treatment with methotrexate. Treatment was augmented with infliximab, and 3 days after the first dose of 400 mg, a resting tremor began in the left leg. Over 4 months, symptoms progressed and now involved the right leg as well as both hands. There was no clinical effect of infliximab treatment, and the treatment was withdrawn 4 months later. The patient then experienced gradual, but continual, improvement of the resting tremor after withdrawal of infliximab. To the best of our knowledge, this is the first case report describing a patient developing parkinsonism after starting treatment with infliximab, with symptoms remitting on discontinuation.

BACKGROUND

Over a 30-year-period, 14 463 people have developed Crohn's disease in Denmark,¹ and the incidence is increasing.²

According to the Danish Health Authority, the total consumption of infliximab in the field of gastroenterology was 1 320 000 defined daily doses (DDD), and 2 667 000 DDD in rheumatology and dermatology in the years covering 1999–2011, in Denmark alone. The nationwide consumption is continually increasing.³

Given the frequent prescription, as well as an increase in disease incidence, the number of side effects from infliximab treatment will likely increase.

In this case report, we describe a 64-year-old man with Crohn's disease, who experienced parkinsonism as a side effect of treatment with infliximab.

CASE PRESENTATION

A 64-year-old man with Crohn's disease was treated with a combination of methotrexate and infliximab. The patient had a 30-year history of Crohn's disease with recurrent small bowel obstructions and fistulas. He had undergone 11 surgical resections of diseased bowel, and for the past 10 years had received treatment with methotrexate. During the past 2 years, the disease had taken a more aggressive clinical course with attacks of abdominal pain and laboratory signs showing increased activity illustrated by rising levels of faeces calprotectin in the blood. In February of 2014, a surgical resection of a MRI-verified stenosis of an ileocaecal anastomosis provided no relief. Treatment with methotrexate was therefore

augmented with infliximab (Remicade) in the summer of 2014. On four occasions, 22 July, 5 August, 4 September and 30 October 2014, respectively, the patient was treated with a single dose of 400 mg infliximab intravenously. He still received treatment with oral methotrexate 20 mg once weekly, folic acid 5 mg once weekly, vitamin B12 (Betolvex) 1 mg daily and one multivitamin tablet (Vitamineral) once daily. The neurological side effects of infliximab began on the 25 July 2014, 3 days after treatment was started. A resting tremor began in the left leg followed by a gradual increase during the following months. Symptoms progressed, and involved the right leg as well as both hands. Owing to no effect of infliximab treatment, adhesions between the small intestine and abdominal wall were surgically removed in September 2014, without any obvious clinical relief. The gastrointestinal symptoms improved in November 2014 after treatment with ciprofloxacin for suspected intestinal bacterial overgrowth. The patient received no symptomatic dopaminergic therapy to alleviate his symptoms.

Owing to side effects and no clinical effect, the treatment with infliximab was withdrawn in November 2014.

OUTCOME AND FOLLOW-UP

After withdrawal of treatment in November 2014, the patient experienced a gradual improvement of the resting tremor.

On 21 January 2015, neurological examination showed a nearly continuous resting tremor in both legs, slightly more in the right than in the left leg, as well as discrete rigidity in both legs. There was no resting tremor in the hands, no rigidity in the arms and no kinetic tremor, postural tremor, cerebellar ataxia nor paresis. There was normal speech, normal facial expression, normal finger tap, normal rising from the chair as well as normal posture and postural stability. The movement of the hands was normal, and the gait was normal with normal steps and normal arm swing.

On clinical follow-up on 30 March 2015, the patient had experienced further symptom regression. On examination, there were clear objective improvements and now only a discrete intermittent resting tremor of the left leg was seen. Otherwise, there was a normal neurological examination, and there was no definite rigidity in the legs. MRI including diffusion-weighted images of the brain, the cervical medulla and thoracic medulla, were normal, save for asymptomatic spondylosis of the cervical spine.

On follow-up at the end of February 2016, the patient had a dopamine transporter (DaT) scan

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performed. Bilateral values for the caudate nucleus, the putamen as well as the putamen/caudate nucleus were given. The value for the right putamen (1.18) was slightly below the age-adjusted reference range of 1.21–2.21, with the rest of the values being within the age-adjusted reference range. The DaT scan has reported sensitivity and specificity between 74% and 97% in clinical trials, and a pathological scan is therefore not diagnostic of Parkinson's disease, but rather a supportive tool for the physician in making a clinical diagnosis.⁴ The DaT scan strongly supported the notion that the patient's symptoms were caused by a presynaptic dopaminergic deficit in the nigrostriatal pathway. The patient currently only has isolated tremor in one leg and does not fulfil the clinical criteria for idiopathic Parkinson's disease. However, since the DaT scan can be indicative of a developing parkinsonian syndrome, clinical follow-up is planned.

