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Case Report

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

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ARTICLE INFO

Handling Editor: DR AC Amit Chopra

Keywords: PNHS Cramp-fasciculation syndrome Post-infective disorders CFTR

#### 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  $^{\circ}$ 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

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https://doi.org/10.1016/j.rmcr.2024.102139

Available online 16 November 2024





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Received 15 May 2024; Received in revised form 15 October 2024; Accepted 11 November 2024

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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: contactinassociated 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.

| General cannination (a presentation)setNeutrophils (s 10°9/L)16.80400-1000Neutrophils (s 10°9/L)7.691.50-7.50Neutrophils (s 10°9/L)5.304.56.4.10Hemoglobh (g/dl)16.2140-18.0Hemoglobh (g/dl)16.2333140-4400Patalets (s 10°9/L)233140-18.0Patalets (s 10°9/L)370200-400Serum glucose (mg/dl)7765.110Creatinine (mg/dl)1.00070-1.30Serum glucose (mg/dl)1.00070-1.30Serum glucose (mg/dl)1.00070-1.30Serum (mg/dl)1.000.51.15Chold (mg/dl)1.0095-110Chold (mg/dl)1.0095-110Chold (mg/dl)1.0095-110Chold (mg/dl)9.48.5.16.2Att (U/A)9.43.5.36Att (U/A)571.0-50Satt (U/A)571.0-50Satt (U/A)1.000.2-1.0Satt (U/A)1.000.2-1.0Satt (U/A)1.000.2-1.0Satt (U/A)1.20.2-7.4.20Satt (U/A)1.20.2-7.4.20Satt (U/A)1.50.1-7.6Satt (U/A)1.50.1-7.6Satt (U/A)1.50.1-7.6Satt (U/A)1.20.3-30Satt (U/A)1.20.3-30Satt (U/A)1.20.3-30Satt (U/A)1.20.3-30Satt (U/A)1.20.3-30Satt (U/A)1.  | Parameter  | Value                  | Normal value |
|--|--|------------------------|--------------|
| WPC (s10°).18.00400-10.00Nettrophils (10°).7.691.50°.750NBC (10712.1)5.30450-7.50NBC (10712.1)1.621.40-18.00Plantels (10°).1.621.40-18.00Plantels (10°).1.621.40-18.00Plantels (10°).3.301.40-18.00Plantels (10°).3.301.40-18.00Plantels (10°).1.000.61-12Flbringen (mg/dl.)772.00-400Serum glucos (mg/dl.)702.00-400Creating (mg/dl.)1.000.70-1.20Creating (mg/dl.)1.002.55Softum (mg/dl.)1.003.55-11Claitun (mg/dl.)1.003.55-11Claitun (mg/dl.)0.443.55-11Claitun (mg/dl.)0.443.55-11Claitun (mg/dl.)0.443.55-11Claitun (mg/dl.)0.443.55-11Claitun (mg/dl.)0.443.55-11Claitun (mg/dl.)0.443.55-11Claitun (mg/dl.)0.742.10-20Magnesium (mg/dl.)0.742.10-20Claitun (mg/dl.)1.100.50Claitun (mg/dl.)1.100.21-00Claitun (mg/dl.)1.100.27-4.20Claitun (mg/dl.)1.100.27-4.20Claitun (mg/dl.)1.100.20-00Claitun (mg/dl.)1.100.20-00Claitun (mg/dl.)1.100.20-00Claitun (mg/dl.)1.100.20-00Claitun (mg/dl.)1.100.20-00 <td< td=""><td>General examination (at presentation)</td><td></td><td></td></td<>  | General examination (at presentation)                            |                        |              |
