

CASE REPORT

Familial spontaneous pneumothorax and Machado–Joseph disease

Jerald Pelayo^{*,†}, Naraharisetty Rau, Kevin Bryan Lo and Zurab Azmaiparashvili

Department of Medicine, Einstein Medical Center Philadelphia, 5501 Old York Road, Philadelphia, PA 19141, USA

*Correspondence address. Einstein Medical Center Philadelphia, 5501 Old York Road, Philadelphia, PA 19141, USA.
Tel: +909-642-2821; E-mail: pelayoje@einstein.edu

Abstract

We report the first known case of a 42-year-old man diagnosed with spinocerebellar ataxia type 3, also known as Machado–Joseph disease (MJD), who presented with recurrent spontaneous pneumothorax. Six other family members affected with MJD died of the same pulmonary complication. To date, there has been no direct genetic linkage between MJD and familial spontaneous pneumothorax. However, the mutated ataxin-3 (ATXN3) gene in MJD and Serpin Family A Member 1 (SERPINA1) gene in hereditary emphysema share the same loci on chromosome 14q32.1, which is suggestive of genetic proclivity of patients with MJD to develop familial pneumothorax. Furthermore, the abnormal ataxin protein encoded by ATXN3 and the patient's smoking history could have potentiated the dysregulation of the ubiquitin-proteasome system further aggravating his genetic predisposition to develop recurrent pneumothorax. These unexplored areas of inquiry invoke further molecular characterization to give an accent to medical knowledge as well as guide novel therapies in the future.

INTRODUCTION

Spinocerebellar ataxias (SCAs) are rare neurodegenerative disorders predominantly presenting with progressive alteration of coordination, gait and speech. Types are classified according to the genetic loci of the SCA. Of over 35 types of SCA identified, the most common is spinocerebellar ataxia type 3, known as Machado–Joseph disease (MJD), which is caused by cytosine–adenine–guanine (CAG) expansions in the ATXN3 [1]. Since 1997, only one case has been reported on recurrent familial pneumothorax in two siblings with spinocerebellar ataxia type 1 [2]. To date, there has been no genetic linkage established between MJD and primary spontaneous pneumothorax (PSP). In fact, established genetic variants in PSP only include human leukocyte antigen haplotype A2B40, alpha-1 antitrypsin, fibrillin 1 and folliculin mutations [3]. We report the first known case of recurrent familial spontaneous pneumothorax in a patient

diagnosed with MJD highlighting the possible genetic correlation between these two disease entities.

CASE REPORT

Our patient is a 42-year-old African American man who presented to the emergency department with acute chest pain and shortness of breath. He had oropharyngeal dysphagia, productive cough, weight loss, blurred vision, and excessive daytime sleepiness. Since the age of 18 when he was diagnosed with MJD, he had progressively lost muscle control and coordination of his extremities until he was wheelchair-bound by age 38. He reported having recurrent aspiration pneumonia in his late 30s. In the previous year, he had two episodes of left-sided pneumothorax, which required thoracoscopic drainage and decortication. He had a 20-pack-year history of smoking.

[†]Jerald Pelayo, <http://orcid.org/0000-0002-5603-7078>

Received: May 13, 2020; Revised: June 14, 2020; Accepted: July 24, 2020

© The Author(s) 2020. Published by Oxford University Press. All rights reserved. For Permissions, please email: journals.permissions@oup.com

This is an Open Access article distributed under the terms of the Creative Commons Attribution Non-Commercial License (<http://creativecommons.org/licenses/by-nc/4.0/>), which permits non-commercial re-use, distribution, and reproduction in any medium, provided the original work is properly cited.

For commercial re-use, please contact journals.permissions@oup.com



Figure 1: Chest radiograph showing large right pneumothorax with leftward mediastinal shifting.

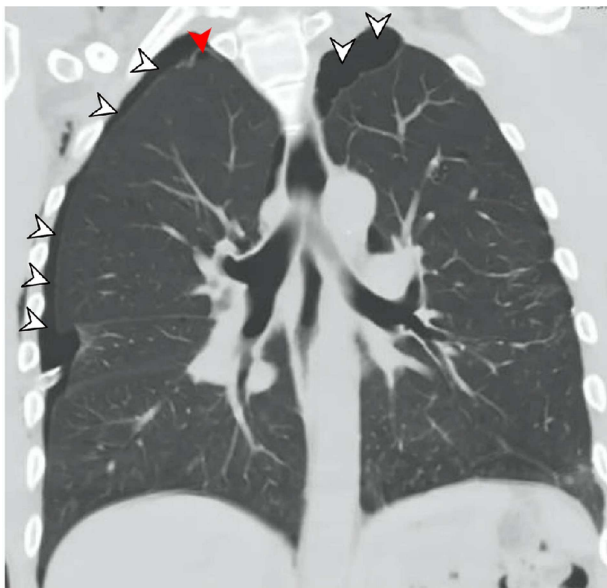


Figure 2: CT chest demonstrating bilateral paraseptal emphysematous changes and apical bulla (red arrow) resulting in pneumothorax (white arrows).

