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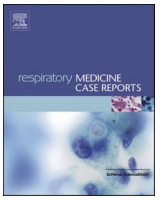

Case Report

Post-infective neuromuscular hyperexcitability syndrome in a young man with cystic fibrosis: A case report

Roberta Maria Antonello [a,*], Beatrice Borchi [b], Annalisa Cavallo [b], Jessica Mencarini [b], Gianmarco Somma [a], Alessandro Bartoloni [a,b], Antonello Grippo [c], Alessandro Barilaro [d], Antonio Lotti [e], Silvia Bresci [b]

[a] Department of Experimental and Clinical Medicine, University of Florence, Florence, Italy
[b] Infectious and Tropical Diseases Unit, Careggi University Hospital, Florence, Italy
[c] SOD Neurofisiopatologia, Dipartimento Neuromuscolo-Scheletrico e degli Organi di Senso, Azienda Ospedaliero Universitaria Careggi, Florence, Italy
[d] SOD Neurologia 2, Dipartimento Neuromuscolo-Scheletrico e degli Organi di Senso, Azienda Ospedaliero Universitaria Careggi, Florence, Italy
[e] Department of Neurosciences, Drug and Child Health, University of Florence, Florence, Italy

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ABSTRACT

Cystic fibrosis (CF)-related central (CNS) and peripheral nervous system (PNS) disorders have not yet been fully described. We report the first case of post-infective neuromuscular hyperexcitability syndrome in a 23-year-old male patient with CF and pulmonary exacerbation. CNS radiological investigations were unremarkable and no autoantibodies were detected. The patient fully recovered after infectious state control and multidisciplinary assessment and no recurrence was observed at follow-up. In view of the rarity of this condition, an additional effort is advisable to collect data and define the optimal management strategy in patients with CF.

1. Introduction

Cystic fibrosis (CF) is a genetic disease with multi-organ involvement. As for the central (CNS) and peripheral nervous system (PNS), little is known in the setting of CF-related clinical pictures and there is limited evidence about the impact of respiratory acute infections on infection-related CNS/PNS disorders. We describe the first case of post-infective neuromuscular hyperexcitability syndrome in a male patient with CF.

2. Case presentation

A 23-year-old Italian man with CF (diagnosis at birth with positive sweat test, CFTR genotype G542X/E585X) presented with fever (38 °C), cough and neuromuscular disorders.

His medical history was remarkable for good pulmonary function tests and methicillin-susceptible *Staphylococcus aureus* (MSSA) and pansusceptible *Pseudomonas aeruginosa* chronic lung colonization, occasionally requiring oral antibiotic courses. Since CF diagnosis, he had no relevant medical history and he had never been hospitalized before. He never reported drug allergies or side effects to

* Corresponding author.
E-mail address: robertamaria.antonello@unifi.it (R.M. Antonello).

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any medications. His home treatment included inhalation therapy (salbutamol sulphate, budesonide/formoterol, dornasum alfa), cholecalciferol, pancreatic enzyme replacement, and it had not been changed in the previous months. He worked as a storekeeper and he practiced sport activities at least three times a week (mostly cycling).

In the previous weeks he complained of weight loss, concentration difficulties, night sweats, and occasional flushing. One week prior to presentation during working time he experienced right superior limb pain, sudden muscle stiffness and twitching with impossibility to hold objects. Few hours later, while walking, similar symptoms occurred again involving both legs at proximal level with discomfort and difficulties in carrying out daily activities. He did not have fever, cough, or gastrointestinal symptoms. The general

Table 1
Laboratory diagnostic work-up. ALT: alanine aminotransferase; AMPA: anti-glutamate receptor; AST: aspartate transaminase; CASPR2: contactin-associated protein-like 2; CMV: cytomegalovirus; CNS: central nervous system; CPK: creatine phosphokinase; CRP: C reactive protein; DPP: dipeptidyl peptidase; EBNA: EBV nuclear antigen; EBV: Epstein-Barr virus; ERS: erythrocyte sedimentation rate; GABA: gamma-aminobutyric acid; HCV: hepatitis C virus; HIV: human immunodeficiency virus; LGI1: leucin-rich-glioma-inactivated 1; MSSA: methicillin-susceptible *Staphylococcus aureus*; NMDA: N-methyl-D-aspartate; RBC: red blood cells; TSH: thyroid stimulating hormone; VCA: viral capside antigen; WBC: white blood cells.