| Neutrophils (x 10%,L)109-7.50109-7.50BRG (x 107,L)53140-18.0Hemaglobia (x/A)23304-40Parters (x 10%,L)03305-1.2Parters (x 10%,L)37005-1.0Serum glucos (my,dl)07005-1.0Serum glucos (my,dl)100070Serum glucos (my,dl)10005-1.0Creatinane (my,dl)10005-1.0Soldian (mg/dl)10035-1.45Soldian (mg/dl)10035-1.45Colorido (mg/dl)10035-1.45Colorido (mg/dl)10035-1.45Colorido (mg/dl)10035-1.45Colorido (mg/dl)0.035-1.10Calcian (mg/dl)0.035-1.10Calcian (mg/dl)0.035-1.10Calcian (mg/dl)0.035-1.10Calcian (mg/dl)0.136-1.02Calcian (mg/dl)0.136-1.02Calcian (mg/dl)10.036-1.02Calcian (mg/dl)10.036-   | WBC (x $10^9/L$ )  | 18.60                  | 4.00-10.00   |
| BBC (2012/L)Sa0450-A10Henoglobin (vold)16.2140-H00Plancles (x107)/L)233140-H00Plancles (x107)/L)370200-H00Serma ghose (rog,dL)7765-10Creating (mg,dL)70200-H00Creating (mg,dL)77200-H00Creating (mg,dL)1000.70-L20Creating (mg,dL)13935-11Creating (mg,dL)10095-10Calcing (mg,dL)10095-10Calcing (mg,dL)2517-23Softm (mg,dL)2517-23Att (U/A)5710-50Calcing (mg,dL)8710-50Calcing (mg,dL)2120-10Calcing (mg,dL)2120-27Softm (mg,dL)2120-27Softm (mg,dL)1.5020-27Softm (mg,dL)1.50 <td>Neutrophils (x 10<sup>9</sup>/L)</td> <td>7.69</td> <td>1.50-7.50</td>  | Neutrophils (x 10 <sup>9</sup> /L)                               | 7.69                   | 1.50-7.50    |
| Hemsghöln (pdl)16.214.0-180Planetes (t 197)15.210-4040Protrombin tine100.5-12Protrombin tine100.5-12Protrombin tine100.5-130Constante (trag,dl)1000.5-130Serim glucos (trag,dl)1000.5-130Coreatiniae (trag,dl)1000.5-130EBS (tran,d)1000.5-130EBS (tran,dl)1000.5-130Colondia (trag,dl)1000.5-130Colondia (trag,dl)0.000.5-130Colondia (trag,dl)0.000.5-130Colondia (trag,dl)0.000.5-130Colondia (trag,dl)0.000.5-130Colondia (trag,dl)0.000.5-130Colondia (trag,dl)0.50.5-130Colondia (trag,dl)0.50.5-130Colondia (trag,dl)0.50.5-130Colondia (trag,dl)0.50.5-130Colondia (trag,dl)0.50.5-130Colondia (trag,dl)0.50.5-130Colondia (trag,dl)0.100.5-130Colondia (trag,dl)0.100.5-130Colondia (trag,dl)0.100.5-130Colondia (trag,dl)0.100.5-130Colondia (trag,dl)0.100.5-130Colondia (trag,dl)0.100.5-130Colondia (trag,dl)0.100.5-130Colondia (trag,dl)0.100.5-130Colondia (trag,dl)0.100.5-130Colondia (trag,dl)0.100.5-130 <td>RBC (x10^12/L)</td> <td>5.30</td> <td>4.50-6.10</td>  | RBC (x10^12/L)   | 5.30                   | 4.50-6.10    |
| Planetics (r. 10%/L)10.4410.44Protromahin time1.00.8-1.2Fibringer (ng./L)370200-400Serum gluose (ng./L)770.6-1.10Creatinge (ng./L)1.000.7-1.20Past (ng./L)1.000.7-1.20Past (ng./L)1.000.7-1.20Past (ng./L)1.000.7-1.20Past (ng./L)1.000.7-2.5Pointsim (ng./L)1.000.5-51Chords (ng./L)0.0095-110Chords (ng./L)0.0095-110Chords (ng./L)0.0095-100Calcium (ng./L)0.0095-100Calcium (ng./L)0.0095-100Calcium (ng./L)0.100.10Calcium (ng./L)0.100.10Calcium (ng./L)0.100.10Calcium (ng./L)0.100.21Calcium (ng./L)1.000.27-4.20Sti (ndircoU/nL)1.500.17-2.6Sti (ndircoU/nL)1.500.17-2.6Sti (ndircoU/nL)1.510.17-2.6Hold (nd./L)1.000.27-4.20Vis (nd./L)1.000.27-4.20Sti (ndircoU/nL)1.000.27-4.20Sti (ndircoU/nL)1.000.17-0.6Hold (nd./L)1.000.27-4.20CAR (ng./L)1.000.27-4.20Sti (ndircoU/nL)1.000.27-4.20Sti (ndircoU/nL)1.000.27-4.20Sti (ndircoU/nL)0.120.00Calcium (ndird (ndircog.24h)0.00<  | Hemoglobin $(g/dL)$  | 16.2                   | 14.0-18.0    |
