Journal of the Neurological Sciences 362 (2016) 40–46

Contents lists available at ScienceDirect

Journal of the Neurological Sciences

journal homepage: www.elsevier.com/locate/jns

Autoimmune atypical parkinsonism — A group of treatable parkinsonism

Sudheeran Kannoth [a,b,*], Anandkumar Anandakkuttan [a], Annamma Mathai [a,b], Anuja Nirmala Sasikumar [a,b], Vivek Nambiar [a]

[a] Department of Neurology, Amrita Institute of Medical Sciences, Ponekkara PO, Kochi 682041, Kerala, India
[b] Neuroimmunology Laboratory, Amrita Institute of Medical Sciences, Ponekkara PO, Kochi 682041, Kerala, India

ARTICLE INFO

Article history:
Received 24 August 2015
Received in revised form 11 December 2015
Accepted 4 January 2016
Available online 13 January 2016

Keywords:
Atypical parkinsonism
Parkinson plus syndrome
Autoimmune atypical parkinsonism
Progressive supranuclear palsy
Multiple system atrophy

ABSTRACT

Background: Immunological causes of atypical parkinsonism/Parkinson plus syndromes are rare.
Objective: To study the clinical and laboratory features and treatment outcome of autoimmune atypical parkinsonism.
Methods: Retrospective case series. Patients with atypical parkinsonism and positive antibodies were identified retrospectively. Those who received immunotherapy (intravenous methyl prednisolone 1 g daily for five days followed by mycophenylate mofetil 2 g daily or azathioprine 2–3 mg/kg/day) and consented for publication of non-anonymized videos were included.
Results: There were ten cases (nine males, age range 49–75 years, disease duration 2 months to 13 years, follow-up 1–7 months) of atypical parkinsonism [probable multiple system atrophy (MSA)-2, possible progressive supranuclear palsy (PSP)-1, probable PSP-3]. Eight had new uncharacterized neuronal antibodies, leucine rich glioma associated protein 1 (LGI1) antibody in one, and the other had another uncharacterized neuronal antibody along with LGI1 antibody. Four had abnormal CSF. There was a prompt, dramatic improvement in terms of Unified Parkinson Disease Rating Scale motor scale and or modified Rankin Scale as well as improvement in eye movement, postural instability, cerebellar, autonomic and non-motor symptoms. Two had reappearance of symptoms on discontinuing steroids and improvement on restarting. One died of infection despite good recovery of encephalopathy and parkinsonism.
Conclusion: Autoimmune atypical parkinsonism is characterized by atypical parkinsonism with neuronal specific antibodies, sometimes associated with abnormal CSF and significant response to immunotherapy.

1. Introduction

Parkinson plus syndromes or atypical parkinsonism is a heterogeneous group of neurological disorders characterized by parkinsonian features (bradykinesia, rigidity, tremor, postural imbalance), poor response to levodopa and additional clinical features. Early onset of the following additional clinical features suggests the possibility of Parkinson plus syndrome—dementia, postural instability, psychosis with low dose levodopa or dopamine agonists and dystonia. Eye movement abnormalities like vertical gaze palsy, blepharospasm, eyelid apraxia, pyramidal signs, autonomic symptoms like postural hypotension and incontinence, prominent motor apraxia, alien limb phenomenon, marked symmetry of signs from the onset are the other features [1].

The diagnosis of Parkinson's plus syndromes is mainly clinical. A definitive diagnosis is made by histopathology. Current criteria are clinical which allows the diagnosis of probable and possible cases [2–5]. Exclusion of a treatable cause is important as these diagnoses imply irreversible progressive brain damage. There is sparse literature on autoimmune parkinsonism. Autoimmune parkinsonism in the form of paraneoplastic syndrome was reported earlier as single cases [6–9] by four papers. Dalmau et al. [10] in 2004, reported three cases, of which one showed response to treatment. In the Mayo series of Glutamic acid decarboxylase (GAD) 65 antibody positive patients [11], four cases were classified as multiple system degeneration/atrophy, progressive supranuclear palsy (PSP) and olivo ponto cerebellar atrophy (OPCA). Only one of them showed partial response to immunotherapy. Eight cases of Voltage gated potassium channel (VGKC) complex antibodies associated with parkinsonism were reported from Mayo clinic earlier [12]. But the full clinical details and treatment responses were not described in the paper. However a recent series from the same center with positive leucine rich glioma associated protein (LGI)1/contactin-2 associated protein (CASPR 2) antibody, had no parkinsonism [13]. Autoimmune parkinsonism was reported earlier with Sjogren's syndrome [14] and systemic lupus erythematosis [15]. Two papers, mostly involving in children were reported by Dale et al. in 2004 and 2012. The first one was twenty cases of encephalitis lethargica

