Pearls & Oy-sters: Pisa syndrome

An unusual feature of adult-onset fulminant SSPE

Hardeep Singh Malhotra,
MD, DM
Ravindra Kumar Garg,
MD, DM

Correspondence to
Dr. Malhotra:
drhsmalhotra@gmail.com

PEARLS

- Subacute sclerosing panencephalitis (SSPE) is a delayed, almost invariably fatal, widespread inflammatory response to a defective, persistent, intracellular measles virus infection.
- SSPE commonly presents with a combination of cognitive impairment, cortical blindness, slow myoclonus, and seizures.

OY-STERS

- Parkinsonism is an uncommon initial manifestation of SSPE seen in approximately 5% of patients.
- Pisa syndrome (pleurothotonus) is a rare extrapyramidal manifestation of SSPE and may be confused with young-onset Parkinson disease and related syndromes.
- Myoclonus in such patients may be misinterpreted to be part of a genetic parkinsonian syndrome.

CASE REPORT A 25-year-old man was referred to our department, a tertiary care neurology facility, with complaints of slowness of movements and a body tilt to the right for 3 months. These complaints were accompanied by multiple falls and behavioral changes, including apathy, lack of self-care, and decreased verbal output. He had a history of high-grade fever lasting for 5 days prior to onset of these symptoms. The patient had a history of measles at age 3 years; he had not been vaccinated owing to sociocultural beliefs. The family history was not suggestive of juvenile parkinsonism, Huntington disease, genetic dystonias, or spinocerebellar ataxias.

On examination, the patient was conscious but apathetic, with masked facies and a blink rate of 9–10 per minute. The vital parameters were normal and there was no postural drop in blood pressure. There was decreased verbal output with intact comprehension for simple commands. Mini Mental State Examination score was 20/30. The range of ocular movements was full with slowing of saccades. Rigidity without cogwheeling was present in all 4 limbs while the power

was normal. Involuntary shock-like movements involving the trunk and limbs (left > right) were noted. The deep tendon jerks and superficial reflexes were normal. There were no frontal release signs. Bradykinesia was present while the pull test was positive. Gait analysis revealed a relatively wide-spaced stance with small, hesitant steps. The gait was interrupted by myoclonic jerks (video on the *Neurology*® Web site at Neurology.org). Lateral bending of the trunk (truncal dystonia, pleurothotonus) (figure 1) and striatal toe were noted in addition; there was no suggestion of dystonia elsewhere in the body.

Hemogram, blood sugar, liver function tests, renal function tests, and thyroid function tests were normal. Enzyme-linked immunosorbent assay for HIV and tests for hepatitis B and hepatitis C viruses were also negative. EEG revealed a background of an average 20 μ V amplitude α activity, interrupted by generalized periodic bursts of stereotypic high-amplitude slow wave R complexes occurring every 2–3 seconds (figure e-1). CSF analysis revealed 10 cells, all lymphocytes, protein 28 mg/dL, and sugar 85 mg/dL, with corresponding blood sugar of 103 mg/dL. CSF immunoglobulin G antimeasles antibody titers were 23.05 Novatech units (NTU) (normal <9 NTU, indeterminate 9–11 NTU, increased >11 NTU; Novatech Immune Diagnostica GmbH, Germany). CSF was negative for other viral markers. MRI of the brain showed subcortical white matter hyperintensities involving the frontal, parietal, and occipital regions on T2-weighted and fluid-attenuated inversion recovery sequences; no contrast enhancement was observed.

The patient was initiated on clonazepam and trihexyphenidyl, and the dosage was titrated to 3 mg of clonazepam in 3 divided doses and 12 mg of trihexyphenidyl in 3 divided doses. He was also administered interferon- α 6 million units intrathecally, once a week.

The patient had a rapidly progressive downhill course. He became bedbound in 10 days and died on the 26th day of admission. Genetic test reports, available posthumously, revealed heterozygous *TLR3* (Toll-like receptor 3) gene polymorphisms involving rs3775290, rs3775291, and rs3775296.

Supplemental data
at Neurology.org

From the Department of Neurology, King George's Medical University, Lucknow, India.

Go to Neurology.org for full disclosures. Funding information and disclosures deemed relevant by the authors, if any, are provided at the end of the article.