DISCUSSION

Infliximab is a monoclonal human murine antibody targeted at tumour necrosis factor α (TNF- α), thereby inhibiting its functional activity. Plasma half-life is 8–9 days. The exact elimination pathways are not yet clearly established. However, unchanged infliximab has not been detected in urine.⁵ There is indication that concentrations in plasma of substrates of cytochrome P450 3A4 (CYP3A4) change when coadministered with infliximab. Owing to the action of chronic inflammation on the effect of CYP3A4 by among other things TNF- α , influencing the concentration of TNF- α will likely have an effect on the metabolising capacity of CYP3A4.⁷

To the best of our knowledge, this is the first reported incidence of a patient developing parkinsonism after initiating treatment with infliximab. The symptoms remitted after withdrawal of the drug. To date, very few reports about parkinsonism during treatment with infliximab exist, and no direct causality have been proven. On the basis of these few reports, it has been speculated on whether or not infliximab is able to unmask or accelerate underlying Parkinson's disease.

Only one case report describing parkinsonism as a possible side effect of infliximab has been located. This 72-year-old woman's rheumatic arthritis (RA) was very successfully managed with intravenous infliximab, but soon after initiating treatment, she experienced worsening stiffness and tremor in the right arm. On 1-year follow-up, her RA was in full remission, but now the patient was unable to walk, had difficulty swallowing as well as drawing deep breaths due to severe generalised rigidity and tremor. Since infliximab was not discontinued, we do not know whether infliximab caused parkinsonism, or whether underlying Parkinson's disease was accelerated or demasked.⁸

One abstract has been located describing four patients, with two of them having parkinsonistic side effects during treatment with a TNF- α -drug. A 63-year-old man was treated for psoriasis with ustekinumab and developed left-sided parkinsonism, and a 57-year-old woman was treated for RA with adalimumab and developed right-sided parkinsonism. Both patients had normal MRI scans, but pathological DaT scans. The biological treatment was stopped, and the symptoms treated with levodopa.⁹ Unfortunately, further information about the patients has not been found.

The Danish Health Authorities have received one reported incidence of parkinsonism (this case), one reported incidence of Parkinson's disease, one report of muscle twitching, one report of dystasia and five reports of tremor, as suspected side effects of infliximab treatment.¹⁰

The European Medicines Agency's database of Adverse Drug Reactions contains 23 reported incidents of Parkinson's disease with eight reported as 'not recovered/not resolved' and 15 'unknown', concerning Remicade.¹¹ Of these, 14 are men, 8 are women and one is not specified.

In the same database, for Remicade, there are nine reports of parkinsonism, including this case. Five of these are women, three are men and one is not specified. The outcome is unknown in four cases, whereas three are listed as not recovering/not resolved, one is listed as recovering/resolving and one is listed as recovered/resolved.¹¹

However, the reports were made on the basis of suspected side effects, and the information contained therein is extremely limited. Causality can therefore not be proven by these reports alone.

From the existing literature, there are several proposed mechanisms that are interesting in the light of our patient's symptoms and course of disease.

The patient's experience of a rather abrupt onset of symptoms may suggest an acute vascular lesion. Parkinsonism as a symptom of acute cerebral infarction is described due to a variety of vascular lesions in the midbrain and basal ganglia. However, the lack of other focal neurological deficits, the following gradual increase and development of symptoms together with the normal MRI without any sign of cerebrovascular disease, provide strong evidence against acute ischaemia as the cause of the symptoms.

Another mechanism is based on genes, as there seems to be a genetic association between Crohn's disease and Parkinson's disease. Based on genome-wide association studies, spatially overlapping disease associated loci have been found in the two diseases, indicating a common genetic background.¹² By this account, the coincidence of our patient's parkinsonism and state of Crohn's disease prompting infliximab treatment could be due to natural disease progression of the two diseases. However, neither before nor after infliximab was given was there change in the course of the patient's Crohn's disease, while the parkinsonism started with infliximab and continued to worsen, only to be alleviated by drug discontinuation. In this case, it would thus seem unlikely that the two diseases were interconnected.

Infections of the neuronal system is another proposed mechanism. Theories about Parkinson's disease as an ascending infection stemming from the gut and travelling via the vagal nerve has been postulated based on experimental animals studies. Furthermore, a national case-control study of patients with previous vagal surgery showed a reduced relative risk of Parkinson's disease after full vagotomy.¹³ The barrier protecting the gut from infection could be affected by an underlying inflammatory condition such as Crohn's disease. When treated with an immunomodulatory agent such as anti-TNF- α , this barrier might have changed even more, thus predisposing for a neurotropic infection of the gut.