* Corresponding author at: Neuroimmunology Laboratory (T6F3), Department of Neurology, Amrita Institute of Medical Sciences, Ponekkara PO, Kochi 682041, Kerala, India.
E-mail address: sudheerank@aims.amrita.edu (S. Kannoth).

http://dx.doi.org/10.1016/j.jns.2016.01.006
0022-510X/

syndrome, where sleep disturbance and lethargy were prominent features along with parkinsonism. The second one was on dopamine receptor antibody where seventeen pediatric cases were reported, of which seven had parkinsonism [16,17].

We report a series of Indian patients who had dominant features of parkinsonism. Most of them fulfill the probable and possible clinical diagnostic criteria for the different Parkinson plus syndromes — including multiple system atrophy (MSA) and progressive supranuclear palsy (PSP). However we were able to find an underlying neuroimmunological cause and treat them successfully.

2. Materials and methods

Patients with atypical parkinsonism and positive antibodies (neuronal antibodies, N-Methyl-D-Aspartate (NMDA), LGI1, or GAD 65 antibodies) were identified retrospectively by review of medical records. These patients attended the neurology services of Amrita Institute of Medical Sciences (AIMS), Kochi, Kerala, (which is a tertiary care referral university teaching hospital in South India, serving a population of 30 million) from 1st May 2013 to 15th April 2014. Apart from clinical history and examination, MRI brain, CSF study and neuroimmunology laboratory evaluations were performed in all the patients. This included testing for LGI1 and contactin-2 associated protein (CASPR2) antibodies, NMDA receptor antibodies and paraneoplastic antibodies by indirect immunofluorescence and GAD 65 antibodies by enzyme linked immunosorbent assay (ELISA).We have tested the LGI1 antibodies, CASPR2 antibodies and NR1 subunit of NMDA receptor antibody by indirect immunofluorescence on human embryonic kidney cell 293 transfected with corresponding antigens (Euroimmun AG, Lubeck, Germany). Immunofluorescence at a dilution of 1:10 is taken as positive as instructed by the manufacturer. Paraneoplastic antibodies were tested on a substrate containing monkey cerebellum, sural nerve and intestine (neurology mosaic, Euroimmun AG, Lubeck, Germany) by indirect immunofluorescence. Paraneoplastic neuronal antibodies [antineuronal nuclear antibody (ANNA) 1, 2 &3, antiglial nuclear antibody (AGNA)1, purkinje cell cytoplasmic antibody (PCA) 1, 2 & Tr, amphiphysin antibody, collapsin response mediator protein (CRMP)-5, Ma/Ta antibody] were identified with immunofluorescence and confirmed with Euroline neuronal antigen profile 2 (Euroimmun AG, Lubeck, Germany). In cases where antibodies were identified by immunofluorescence but did not fall into the above-mentioned 10 categories of paraneoplastic antibodies or the other named antibodies (e.g., NMDA, VGKC, Gamma Amino Butyric Acid (GABA) B, α-Amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA), homer, anti Ca, metabotropic Glutamate Receptor 1 (mGluR1), such cases were termed as uncharacterized antibodies. Immunofluorescence at a titer of 1:10 was taken as positive as instructed by the manufacturer. Autonomic function tests and detailed neuropsychological tests were performed on relevant cases. Malayalam version of mini mental status examination (MMSE) and Addenbrooke's cognitive examination (ACE) were used [18].

Whole body PET CT was performed in five patients and limited paraneoplastic work up-chest X-ray, ultrasound abdomen and pelvis was done in others.