A comparative depiction of leaning tower of Pisa with the patient's stance.

DISCUSSION A mutated measles virus that can remain dormant intracellularly for up to a decade causes SSPE. The reactivation occurs due to an unknown trigger and leads to widespread inflammatory neuronal damage.¹ It is clinically characterized by rapidly progressive cognitive impairment, scholastic backwardness, behavioral changes, seizures, myoclonic jerks, extrapyramidal involvement, language disturbances, optic atrophy, macular degeneration, and cortical blindness, in variable combinations.² SSPE has been observed to be more common in males, in those with history of measles at less than 2 years of age, and in situations lacking adequate vaccination against measles. Adult-onset SSPE is not significantly different from childhood-onset SSPE except that the latency of measles virus activation is more prolonged in adult SSPE.^{2,3} Our patient had not been vaccinated, and had a history of childhood measles, as well. In its typical form, most patients with SSPE survive for about 18 months (range 1–3 years); our patient had the fulminant form of SSPE where death occurs by 6 months of diagnosis.

Pisa syndrome is an uncommon form of truncal dystonia characterized by lateral bending of the trunk or pleurothotonus. It was first described by Swedish neurologist Karl Axel Ekbom and colleagues⁴ as an untoward reaction to haloperidol in an elderly woman. The epithet, Pisa syndrome, owes its inspiration to the famous leaning tower of Pisa in Italy for its unintended 5.5° tilt. It is clinically defined as a lateral flexion of more than 10° in the standing position due to axial dystonia.⁵ After the

initial documentation as an adverse drug reaction, this syndrome has been observed in several disorders, such as Parkinson disease, multiple system atrophy, and as a reaction to neuroleptics.^{5–7}

The exact pathogenesis of Pisa syndrome remains elusive, and many theories have been postulated. Women and elderly with organic brain disease appear to be at increased risk.⁷ It can occur as an acute dystonic reaction and more commonly as an atypical form of tardive dystonia. The response to anticholinergics and reduction or withdrawal of neuroleptics suggest the possible role of cholinergic excess or imbalance between cholinergic and dopaminergic neurotransmission in the development of this rare syndrome.^{6,7} The abnormality in recruitment of truncal muscles or abnormal proprioceptive motor control have also been postulated as major reasons behind Pisa syndrome in Parkinson disease.⁵ The marked hyperactivity in the paraspinal muscles on the less affected side is considered another plausible cause for Pisa syndrome in Parkinson disease. Tassorelli et al.⁸ observed that Pisa syndrome occurs in patients with advanced disease and in those with marked asymmetry; the bending is usually noted contralateral to the onset of the disease. In their series, almost 40% of patients responded to anticholinergic therapy. It may be noted that only acute dystonic reactions might respond to anticholinergics and not the more commonly observed tardive dystonias, which typically worsen with anticholinergics; clonazepam may serve as an alternative in the latter category.

Dystonia and parkinsonism are uncommon manifestations of SSPE. In a series of adult-onset SSPE, myoclonus was the commonest presentation and extrapyramidal symptoms were observed in only 2 of 39 patients (5.1%).² Recently, status dystonicus and rhabdomyolysis were reported in a patient with SSPE occurring secondary to pneumonia.⁹ Misra et al.¹⁰ reported 2 adolescents with SSPE who presented with parkinsonian features prior to myoclonic jerks. To our knowledge, Pisa syndrome has not been described in the literature in association with SSPE; it should be considered in patients presenting with a new focal dystonia and rapid cognitive decline.

In a study of 40 patients with SSPE, it has been concluded that the *TLR3* gene may confer host genetic susceptibility to SSPE in Japanese individuals.¹¹ Our patient was detected having heterozygous *TLR3* gene polymorphism affecting *rs3775290*, *rs3775291*, and *rs3775296*, simultaneously, which has not been observed earlier. Whether this simultaneous occurrence, vis-a-vis single *TLR3* polymorphism, portends a fulminant course needs to be seen in more patients with SSPE.

Pisa syndrome is a novel presentation of SSPE that may be confused with genetically determined parkinsonian syndromes on the background of adult onset of symptoms and subtle myoclonus. This case is also atypical for its fulminant and fatal course. SSPE should be added to the list of causes of Pisa syndrome.