| Protectional1.00.8-1.2Florinager (ray,dL)370050-000Serum glucose (ray,dL)7705.110Creatinine (ray,dL)1.000.70-1.20BS (mm/h)26-2.25Sodium (rafz,L)139135-145Protassium (rafz,L)0.0095-110Calcium (rag,dL)0.0095-110Calcium (rag,dL)0.0095-110Calcium (rag,dL)0.0005-10.1Calcium (rag,dL)2.51.72-2.5Alt,T (U/L)530.50AST (U/L)749.308Vyoglobin (rag,dL)2.100.21-10Orab blirbin (rag,dL)0.120.27-1.0CPK (u/L)1.500.27-4.20CPK (u/L)1.500.27-4.20CPR (rag,fL)1.220.5Vyoglobin (rag,mL)1.210.5CPR (rag,fL)1.220.5Vyoglobin (rag,mL)1.210.5CPR (rag,fL)1.220.5Vyoglobin (rag,mL)1.210.30Vyoglobin (rag,mL)0.120.5Vyoglobin (rag,mL)1.210.30Vyoglobin (rag,mL)0.120.5Vyoglobin (rag,mL)0.120.5Vyoglobin (rag,mL)0.120.5Vyoglobin (rag,mL)0.120.5Vyoglobin (rag,mL)0.300.1-7.6HbA12 (rag,mL)1.200.5Vyoglobin (rag,mL)0.1-7.60.1-7.6HbA12 (rag,mL)0.120.5Vyoglobin (rag,mL)  | Platelets (x $10^{9}/L$ )  | 233                    | 140-440      |
| Fibringen (mg/dL)20°20°00Serum glucose (mg/dL)7765-110Creatinine (mg/dL)1.000.70-1.20ENS (mn/h)262-25Sodium (ntg/dL)139-14135-5.1Cholade (mtg/dL)10065-110Calcium (mg/dL)0.0165-110Calcium (mg/dL)0.048.6-10.2Magnesim (mg/dL)2.510-50Calcium (mg/dL)3310-50Calcium (mg/dL)0.70.21.0CPK (U/L)740.21.0CPK (U/L)740.21.0Synbin (mg/dL)1.500.27.4.20Synbin (mg/dL)1.500.27.4.20Synbin (mg/dL)1.500.27.4.20Synbin (mg/dL)1.500.27.4.20Synbin (mg/dL)1.50.17.6Synbin (mg/dL)1.50.17.6Synbin (mg/dL)1.21.65Aldolai (U/L)1.550.17.6HbA1c (mmol/mol)1.42.300NormelaristionNo abnormalities found.20.38Microbiotical investigation/serolary of nifectious agents.21.300Urine physical cauninationNo abnormalities found.21CW 1/g GNormiter of mysical caunination.21.230Normelaristing Urige JobNogative.21.21CW 1/g GNogative.21.230Synbin 1/G GNogative.21.230Synbin 1/G GNogative.21.230Creative Lipsical investigation/serolary of ni   | Protrombin time  | 10                     | 0.8-1.2      |
| Serm glucos (ng/dl.)65.10Creatinic (ng/dl.)1000.70-1.20RS (nm/h)262-25Sodiun (nfd/L)139135-145Protasiun (nfd/L)10035-5.1Childe (nfd/L)0.0035-10Calciun (ng/dl.)9466-10.2Calciun (ng/dl.)0.0085-110Calciun (ng/dl.)2.51.72-25Alt (U/L)531.72-25Alt (U/L)330.50Vogolio (ng/dl.)0.70.50Vogolio (ng/dl.)0.70.50Vogolio (ng/dl.)0.70.21.0Vogolio (ng/dl.)210.24.10Vogolio (ng/dl.)1.500.27-4.20CRP (ng/L)1.500.27-4.20CRP (ng/L)1.520.17-6Vogolio (ng/ml.)1.12-0.5Vogolio (ng/ml.)1.12-0.5Vogolio (ng/ml.)1.2-0.5Vogolio (ng/ml.) <td< td=""><td>Fibringen (mg/dL)</td><td>370</td><td>200_400</td></td<>  | Fibringen (mg/dL)  | 370                    | 200_400      |
| Creating (mg/d)10007.0 - 1.20ERS (mm/h)262.25Solum (mEq/L)135-145Potassium (mEq/L)4.43.5-5.1Chorde (mEq/L)0.096-11.0Calcium (mg/d)9.48.6-10.2Magnesium (mg/d)2.51.7-2.5ALT (U/L)531.6-50ST (U/L)531.6-50Total bilirubin (mg/d).0.72.2-1.0CYK (U/L)7439.308Myoglobin (ng/mL)1.500.27-4.20St (I/L)1.500.27-4.20St (I/L)1.500.27-4.20St (I/L)1.500.27-4.20St (I/L)1.500.27-4.20St (I/L)1.500.27-4.20St (I/L)1.550.1-76Hohal (U/L)1.550.1-76Hohal (U/L)1.42-320St (I/L)1.42-320St (I/L)1.42-320  | Serum glucose (mg/dL)  | 77                     | 65-110       |
| BRS (mm,h)   | Creatinine (mg/dL)   | 1.00                   | 0.70-1.20    |