On presentation, blood pressure was 130/70 mmHg, heart rate was 110 beats/min, respiration was 28 breaths/min and temperature was 37°C. He appeared chronically ill with generalized muscle wasting. Decreased tactile fremitus, hyperresonance and absent breath sounds in the right hemithorax were noted. Significant neurological exam findings included slow saccades, dysarthria, tongue fasciculations, rigid extremities with hyperreflexia, bilateral extensor plantar response, dysmetria and dysdiadochokinesia, without sensorimotor deficits. Chest radiograph showed a large pneumothorax of the right lung with contralateral mediastinal shift (Fig. 1). Chest CT scan showed right-sided pneumothorax with bilateral paraseptal emphysematous and bullous changes in the lung apices (Figs 2 and 3).



Figure 3: Chest CT showing right-sided pneumothorax (white arrows) predominantly along the anterior aspect of the right hemithorax with chest tube in the major fissure (black circle). Significant bleb disease is also seen in the left lung.

MJD was first diagnosed in his paternal grandmother in her 30s, his father, two uncles and three aunts in their late 20s and his younger sister in her late teens. His sister succumbed to aspiration pneumonia, his mother to an undiagnosed cardiac disease, while the others to pneumothorax complications (Fig. 4).

Supplemental oxygen was given, and a chest tube was initially placed at the ED. He eventually underwent right-sided thoracoscopic drainage of effusion, decortication and reinflation, which afforded maximal clinical improvement. He was discharged after 2 weeks. Repeat chest radiography after 2 weeks demonstrated a small right-sided pleural effusion and subpleural blebs without recurrence of pneumothorax.

DISCUSSION

MJD is one of nine known polyglutamine neurodegenerative diseases and is the most common autosomal dominant ataxia [4–7]. The patient's family pedigree demonstrates the well-established 10-year 'anticipation' of worsening disease progression, suggesting that the larger numbers of CAG repeats will manifest in more progressive and severe disease with each successive generation [4]. Furthermore, our patient had clinical manifestations demonstrative of the early onset subtype with progressive motor coordination and muscle control loss, resulting in being wheelchair-bound at age 38.

Spontaneous pneumothorax is a manifestation that, to our knowledge, has not been previously linked to MJD. It occurs without preceding trauma or obvious precipitating causes. In the absence of an underlying lung disease, it is termed primary spontaneous pneumothorax (PSP) with an annual incidence of 7.4–37 per 100 000 in men and 1.2–15.4 per 100 000 in women and typically seen among young adults [8, 9]. One retrospective study found 23.5% recurrence of PSP within the first 6 months [8]. The presence of subpleural blebs and bullae is seen in 80–90% of PSP cases. Other risk factors include cigarette smoke exposure, cannabis smoking and genetic predisposition. On the other hand, 80% of secondary spontaneous pneumothorax cases are seen in patients older than 55. Its typical causes include emphysema, interstitial lung disease, malignancy and necrotizing pneumonia [8, 9].

Given the presence of an underlying lung disease as well as contributing risk factors of smoking and recurrent aspiration

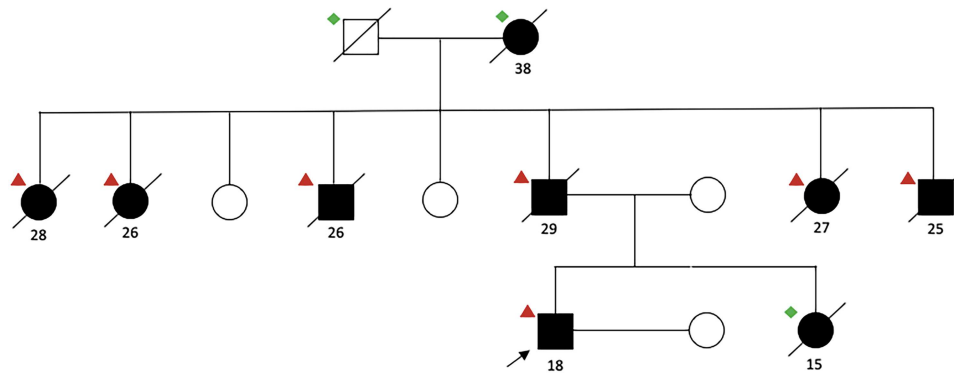


Figure 4: Pedigree structure of family.

pneumonia, the diagnosis of primary spontaneous pneumothorax in our patient would seem less likely. However, with his significant history of MJD, and collateral history that six affected members died of pneumothorax complications, we believe that our patient has inherited susceptibility to spontaneous pneumothorax.