Those who were positive for antibodies were treated with intravenous methyl prednisolone (IVMP), 1 g once daily, for five days followed mycophenylate mofetil (1 g twice daily) or azathioprine (2-3 mg/kg/day). There was an overlap regimen of oral steroid for all the patients, prednisolone 1 mg/kg/day was continued for 6 weeks for patients on mycophenylate mofetil and 12 weeks for patients on azathioprine, after which it was tapered and stopped. Clinical response was assessed based on improvement of Unified Parkinson Disease Rating Scale (UPDRS) motor scores, improvement in eye movement, sensorium, cognition and other clinical signs like signs of cerebellar dysfunction. Level of function was assessed with modified Rankin scale (mRS) scores using mRS-9Q before and after treatment, using the online version [19]. Diagnosis, clinical assessments and scoring were done by neurologists.

The study was approved by the AIMS Institutional Ethics Committee. Only those patients and family who were willing for informed consent for participation in the study as well as for publication of non-anonymized videos were included in the study. This research received no specific grant from any funding agency in the public, commercial or not-for-profit sectors.

3. Results

There are ten cases of atypical parkinsonism (nine males, one female) included in the study. Age ranged from 49 to 75 years (Mean + SD − 63.7 ± 9.92 years). Duration of disease ranges from 4 months to 13 years. Two patients had probable MSA, one had possible PSP and three had probable PSP. Four others had parkinsonian syndromes that did not fulfill the diagnostic criteria of the known syndromes [PSP, MSA or of corticobasal syndrome (CBS)]. One had features suggestive of PSP, but had significant cerebellar ataxia, the other had features of CBS, but associated with marked ataxia. One had parkinsonism that required very high dose of levodopa (>1000 mg/day) and psychosis at the onset of the disease as well as later. A fourth patient had parkinsonism with cerebellar ataxia of short duration. New uncharacterized neuronal antibodies were seen in eight patients, LGI 1 antibody was seen in one and one patient had an uncharacterized neuronal antibody along with LGI1 antibody. None of the neuronal antibodies were identical. CSF studies were done in all 10 patients. Four patients had abnormal CSF. One of them had pleocytosis, but three others had elevated protein ranging from 47.5 to 117.5 mg/dl. We did not do any oligoclonal band (OCB)/IgG analysis in CSF (Table 1).

Malignancy was seen in only one patient. He was positive for LGI1 antibody and uncharacterized neuronal antibody, had a lung malignancy in PET CT, but could not be confirmed with biopsy.

There was a prompt and dramatic clinical improvement in terms of UPDRS motor scale (>25% reduction after completion of 5 doses of IVMP) and or mRS (Ref Table 2, Fig. 1). There was an improvement in eye movement, postural instability and associated cerebellar and autonomic symptoms. Two patients had reappearance of symptoms on stopping the steroid and improvement on restarting steroid. One patient died of infection though there was a good response to treatment. Follow-up period ranged from 1 month to 7 months. Some of the representative cases are given below. For the clinical details and immunofluorescence patterns please refer to the supplementary material.

3.1. Case 1

This patient was a seventy-five year old military veteran with history of coronary artery disease and peripheral vasooclusive disease who presented with an insidious onset slowly progressive neurological disease for past 4 months. It started with hesitancy of micturition, urgency and occasional urge incontinence along with orthostatic light headedness. One month later, he developed gait disturbance in the form of slowness and imbalance with tendency to sway to either side with a stooped posture. A month prior to presentation to our hospital, he developed mild impairment of recent memory. On examination he had significant postural fall of blood pressure(more than >30 mm Hg systolic and 10 mm Hg diastolic with syncope during tilt table testing), MMSE showed a score of 24/30, cranial nerve examination was normal, no axial rigidity and limb power was normal. There was cog wheel rigidity grade 2 in upper limb, right more than left, bradykinesia grade 2, spasticity grade 2 in lower limbs, DTRs were normal, plantars were flexor. Sensory examination was normal. He had mild dysdiadochokinesia and past pointing of left upper limb and gait ataxia. He walked with stooped posture with wide base gait, short steps with circumduction and marked postural instability. His MRI brain showed age related