| notionnotionnotionSolum (nEq/L)139-145Potassium (nEq/L)135-161Calcim (ng/L)100Calcim (ng/L)9.4Magnesim (ng/L)2.5ALT (U/L)53ALT (U/L)53ATT (U/L)74Total bilirubin (ng/dL)0.7CPK (U/L)74Total bilirubin (ng/dL)0.7CPK (U/L)1.50Total bilirubin (ng/dL)0.7CPK (U/L)1.50CPK (U/L)1.50CPK (U/L)0.12CPK (U/L)1.5CPK (U/L)1.5CPK (U/L)1.5CPK (U/L)1.5CPK (U/L)1.6CPK (U/L) <td>FRS (mm/h)</td> <td>26</td> <td>2_25</td>   | FRS (mm/h)   | 26                     | 2_25         |
| Potassium (mEg/1)1010Chloride (mEg/1)10095-5.1Chloride (mEg/1)10095-110Calcium (mg/dL)9.48.6-10.2Magnesium (mg/dL)2.51.7-2.5ALT (U/L)S30.5.51AST (U/L)870.2.1.0CYU/L)7439-308Myoglobin (mg/dL)1.00.7CPK (U/L)7439-308Myoglobin (mg/dL)1.500.27-4.20CPK (u/L)1.500.27-4.20CPK (mg/L)1.50.1-7.6Aldolai (U/L)1.5.50.1-7.6Aldolai (U/L)1.5.50.1-7.6Aldolai (U/L)1.5.50.1-7.6Aldolai (U/L)1.5.50.1-7.6Aldolai (U/L)1.1-390Proteal: filterog/24h)1.1-390Protein electrophoresisVol Microphoresis-Microbiological investigation/serology for infectious agentsMire Dysical examinatioNegativeMire Dysical (GPC)NegativeMire Dysical (GPC)NegativeMire Dysical for SARS-CoV-2NegativeAnti-terplotysin ONegativeSybhils IgG-IgMNegativeSybhils IgG-IgMNegativeSybhils IgG-IgMNegativeAnti-terplotysin ONegativeSybhils IgG-IgMNegativeNappa   | Sodium (mFa/L)   | 139                    | 135_145      |
| Chorde (migr)nnn <t< td=""><td>Potassium (mFa/L)</td><td>4 4</td><td>35-51</td></t<>   | Potassium (mFa/L)  | 4 4                    | 35-51        |
| Calcium (mg/dL)10010-110Magnesium (mg/dL)2,51,7-2,5ALT (U/L)5310-50AST (U/L)870.2-1,00Calcium (mg/dL)7439-308Myoglobin (ng/nL)2128-72Tisk1 (microUL/mL)1,500.27-4,200CRF (mg/L)1,500.27-4,200CRF (mg/L)1,500.27-4,200Metanetrina urinaria (microg/24h)1,20Normetanetrina urinaria (microg/24h)0.20Normetanetrina urinaria (microg/24h)0.20CMV IgGNegative0.20 </td <td>Chloride (mEq.[])</td> <td>100</td> <td>95_110</td>   | Chloride (mEq.[])  | 100                    | 95_110       |
| CalculationJ-4G-7-2.5ALT (U/1)5317-2.5ALT (U/1)5710-50AST (U/1)870.51CPK (U/1)7493-908Myoglobin (ng/nL)1228-72TSH (microU/mL)1.500.27.4.20CPK (U/1)1.500.27.4.20CPK (U/1)1.500.27.4.20CPK (U/1)1.5.50.1-7.6Hoha (C/10)1.5.50.1-7.6Hoha (cmon/mol)1.5.50.1-7.6Hoha (cmon/mol)1.42-320Metanefrina urinaria (microg/24h)1.42-320Morentaefrina urinaria (microg/24h)1.42-320Morentaefrina urinaria (microg/24h)1.42-320Protein electrophoresiswithin normal range-Urine physical examinationNo abnormalities found-MV IgGNegativeHCV IgGNegativeHCV IgGNegativeEBV VCA IgGPositiveEBV VCA IgGNegativeSptulm microscopy, molecular test, and cultures for mycobacteriaNegative-Sptulm microscopy, molecular test, and cultures for mycobacteriaNegative-AutionumutAutionumutAutionumutAutionumutAutionumutAutionumut </td <td>Calcium (mg/dL)</td> <td>0.4</td> <td>86_10 2</td>  | Calcium (mg/dL)  | 0.4                    | 86_10 2      |
