CASE REPORT

Neurosyphilis presenting as parkinsonism

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SUMMARY

In the postantibiotic era, neurosyphilis continues to have a significant incidence, especially in certain subpopulations. We report, for the first time, neurosyphilis presenting as parkinsonism without more typical neurosyphilitic clinical features. A 53-year-old man developed clinical features of gradual onset consistent with idiopathic Parkinson's disease but was found to have positive treponemal serology and cerebrospinal fluid Venereal Disease Research Laboratory (VDRL) reaction. Antibiotic treatment dramatically improved all the parkinsonian symptoms. However, over the subsequent 15 years, the patient slowly deteriorated again in a manner typical of idiopathic Parkinson's disease. A dopaminergic deficit was demonstrated on (¹²³I)FP-CIT SPECT. This is the first report in the postantibiotic era of neurosyphilis presenting as relatively pure parkinsonism. Blood test screening for syphilis is therefore appropriate if there is any clinical doubt about an idiopathic parkinsonian presentation. The patient's late second deterioration may suggest that the neurosyphilitic basal ganglial insult primed or accelerated development of idiopathic-like disease.

BACKGROUND

While treponemal infection has undoubtedly declined as a major cause of morbidity and mortality since the introduction of antibiotic treatment in the mid-20th century, its worldwide prevalence at the end of the century is nevertheless estimated to be as high as 12 million individuals.¹ Since then, infection rates have increased rapidly in certain subpopulations, with 30–60% co-infection with HIV in some urban areas.²

Infection may involve the central nervous system in a number of ways. Often it may remain asymptomatic or may be associated within the first year after initial infection with a meningitis, sometimes with cranial nerve involvement.³ Late neurosyphilis is classically described as (1) vascular (stroke-like focal ischaemia), (2) tabetic (lightning pains, sensory ataxia or Charcot joints) or (3) parenchymal (general paralysis, psychosis, dementia, pyramidal signs or Argyll-Robertson pupils). Within this last category, parkinsonian features are described,⁴ but in the postantibiotic era few cases have in fact been reported and these all had other clinical features.^{5–8}

We report a case that fulfils diagnostic criteria for neurosyphilis in association with relatively pure parkinsonian features where there was a marked response to antibiotics. The patient later underwent a much slower parkinsonian deterioration over the next 15 years that was typical of idiopathic disease and responded to levodopa. He had a nigrostriatal

deficit apparent on ¹²³IFP-CIT SPECT (DaTSCAN) imaging. It is tempting to suggest that, rather than coincidental concurrence, the neurosyphilitic basal ganglial insult primed or accelerated the course of underlying neurodegenerative Parkinson's disease (PD).

CASE PRESENTATION

A 53-year-old man presented with a 2-year history of slowing of gait, quietness of voice, slowing of upper limb function and small handwriting. On examination at that time, he had hypomimia, a parkinsonian-type dysphonia, marked symmetrical bradykinesia in the upper limbs, truncal and distal rigidity and a stooped shuffling gait. He had occasional myoclonic jerks of the upper limbs when held outstretched. His Mini-Mental State Examination score was 29/30 and neuropsychometric assessment revealed an underlying low motivational state. He had no psychosis, hallucination tendency, cerebellar or sensory ataxia, pyramidal signs or distal sensory loss. His right eye was amblyopic, and both direct and consensual reactions from that eye were slow.

INVESTIGATIONS

Brain MRI showed generalised atrophy. A standard screen of blood tests performed at the time, including copper studies and HIV tests, was normal. By chance, this screen included tests for treponemal disease and it was found that the serum Venereal Disease Research Laboratory (VDRL) reaction was positive at 1:512, *Treponema pallidum* particle agglutination was >1:1280, IgG ELISA was positive, IgM ELISA was positive with antibody index 1.46 and fluorescent treponemal antibody absorption (FTA-ABS) was positive. Cerebrospinal fluid (CSF) was therefore analysed and found to have 8 lymphocytes/mm³, a raised protein of 79 g/L and a positive VDRL titre of 1:32. Assay for 14-3-3 protein was negative.

DIFFERENTIAL DIAGNOSIS

A diagnosis of parkinsonism secondary to neurosyphilis was made. There was no suggestive sexual history or history of primary chancre.