In line with this, neuroinflammation seems to play a part in the pathology of Parkinson's disease with TNF- α being one of the included factors.¹⁴ Demyelination and subsequent multiple sclerosis (MS) during anti-TNF- α therapy (etanercept and adalimumab) has been reported in a case series consisting of four patients. These patients, aged 17–57 years, presented with neurological side effects 8 months to 6 years after starting therapy with anti-TNF- α . Symptoms improved on glucocorticoid therapy and gradually on discontinuation. However, the MRI scans of the four patients showed demyelination, and three of the four fulfilled the criteria for MS. MRI scan on subsequent

follow-up was reported for two of the patients and were unchanged 3–18 months later. The causative mechanism of TNF- α antibodies is interesting as they are largely unable to penetrate the blood brain barrier.¹⁵

In contrast with our current report, these patients developed neurological symptoms several months to years after starting therapy and had changes on their MRI.

Whatever the mechanism, the association in time between the patient's symptoms and treatment with infliximab suggests infliximab as the cause of the symptoms. The mechanism of this effect is yet unknown.

Until further evidence, side effects of a current treatment with anti-TNF- α in a patient presenting with parkinsonism need to be considered.

Learning points

- ▶ Parkinsonism is a putative side effect of infliximab.
- ▶ Safety issues with original biological drugs still exist.
- ▶ Clinical symptoms as a cause of ongoing medical treatment should always be considered.

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REFERENCES

- 1 Jess T, Simonsen J, Jørgensen KT, *et al.* Decreasing risk of colorectal cancer in patients with inflammatory bowel disease over 30 years. *Gastroenterology* 2012;143:375–81.e1; quiz e13–4.
- 2 Vind I, Riis L, Jess T, *et al.* Increasing incidences of inflammatory bowel disease and decreasing surgery rates in Copenhagen City and County, 2003–2005: a population-based study from the Danish Crohn colitis database. *Am J Gastroenterol* 2006;101:1274–82.
- 3 Consumption and Side Effects of Immune Modulating, Biological Drugs in Denmark. June 2013. <http://sundhedsstyrelsen.dk/publ/Publ2013/06jun/BiologiskeLaegemidler.pdf> [IN DANISH].
- 4 Bajaj N, Hauser RA, Grachev ID. Clinical utility of dopamine transporter single photon emission CT (DaT-SPECT) with (123I) ioflupane in diagnosis of parkinsonian syndromes. *J Neurol Neurosurg Psychiatr* 2013;84:1288–95.
- 5 Remicade. <http://www.pro.medicin.dk> (accessed 30 Dec 2015) [IN DANISH].
- 6 Product information 24/07/2014 Remicade -EMEA/H/C/000240 -II/0179 (accessed 30 Dec 2015).
- 7 Infliximab. Drug Interactions (single). Micromedex(R) Healthcare Series, (electronic version). Thomson Micromedex, Greenwood Village, Colorado, USA. <http://www.micromedexsolutions.com> (accessed 30 Dec 2015).
- 8 Hrycaj P, Korczowska I, Łacki JK. Severe Parkinson's disease in rheumatoid arthritis patient treated with infliximab. *Rheumatology (Oxford)* 2003;42:702–3.
- 9 Arias M, Arias-Rivas S, Rodríguez-Osorio X, *et al.* Anti-TNF-alpha inhibitors therapy and non infectious neurologic adverse effects [abstract]. *J Neurol Sci* 2013;333 (Suppl 1):e122–3.
- 10 Infliximab. Drug Analysis Prints. Danish Medicines Agency. <http://laegemiddelstyrelsen.dk/bivirkninger/bivirkninger-ved-medicin/drug-analysis-prints-indberettede-bivirkninger.aspx?letter=l&subletter=m-p> (searched 30 December 2015).
- 11 Remicade. European database of suspected adverse drug reaction reports. <http://www.adrreports.eu/> (searched 30 December 2015).
- 12 Nalls MA, Saad M, Noyce AJ, *et al.* Genetic comorbidities in Parkinson's disease. *Hum Mol Genet* 2014;23:831–41.
- 13 Svensson E, Horváth-Puhó E, Thomsen RW. Vagotomy and subsequent risk of Parkinson's disease. *Ann Neurol* 2015;78:522–9.
- 14 Collins LM, Toulouse A, Connor TJ, *et al.* Contributions of central and systemic inflammation to the pathophysiology of Parkinson's disease. *Neuropharmacology* 2012;62:2154–68.
- 15 Andreadou E, Kemanetzoglou E, Brokalaki CH, *et al.* Demyelinating disease following Anti-TNF α treatment: a causal or coincidental association? Report of four cases and review of the literature. *Case Rep Neurol Med* 2013;2013:671935.

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