| Indegristion (ung/ub)2.31.7 - 2.0ATT (U/1)5310-50AST (U/1)870.7Carls (U/1)7439-308Myoglobin (ng/nL)1128-72CRP (ng/L)120.27-4.20CRP (ng/L)120.27-4.20CRP (ng/L)120.27-4.20CRP (ng/L)120.27-4.20CRP (ng/L)1.20.27-4.20CRP (ng/L)1.20.5Procalcionin (ng/mL)0.120.5Aldolasi (U/1)15.50.17-6HbA1 (mnol/mol)14.00.238Metanefrina urinaria (microg/24h)1410.300Protein electrophoresisWithin normal range-Urine physical examinationNo abornalities found-Microbiological investigation/secrology for infectious agentsCMV Ig6NegativeCMV Ig6NegativeAnti-streptolysin ONegativeAnti-streptolysin ONegativeEBV VCA Ig6PositiveSynthili StG-IgMNegativeHBabNegativeSynthili StG-IgMNegativeSynthili StG-IgMNegativeHBabNegativeNegativeSynthili StG-IgMNegativeNegativeSynthili StG-IgMNegativeNegative  | Magnesium (mg/dL)  | 2.5                    | 1725         |
| Init (rg/d)B70-0-0S7 (U/L)8710-50Total bilirubin (ng/dL)0.70.2-1.0CPK (U/L)7439-308Myoglobin (ng/mL)1.500.27-4.20STH (microU/mL)1.500.27-4.20CRP (ng/L)1.2<5   |  | 53                     | 10-50        |
| Add (OD)OPOPOPCrist (U/L)(70.2-1.0CPK (U/L)740.2-1.0CPK (U/L)2128-72TSH (microUI/mL)1.500.27-4.20CRP (mg/L)1.500.27-4.20CRP (mg/L)1.50.12Procalcionin (ng/mL)0.12<0.5  |  | 97                     | 10-50        |
| India function (ug/ub)0.70.22-1.0Myogiobin (ng/ub)7439-308Myogiobin (ng/ub)2125-27SIN (nicorU/ub)1.500.27-4.20CRP (ng/b)1.50.27-4.20CRP (ng/b)1.50.12-36Procalcitonin (ng/mb)0.12<0.5  | Total bilimbin (mg/dL)   | 0.7                    | 10-30        |
| CrA (O1)7495-306Wyoglobin (ng/mL)2128-72TSH (nnicroUI/mL)1.500.27-4.20CRP (ng/L)12<5   |  | 0.7                    | 20, 208      |
| Mygould (kg/ mL)2426-74TSH (microl/mL)1.500.27-4.20CRP (mg/L)12<5  | CPK (U/L)  | 74                     | 39-308       |
| Inf (Incro01/mic)0.2/-4.00CRP (mg/1)12<5   | TSUL (minimum (mg/min))  | 21                     | 28-72        |
| CAP (mg/L)12<3Procalcitonin (ng/mL)0.12<0.5  | ISH (microul/mL)   | 1.50                   | 0.27-4.20    |
| Proceation0.12<0.5Adolasi (U/L)15.50.1-7.6HbA1c (mmol/mol)41.020-38Metanefrina urinaria (microg/24h)211<390  | CRP (mg/L)   | 12                     | <5           |
| Adolasi (U/L)15.501-7.6HbAlc (mnol/mol)41.020-38Metanefrina urinaria (microg/24h)142<320   | Procalcitonin (ng/mL)  | 0.12                   | < 0.5        |
| HDA1c (mm0/m0i)41.020-38Metanefrina urinaria (microg/24h)142320Normetanefrina urinaria (microg/24h)211<390   |  | 15.5                   | 0.1-7.6      |
| Metaerina urinaria (microg/24h)142<320Normetaeric main (microg/24h)211390Protein electrophoresisWithin normal range-Urine physical examinationNo anormalities found-Microbiological investigation/serology for infectious agentsPositive-CMV IgGNegativeCMV IgGNegativeHCV IgGNegativeHCV IgGNegativeAnti-streptolysin ONegativeEBV VCA IgGPositiveEBV VCA IgGPositiveEBV VCA IgGNegativeEBV VCA IgGNegativeEBV VCA IgGNegativeEBV VCA IgGNegativeEBV VCA IgGNegativeSyptum microscopy, molecular test, and cultures for mycobacteriaNegative-Sputum culturesNegativeNegative-AutoimmunityNegativeNegative-Antibodies anti neuronal surface antigensNegativeNegativeAntibodies anti neuronal surface antigensNegativeNegativeAntibodies anti CASPR2NegativeNegativeNegativeAntibodies anti CASPR2NegativeNegativeNegativeAntibodies anti GABA-B1/2 receptorNegativeNegativeNegativeAntibodies anti GABA-B1/2 receptorNegativeNegativeNegative <td< td=""><td>HDAIc (mmol/mol)</td><td>41.0</td><td>20-38</td></td<>  | HDAIc (mmol/mol)   | 41.0                   | 20-38        |