The underlying pathogenetic defect of MJD is the CAG trinucleotide repeat found within the 5' coding region of ATXN3 gene on chromosome 14q32.1 [1, 4, 5]. Interestingly, this is where the chromosome of the mutated SERPINA1 gene of alpha-1-antitrypsin deficiency underlying hereditary emphysema is located [6, 7, 10]. Recent data shows that the SERPINA1 gene acts as a protective agent in the lungs against neutrophilic proteolytic activity during inflammation [10]. Once mutated, it can predispose affected individuals to emphysema. Additionally, ATXN3 gene is responsible for the formation of the ataxin protein that is expressed in both neuronal and nonneuronal human tissue. A derangement of this system results in the accumulation of inclusional protein. This accounts for the progressive ataxia, dystonia and neuropathy in MJD [5–7].

There is also a growing evidence that the ubiquitin-proteasome mechanism is responsible for homeostasis in the lung. Proteasomes aid in immunological defense against pathogens via antigen presentation. In a patient whose pathway is dysfunctional, this could theoretically lead to lung injury [7, 10]. Furthermore, cigarette smoke also induces protein misfolding and aggregation. We posit that the dysfunction of the ubiquitin-proteasome pathway may have been an additional factor that contributed to the recurrence of spontaneous pneumothorax seen in our patient with MJD.

Further inquiries of the pathogenesis of extra-neuronal manifestations can be useful to our understanding of MJD. Although we don't have sufficient data to prove that no other mutations are present in this patient to explain recurrent pneumothorax, the proximity of the aforementioned genes on the same chromosome loci should not be dismissed, nor should the potential for co-inheritance of these variants. This exploration invokes further molecular characterization to amplify medical knowledge and guide novel therapies that target the degradation of protein/s in MJD.

ACKNOWLEDGEMENTS

Thank you Dr Lo and Dr Azmaiparashvili for the guided supervision in taking care of our patient and in editing this manuscript.

Conflict of interest statement. No conflicts of interest.

FUNDING

There was no monetary or material support for this research investigation.

ETHICAL APPROVAL

No ethical approval is required.

CONSENT

Patient consent form was duly completed before writing the manuscript. The Oxford University Press Patient Consent form was signed by the patient's wife with patient's consent (patient is unable to write due to his clinical condition). It is readily available if requested.

GUARANTOR

Jerald Pelayo.

REFERENCES

1. Kawaguchi Y, Okamoto T, Taniwake M, Aizawa M, Inoue M, Katayama S, et al. CAG expansions in a novel gene for Machado-joseph disease at chromosome 14q32.1. *Nat Genet* 1994;8:221–8.
2. Chiu HK, Garcia CK. Familial spontaneous pneumothorax. *Curr Opin Pulm Med* 2006;12:268–72.
3. Cheng Y, Chou S, Kao E. Familial spontaneous pneumothorax – report of seven cases in two families. *Gaoxiong Yi Xue Ke Xue Za Zhi* 1992;8:390.
4. Fukazawa T, Sasaki H, Kikuchi S, Hamada K, Hamada T, Tashiro K. Spinocerebellar ataxia type 1 and familial spontaneous pneumothorax. *Neurology* 1997;49:1460–2.
5. Paulson H. Machado-Joseph disease/spinocerebellar ataxia type 3. *Handb Clin Neurol* 2012;103:437–49.
6. Jardim LB, Pereira ML, Silveira I, Ferro A, Sequeiros J, Giugliani R. Neurologic findings in Machado-Joseph disease relation

- with disease duration, subtypes, and CAG (n). *Arch Neurol* 2001;58:899–904.
7. Chai Y, Koppenhafer S, Shoesmith S, Perez M, Paulson H. Evidence for proteasome involvement in polyglutamine disease: location to nuclear inclusions in SCA3/MJD and suppression of polyglutamine aggregation in vitro. *Hum Mol Genet* 1999;8:673–82.
 8. Tulay C, Ozsoy E. Spontaneous pneumothorax recurrence and surgery. *Indian J Surg* 2015;77:463–5.
 9. Walker S, Bibby A, Halford P, Staddon L, White P, Maskell N. Recurrence rates in primary spontaneous pneumothorax: a systematic review and meta-analysis. *Eur Respir J* 2018;52:1800864.
 10. Silva D, Oliveira MJ, Guimaraes M, Ricadro L, Gomes S, Seixas S. Alpha-1-antitrypsin (SERPINA1) mutation spectrum: three novel variants and haplotype characterization of rare deficiency alleles identified in Portugal. *Respir Med* 2016; 116:8–18.