AUTHOR CONTRIBUTIONS

Hardeep Singh Malhotra: drafting/revising the manuscript, study concept or design, analysis or interpretation of data, accepts responsibility for conduct of research and final approval. Ravindra Kumar Garg: drafting/revising the manuscript, study concept or design, analysis or interpretation of data, accepts responsibility for conduct of research and final approval.

STUDY FUNDING

No targeted funding reported.

DISCLOSURE

The authors report no disclosures relevant to the manuscript. Go to Neurology.org for full disclosures.

REFERENCES

1. Garg RK. Subacute sclerosing panencephalitis. *J Neurol* 2008;255:1861–1871.
2. Prashanth LK, Taly AB, Ravi V, Sinha S, Arunodaya GR. Adult onset subacute sclerosing panencephalitis: clinical profile of 39 patients from a tertiary care centre. *J Neurol Neurosurg Psychiatry* 2006;77:630–633.
3. Sonia M, Lalit D, Shobha B, et al. Subacute sclerosing panencephalitis in a tertiary care centre in post measles vaccination era. *J Commun Dis* 2009;41:161–167.
4. Ekblom K, Lindholm H, Ljungberg L. New dystonic syndrome associated with butyrophenone therapy. *Z Neurol* 1972;202:94–103.
5. Doherty KM, Davagnanam I, Molloy S, Silveira-Moriyama L, Lees AJ. Pisa syndrome in Parkinson's disease: a mobile or fixed deformity? *J Neurol Neurosurg Psychiatry* 2013;84:1400–1403.
6. Villarejo A, Camacho A, García-Ramos R, et al. Cholinergic-dopaminergic imbalance in Pisa syndrome. *Clin Neuropharmacol* 2003;26:119–121.
7. Suzuki T, Matsuzaka H. Drug-induced Pisa syndrome (pleurothotonus): epidemiology and management. *CNS Drugs* 2002;16:165–174.
8. Tassorelli C, Furnari A, Buscone S, et al. Pisa syndrome in Parkinson's disease: clinical, electromyographic, and radiological characterization. *Mov Disord* 2012;27:227–235.
9. Yiş U. Status dystonicus and rhabdomyolysis in a patient with subacute sclerosing panencephalitis. *Turk J Pediatr* 2012;54:90–91.
10. Misra A, Roy A, Das S. Parkinsonian presentation of SSPE: report of two cases. *Neurol Asia* 2008;13:117–120.
11. Ishizaki Y, Takemoto M, Kira R, et al. Association of toll-like receptor 3 gene polymorphisms with subacute sclerosing panencephalitis. *J Neurovirol* 2008;14:486–491.

Neurology®

Pearls & Oy-sters: Pisa syndrome: An unusual feature of adult-onset fulminant SSPE

Hardeep Singh Malhotra and Ravindra Kumar Garg

Neurology 2015;84:e12-e14

DOI 10.1212/WNL.0000000000001161

This information is current as of January 19, 2015

Updated Information & Services	including high resolution figures, can be found at: http://n.neurology.org/content/84/3/e12.full
Supplementary Material	Supplementary material can be found at: http://n.neurology.org/content/suppl/2015/01/18/WNL.0000000000001161.DC1 http://n.neurology.org/content/suppl/2015/01/18/WNL.0000000000001161.DC2
References	This article cites 11 articles, 2 of which you can access for free at: http://n.neurology.org/content/84/3/e12.full#ref-list-1
Subspecialty Collections	This article, along with others on similar topics, appears in the following collection(s): Encephalitis http://n.neurology.org/cgi/collection/encephalitis Myoclonus http://n.neurology.org/cgi/collection/myoclonus Parkinson's disease/Parkinsonism http://n.neurology.org/cgi/collection/parkinsons_disease_parkinsonism Prognosis http://n.neurology.org/cgi/collection/prognosis
Permissions & Licensing	Information about reproducing this article in parts (figures, tables) or in its entirety can be found online at: http://www.neurology.org/about/about_the_journal#permissions
Reprints	Information about ordering reprints can be found online: http://n.neurology.org/subscribers/advertise

Neurology® is the official journal of the American Academy of Neurology. Published continuously since 1951, it is now a weekly with 48 issues per year. Copyright © 2015 American Academy of Neurology. All rights reserved. Print ISSN: 0028-3878. Online ISSN: 1526-632X.