| Normetanetrina trinaria (microg/24h)211<390Protein electrophoresisWithin normal range-Urine physical examinationNo abnormalities found-Microbiological investigation/serology for infectious agentsCMV IgGNegativeCMV IgGNegativeHCV IgGNegativeHTV 1-2 Ag/AbNegativeAnti-streptolysin ONegativeEBV VCA IgGPositiveEBV VCA IgGPositiveEBV VCA IgGNegativeEBV VCA IgGNegativeSyphilis IgG-IgMNegativeHBSAbNegativeNegativeSputum microscopy, molecular test, and cultures for mycobacteriaNegative-Nasopharyngeal swab for SARS-CoV-2NegativeNegative-AutionumityAutiongies ant MDA receptorNegativeNegative-Antibodies anti MDA receptorNegativeNega   | Metanetrina urinaria (microg/24h)                                | 142                    | <320         |
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| Urine physical examinationo kabnormalities found-Microbiological investigation/serology for infectious agents-CMV lgGPositive-CMV lgGNegative-HCV lgGNegative-H1V 1-2 Ag/AbNegative-Anti-streptolysin ONegative-EBV VCA lgGPositive-EBV VCA lgGPositive-EBV VCA lgGPositive-EBV VCA lgGPositive-Syphilis IgG-lgMNegative-Syphilis IgG-lgMNegative-HBsAbNegative-Sputum microscopy, molecular test, and cultures for mycobacteriaNegative for MSSA-Nasopharyngeal swab for SARS-CoV-2Negative-Anti-Otts IgNegativeNegative-Onconcural antibodiesNegativeNegativeNegativeAnti-Otols gNegativeNegativeNegativeAntibodies anti neuronal surface antigensNegativeNegativeAntibodies anti AGBA-B1/2 receptorNegativeNegativeAntibodies anti GABA-B1/2 receptorNegativeNegativeAntibodies anti Guarcecptor (AMPA 1/2)NegativeNegativeAntibodies ant GNBA-B1/2 receptorNegativeNegativeAntibodies anti Guarcecptor (AMPA 1/2)NegativeNegativeAntibodies ant Guarceptor XNegativeNegativeAntibodies ant Guarceptor (AMPA 1/2)NegativeNegativeAntibodies ant Guarceptor (AMPA 1/2) <td< td=""><td>Protein electrophoresis</td><td>Within normal range</td><td>-</td></td<>   | Protein electrophoresis  | Within normal range    | -            |
| Microbiological investigation/serology for infectious agentsCMV IgGPositive-CMV IgGNegative-HCV IgGNegative-HTV 1-2 Ag/AbNegative-Anti-streptolysin ONegative-EBV VCA IgGPositive-EBV VCA IgGPositive-EBV VCA IgGPositive-EBV VCA IgMNegative-Syphilis IgG-IgMNegative-HBsAbNegative-Sputum microscopy, molecular test, and cultures for mycobacteriaNegative-Sputum culturesNegative-Nasopharyngeal swab for SARS-CoV-2Negative-Anti-St IgNegativeNegativeNegativeOnconeural antibodiesNegativeNegativeNegativeAntibodies anti INDA receptorNegativeNegativeNegativeAntibodies anti IG11NegativeNegativeNegativeAntibodies anti GABA-B1/2 receptorNegativeNegativeNegativeAntibodies ant  | Urine physical examination                                       | No abnormalities found | -            |