TREATMENT

The patient was given intramuscular procaine penicillin 2.4 mega units once daily and probenecid 500 mg four times a day for 21 days with prednisolone 20 mg three times a day for 3 days starting the day before the antibiotics. The patient's condition improved considerably over the next few weeks. There was a residual bradykinesia and

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shuffling gait, which subsequently improved on introduction of coheneldopa 250 mg four times a day.

OUTCOME AND FOLLOW-UP

The patient continued to be followed up by the local movement disorders service for the next 15 years. Over that time, there was a slow steady deterioration in gait with worsened hypophonia. He had a typical shuffling stooped gait with festination, symmetrical fatiguing bradykinesia of the upper limbs, and distal and axial rigidity. There was no development of dyskinesia or psychosis. Repeated cerebrospinal fluid analysis revealed no lymphocytosis and persistently negative VDRL reaction, while subsequent MRI showed no worsening of atrophy. A ^{123}I FP-CIT SPECT (DaTSCAN) performed 13 years after presentation revealed reduced uptake especially in the left putamen (figure 1). At around this time, trials of amantadine and anticholinergics were unsuccessful, with no motor benefit and a transient deterioration in cognition. Withdrawal of coheneldopa resulted in further deterioration, which resolved again on restarting the drug.

DISCUSSION

With positive treponemal serology, a lymphocytic cerebrospinal fluid (CSF) with raised protein and a positive CSF VDRL reaction, our case fulfils established criteria for a diagnosis of neurosyphilis.⁴ However, as has long been argued, it is possible that asymptomatic neurosyphilis could occur with co-existent neurodegenerative disease. Certainly considerable doubt must be thrown on reports of parkinsonian neurosyphilis from the pre-antibiotic period.⁴ At that time, there were no clear diagnostic criteria for idiopathic PD, nor was there symptomatic treatment to aid in diagnosis, and no pathological corroboration of neurodegeneration was available. Conversely, there was no way to use response to antibiotic treatment to help confirm a syphilitic cause of neurological disease. Neurosyphilis was common and regarded as the great mimicker; many cases of idiopathic PD must have been misdiagnosed as syphilitic in the presence of a positive VDRL reaction. Other cases may have had postencephalitic parkinsonism or tardive dyskinesia from antipsychotics used to treat psychiatric neurosyphilis.

In the postantibiotic era, the increase in syphilis in the 1990s in association with AIDS may have led to uncertainty over diagnosing parkinsonian neurosyphilis because the presentation may have been coloured by direct HIV pathology or other coincidental infection resulting from the immunocompromised state.⁹ Widespread use of antibiotics may also alter presentation patterns. Nevertheless, previous cases of treponemal parkinsonism reported in the postantibiotic era argue persuasively for a causative association. Three individual case reports describe, as in our case, a lymphocytic CSF and a response to penicillin therapy.^{5–7} However, they not only had parkinsonism but other clinical

features more characteristic of symptomatic rather than just serological neurosyphilis, namely Argyll-Robertson pupils and additional ataxia, and frontal or psychiatric features. The two more recent cases had positive CSF VDRL reactions.^{6 7} Four additional cases from China, identified on retrospective case notes review, had additional ataxia in all cases, schizophrenia in one case, other psychiatric symptoms in one case, cerebral infarctions from meningovascular syphilis in one case, amnesia in two cases and Argyll-Robertson pupils in one case.⁸ Response to treatment was not reported and in three cases, the CSF had borderline or no pleocytosis. Similar to the three cases reported separately, none of these four cases had HIV infection.

There are additional reports that describe neurosyphilis presenting with other movement disorders such as myoclonus, dystonia, orofacial dyskinesia and tongue tremor, often occurring in combination with ataxia, dementia or psychosis.^{4 10–12} Some of these cases also had bradykinesia, arguably of sufficient prominence as to constitute a parkinsonian presentation. Certainly the pattern in previously reported cases of neurosyphilis with parkinsonism or bradykinesia is the presence of accompanying features atypical for idiopathic PD, though not always the classic neurosyphilitic features of psychosis, dementia and Argyll-Robertson pupils.