Parameter	Value	Normal value
General examination (at presentation)		
WBC (x 10^9/L)	18.60	4.00–10.00
Neutrophils (x 10^9/L)	7.69	1.50–7.50
RBC (x10^12/L)	5.30	4.50–6.10
Hemoglobin (g/dL)	16.2	14.0–18.0
Platelets (x 10^9/L)	233	140–440
Protrombin time	1.0	0.8–1.2
Fibrinogen (mg/dL)	370	200–400
Serum glucose (mg/dL)	77	65–110
Creatinine (mg/dL)	1.00	0.70–1.20
ERS (mm/h)	26	2–25
Sodium (mEq/L)	139	135–145
Potassium (mEq/L)	4.4	3.5–5.1
Chloride (mEq/L)	100	95–110
Calcium (mg/dL)	9.4	8.6–10.2
Magnesium (mg/dL)	2.5	1.7–2.5
ALT (U/L)	53	10–50
AST (U/L)	87	10–50
Total bilirubin (mg/dL)	0.7	0.2–1.0
CPK (U/L)	74	39–308
Myoglobin (ng/mL)	21	28–72
TSH (microUI/mL)	1.50	0.27–4.20
CRP (mg/L)	12	<5
Procalcitonin (ng/mL)	0.12	<0.5
Aldolasi (U/L)	15.5	0.1–7.6
HbA1c (mmol/mol)	41.0	20–38
Metanefrina urinaria (microg/24h)	142	<320
Normetanefrina urinaria (microg/24h)	211	<390
Protein electrophoresis	Within normal range	–
Urine physical examination	No abnormalities found	–
Microbiological investigation/serology for infectious agents		
CMV IgG	Positive	–
CMV IgM	Negative	–
HCV IgG	Negative	–
HIV 1–2 Ag/Ab	Negative	–
Anti-streptolysin O	Negative	–
EBV VCA IgG	Positive	–
EBV EBNA IgG	Positive	–
EBV VCA IgM	Positive	–
Syphilis IgG-IgM	Negative	–
HBsAb	Negative	–
Sputum microscopy, molecular test, and cultures for mycobacteria	Negative	–
Sputum cultures	Positive for MSSA	–
Nasopharyngeal swab for SARS-CoV-2	Negative	–
Autoimmunity		
Anti-CNS Ig	Negative	Negative
Onconeural antibodies	Negative	Negative
Antibodies anti neuronal surface antigens		
Antibodies anti NMDA receptor	Negative	Negative
Antibodies anti LGI1	Negative	Negative
Antibodies anti CASPR2	Negative	Negative
Antibodies anti GABA-B1/2 receptor	Negative	Negative
Antibodies anti Glu receptor (AMPA 1/2)	Negative	Negative
Antibodies anti DPP X	Negative	Negative

practitioner prescribed methylprednisolone 16 mg orally q 24 h for one week without any improvement.

On physical examination, he had fine basal crackles on pulmonary auscultation and fine distal tremors and hyposthenia of the right hand. The Mingazzini test was positive for lower limbs with severe pain and inability to raise the limbs. He walked with severe difficulty due to lower limb pain and stiffness. No sensory deficits nor cranial nerve deficits were present. Abnormal muscular twitching, compatible with fasciculations or myokymia of the right triceps, left gastrocnemius and femoral biceps were observed. Brisker deep tendon reflex and a diffuse pathologic increase in the reflexogenic zone were also present.

Blood tests revealed an elevated white blood cell count (18600/mm^3, with elevation in neutrophils) and C-reactive protein 12 mg/L (normal value $<$ 5 mg/L), while myoglobin, creatinine, creatine phosphokinase, procalcitonin and electrolytes (sodium, potassium, calcium, magnesium, phosphate) were within normal range. Arterial blood gas analysis showed pH 7.5, pO2 77 mmHg, pCO2 35.3 mmHg, lactate 1.1 mmol/L, HCO3 28 mmol/L. Chest CT showed bilateral bronchiectasis/bronchiolectasis. A nasopharyngeal swab for SARS-CoV-2 was negative.

As the clinical and laboratory findings were consistent with a respiratory exacerbation, he was admitted to the Infectious Diseases Department and he was prescribed ceftazidime 3 g IV q 8 h and fosfomycin 4 g IV q 6 h, in association with oxygen supplementation with nasal cannula (FiO2 28 %). Sputum cultures were collected and confirmed MSSA colonization.