| CMV IgGPositive-CMV IgGNegative-HCV IgGNegative-HIV 1-2 Ag/AbNegative-Anti-streptolysin ONegative-EBV VCA IgGPositive-EBV EDA IgGPositive-EBV EDA IgGPositive-EBV CCA IgMNegative-Syphilis IgG-IgMNegative-HBsAbNegative-Sputum microscopy, molecular test, and cultures for mycobacteriaNegative-Syntum microscopy, molecular test, and cultures for mycobacteriaNegative-Nasopharyngeal swab for SARS-CoV-2NegativeAutoimunityAnti-CNS IgNegativeNegativeNegative-Onconeural antibodiesAntipodies anti ILG11NegativeNegativeNegativeAntibodies anti ILG11NegativeNegativeNegative-Antibodies anti GABA-B1/2 receptorNegativeNegativeNegativeAntibodies anti GABA-B1/2 receptorNegativeNegativeNegativeAntibodies anti Glu receptor (AMPA 1/2)NegativeNegativeNegativeAntibodies anti DPP XNegativeNegativeNegativeNegative   | Microbiological investigation/serology for infectious agents     |                        |              |
| CMV IgMNegative-HCV IgGNegative-HCV IgGNegative-Anti-streptolysin ONegative-EBV VCA IgGPositive-EBV VCA IgGPositive-EBV EBNA IgGPositive-EBV IgGNegative-EBV VCA IgMNegative-Syphilis IgG-IgMNegative-HBsAbNegative-Sputum microscopy, molecular test, and cultures for mycobacteriaNegative-Nasopharyngeal swab for SARS-CoV-2Negative-Anti-CNS IgNegativeNegativeNegativeOnconeural antibodiesNegativeNegativeNegativeAnti-CNS IgNegativeNegativeNegativeAntibodies anti neuronal surface antigensNegativeNegativeNegativeAntibodies anti NMDA receptorNegativeNegativeNegativeAntibodies anti CASPR2NegativeNegativeNegativeAntibodies anti GABA-B1/2 receptorNegativeNegativeNegativeAntibodies anti GABA-B1/2 receptorNegativeNegativeNegativeAntibodies anti GU receptor (AMPA 1/2)NegativeNegativeNegativeAntibodies anti GU receptor (AMPA 1/2)Nega  | CMV IgG  | Positive               | -            |
| HCV IgGNegative-HIV 1-2 Ag/AbNegative-Anti-streptolysin ONegative-EBV VCA IgGPositive-EBV VCA IgGPositive-EBV CA IgGPositive-EBV CA IgMNegative-Syphilis IgG-IgMNegative-HBsAbNegative-Sputum microscopy, molecular test, and cultures for mycobacteriaNegative-Sputum microscopy, molecular test, and cultures for mycobacteriaNegative-Nasopharyngeal swab for SARS-CoV-2Negative-Anti-CNS IgNegativeNegativeNegativeOnconeural antibodiesNegativeNegativeNegativeAntibodies anti INMDA receptorNegativeNegativeNegativeAntibodies anti CASPR2NegativeNegativeNegativeAntibodies anti GABA-B1/2 receptorNegativeNegativeNegativeAntibodies anti GABA-B1/2 receptor <td< td=""><td>CMV IgM</td><td>Negative</td><td>-</td></td<>  | CMV IgM  | Negative               | -            |
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| EBV VCA IgGPositive-EBV EBNA IgGPositive-EBV EBNA IgGPositive-EBV VCA IgMPositive-Syphilis IgG-IgMNegative-HBsAbNegative-Sputum microscopy, molecular test, and cultures for mycobacteriaNegative-Sputum culturesNegative-Syphilis IgG IgMNegative-Ansopharyngeal swab for SARS-CoV-2Negative-Anti-CNS IgNegativeNegativeOnconeural antibodiesNegativeNegativeAntibodies anti neuronal surface antigensNegativeNegativeAntibodies anti ICASPR2NegativeNegativeAntibodies anti CASPR2NegativeNegativeAntibodies anti GABA-B1/2 receptorNegativeNegativeAntibodies anti GIB receptor (AMPA 1/2)NegativeNegativeAntibodies anti DPP XNegativeNegativeNegativeNegativeNegativeNatibodies anti DPP XNegativeNegative  | Anti-streptolysin O  | Negative               | -            |