Our case therefore appears unique among those reported in the postantibiotic era in lacking clear additional non-parkinsonian features; the only potential clinical clue was the early onset myoclonus, which subsequently settled after antibiotic treatment, though myoclonus is also described in idiopathic PD.¹³ Nevertheless, the clear response of all clinical features to penicillin therapy in a patient with neurosyphilitic CSF is strongly suggestive of treponemal parkinsonism. The incomplete response rather than complete resolution following antibiotics is also typical for neurosyphilis.⁴

The 15 years of follow-up in our case revealed that the patient did not actually remain stable after antibiotic treatment. Instead, he followed a deteriorating course suggestive of very slowly progressive idiopathic PD with continued levodopa responsiveness and no further change in MRI appearances. In addition, an asymmetrical dopaminergic deficit was demonstrated on DaTSCAN. Although the clinical symptoms were symmetrical, it has nevertheless been reported that only around 70% of idiopathic PD cases show imaging asymmetry corresponding with contralateral clinical asymmetry.¹⁴ Reactivation of neurosyphilis after treatment has been described in 12% of a large series of mainly HIV negative cases,¹⁵ perhaps dependent on the treatment regime. However, our case was treated according to current recommendations and there was no evidence of infective reactivation on CSF analysis.

There would therefore appear to be two phases to this patient's parkinsonian condition: an initial antibiotic-responsive

Figure 1 ^{123}I FP-CIT SPECT (DaTSCAN) performed 13 years after presentation with neurosyphilitic parkinsonism and subsequent slow deterioration after initial response to antibiotic therapy. The four contiguous axial slices (inferior to superior slices arranged from left to right) showing reduced tracer uptake in the left putamen indicating depleted presynaptic dopamine transporter activity.

syphilitic phase and a subsequent idiopathic-like phase. While underlying idiopathic disease might here be entirely coincidental, a similar phenomenon of initial insult followed by delayed deterioration has been described following other basal ganglial insults such as vascular midbrain lesions, toxic effects of carbon monoxide or organophosphates, or indeed other infections such as encephalitis lethargica and other presumed viral encephalitis.^{16–19} Perhaps such a double aetiology is in fact common in idiopathic PD; individuals with a predisposition from their genetic make-up to age-related nigral neurodegeneration are exposed during their lifetime to mild cerebral insults, such as viral infections, that involve the substantia nigra to a degree insufficient to result in extrapyramidal symptoms. The accumulated damage from these minor insults and from underlying slowly progressive neurodegeneration may nevertheless prove sufficient to prime these individuals to develop clinical PD before the end of their natural life span. Conversely, a single more severe basal ganglial insult could result in presentation at the time of occurrence followed by subsequent further symptomatic deterioration where such may not otherwise have occurred for many years if at all.

If, as we have argued, our case did have treponemal parkinsonism without other clinical signs more typical of neurosyphilis, serological analysis should perhaps be revived as a routine screening test in patients presenting with parkinsonism, especially if of young onset, in an at-risk subpopulation or if

the presentation is in any way atypical. If positive and there is subsequent CSF corroboration, prompt penicillin treatment in such cases where the brunt of parenchymal involvement has been borne by the basal ganglia may not only ameliorate the presenting features but could also minimise the acceleration of underlying neurodegenerative parkinsonism.

Contributors JM managed the patient clinically throughout his illness and GH reviewed the MRI and functional imaging. JM wrote and GH reviewed the manuscript.

Competing interests None declared.

Patient consent Obtained.

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Learning points

- Neurosyphilis remains a significant cause of morbidity, especially but not exclusively in the HIV population.
- This case shows that neurosyphilis may present in a manner similar to idiopathic Parkinson's disease. Patients presenting with parkinsonism are not usually screened with treponemal serology tests, making the true incidence of relatively pure parkinsonism from neurosyphilis unknown, but we recommend such screening if there are any atypical accompanying clinical features, an unusually rapid progression or a poor response to dopaminergic therapy.
- The patient's late subsequent deterioration is reminiscent of that following other infective or traumatic basal ganglial insults and provides support for the notion that clinical or subclinical insults in general may prime or accelerate development of Parkinson's disease in genetically susceptible individuals.

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