A brain CT scan and a brain and cervical spine magnetic resonance imaging were unremarkable, with the exception of signs of sinusopathy. Electromyography (EMG) and nerve conductions studies (NCS) were performed. NCS revealed sustained firing actions potentials in the setting of F wave attributable to afterdischarges and fasciculation potentials firing in doublets and triplets were recorded on EMG after ischemia-hyperpnea test: both signs consistent with neuromuscular hyperexcitability.

A comprehensive diagnostic work-up was performed, investigating both infective and non-infective underlying conditions (Table 1).

A post-infective neuromuscular hyperexcitability syndrome was diagnosed and pregabalin 75 mg orally q 24 h for four days, followed by 75 mg orally q 12 h, was started. Pregabalin was suspended after one week, following multidisciplinary re-evaluation, as no clinical benefits were reported and no data were available on its use in CF people. The patient was discharged home a few days later.

He was readmitted 20 days later due to worsening respiratory symptoms (dyspnoea and tachycardia with minimal exertion, apical wheezing on lung auscultation, peripheral blood oxygenation 93 % on room air). He was started on piperacillin/tazobactam 4 g/0.5 g IV q 6 h (extended infusion over 3 hours) and levofloxacin 500 mg IV q 12 h for 14 days and intravenous methylprednisolone 20 mg q 12 h, followed by methylprednisolone 20 mg q 24 h for a total of 12 days. Two months later, due to the persistence of mild respiratory symptoms, he was prescribed an oral antibiotic course with trimethoprim/sulfamethoxazole 800/160 mg q 8 h and levofloxacin 500 mg q 12 h for 14 days. A follow-up EMG showed resolution of previously reported abnormalities.

On follow-up, a complete spontaneous resolution of symptoms was observed during a 4-month period. No recurrence was observed over the subsequent follow-up period (8 months).

3. Discussion

To our knowledge, this is the first case report of post-infective neuromuscular hyperexcitability syndrome in a CF patient.

Peripheral nerve hyperexcitability syndromes (PNHS) are determined by ectopic discharges from the motor neuron and include a variety of clinical presentations of PNS disorders (e.g. Isaacs syndrome, Morvan syndrome, cramp-fasciculation syndrome) which could be both inherited or acquired [1]. Autoantibodies are often found, in particular targeting proteins of voltage-gated potassium channel complex (e.g. CASPR2, LGI1), but cases of seronegative PNHS are also reported. However, it remains difficult to define the role of autoimmunity in PNHS as other autoimmune disorders (e.g. myasthenia gravis), or solid and hematologic malignancies, are often associated [2,3]. Few cases of para/post infectious PNHS have also been reported, especially after *S. aureus* infections [4].

Typical electrophysiological features include fasciculation and cramps potentials, myokymia, neuromyotonia and afterdischarges [1,3,5].

Differential diagnosis is complex as clinical phenomenology and neurophysiologic findings overlap with many PNS and muscle disorders and it requires a high index of suspicion. A comprehensive and multidisciplinary work-up aiming at identifying and managing possible underlying comorbidities remains crucial to reduce the clinical impact of PNHS.

The optimal treatment of PNHS is still to be established as it is mainly based on expert opinion, case reports, small case series or retrospective data collection based on a limited number of patients. In the case we described, no PNHS-targeted specific treatment was continued as pregabalin provided no clinical benefits after one week of treatment. The patient recovered completely after appropriate antibiotic treatment and management of the underlying respiratory infection, with no recurrence observed in a 8-month period of follow-up.

Taking into account the lack of guidelines or consolidated clinical practices in the peculiar setting of CF, a multidisciplinary evaluation is strongly encouraged to tailor the therapeutic approach on a case -by-case basis.

4. Conclusion

Our case suggests the need for a collection of similar cases to collect possible clinical presentations and compare different treatment strategies to provide the best evidence-based management in the peculiar setting of CF.

CRediT authorship contribution statement

Roberta Maria Antonello: Writing – original draft, Data curation, Conceptualization. **Beatrice Borchi:** Writing – review & editing, Supervision, Conceptualization. **Annalisa Cavallo:** Writing – review & editing, Supervision. **Jessica Mencarini:** Writing – review & editing, Supervision. **Gianmarco Somma:** Writing – original draft, Data curation. **Alessandro Bartoloni:** Writing – review & editing, Supervision, Conceptualization. **Antonello Grippo:** Writing – review & editing, Supervision, Conceptualization. **Alessandro Barilaro:** Writing – review & editing, Supervision, Conceptualization. **Antonio Lotti:** Writing – original draft, Data curation, Conceptualization. **Silvia Bresci:** Writing – review & editing, Supervision, Conceptualization.

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Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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