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| Nasopharyngeal swab for SARS-CoV-2Negative-AutoimmunityNegativeNegativeAnti-CNS IgNegativeNegativeOnconeural antibodiesNegativeNegativeAntibodies anti neuronal surface antigensNegativeNegativeAntibodies anti ICAS PR2NegativeNegativeAntibodies anti CASPR2NegativeNegativeAntibodies anti GABA-B1/2 receptor (AMPA 1/2)NegativeNegativeAntibodies anti Dur preptor (AMPA 1/2)NegativeNegativeAntibodies anti Dur preptor (AMPA 1/2)NegativeNegativeAntibodies anti Dur preptor (AMPA 1/2)NegativeNegativeNegativeNegativeNegativeAntibodies anti Dur preptor (AMPA 1/2)NegativeNegativeNegativeNegativeNegativeNatibodies anti Dur preptor (AMPA 1/2)NegativeNegative  | Sputum cultures  | Positive for MSSA      | -            |
| AutoimmunityNegativeAnti-CNS IgNegativeNegativeOnconeural antibodiesNegativeNegativeAntibodies anti neuronal surface antigensNegativeNegativeAntibodies anti ILGI1NegativeNegativeAntibodies anti CASPR2NegativeNegativeAntibodies anti GABA-B1/2 receptorNegativeNegativeAntibodies anti Glu receptor (AMPA 1/2)NegativeNegativeAntibodies anti DPP XNegativeNegative   | Nasopharyngeal swab for SARS-CoV-2                               | Negative               | -            |
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| Onconeural antibodiesNegativeNegativeAntibodies anti neuronal surface antigensAntibodies anti NMDA receptorNegativeNegativeAntibodies anti LG11NegativeNegativeAntibodies anti CASPR2NegativeNegativeAntibodies anti GABA-B1/2 receptorNegativeNegativeAntibodies anti Glu receptor (AMPA 1/2)NegativeNegativeAntibodies anti DPP XNegativeNegative  | Anti-CNS Ig  | Negative               | Negative     |
| Antibodies anti neuronal surface antigensNegativeAntibodies anti NMDA receptorNegativeAntibodies anti LGI1NegativeAntibodies anti CASPR2NegativeAntibodies anti GABA-B1/2 receptorNegativeAntibodies anti GABA-B1/2 receptor (AMPA 1/2)NegativeAntibodies anti DPP XNegative   | Onconeural antibodies  | Negative               | Negative     |
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| 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  | Antibodies anti LGI1   | 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   | Antibodies anti CASPR2   | Negative               | Negative     |
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| Antibodies anti DPP X Negative Negative  | Antibodies anti Glu receptor (AMPA 1/2)                          | Negative               | Negative     |
|  | Antibodies anti DPP X  | Negative               | Negative     |

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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<sup>3</sup>, 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 Bartoloni:** Writing – review & editing, Supervision, Conceptualization. **Alessandro Barilaro:** Writing – review & editing, Supervision, Conceptualization. **Alessandro Barilaro:** Writing – review & editing, Supervision, Conceptualization. **Antonello Grippo:** Writing – review & editing – original draft, Data curation, Conceptualization. **Silvia Bresci:** Writing – review & editing, Supervision, Conceptualization.

#### Funding

None.

#### 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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