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ORIGINAL ARTICLES AND REVIEWS

Guillain-Barré syndrome in patients dying with COVID-19 in Italy: a retrospective study

Elisa Colaizzo[1], Maria Puopolo[1], Dorina Tiple[1], Luana Vaianella[1], Nicola Vanacore[2], Alberto Milanese[3], Luigi Palmieri[4], Cinzia Lo Noce[4], Marco Canevelli[5], Alessia Perna[6], Graziano Onder[4] and the Italian National Institute of Health COVID-19 Mortality Group*

[1]*Dipartimento di Neuroscienze, Istituto Superiore di Sanità, Rome, Italy*
[2]*Centro Nazionale per la Prevenzione delle Malattie e Promozione della Salute, Istituto Superiore di Sanità, Rome, Italy*
[3]*Dipartimento di Sanità Pubblica e Malattie Infettive, Sapienza Università di Roma, Rome, Italy*
[4]*Dipartimento Malattie Cardiovascolari, Endocrino-Metaboliche e Invecchiamento, Istituto Superiore di Sanità, Rome, Italy*
[5]*Dipartimento di Neuroscienze Umane, Sapienza Università di Roma, Rome, Italy*
[6]*Istituto di Neurologia, Università Cattolica del Sacro Cuore, Rome, Italy*
**The members of the Italian National Institute of Health COVID-19 Mortality Group are reported before the References*

Abstract

Introduction. We presented a four-case series of COVID-19 related deaths occurred in patients with Guillain-Barré syndrome (GBS) between February 2020 and January 2022 in Italy.

Methods. They were extracted from 8,436 medical charts of COVID-19 patients dying. All cases, ranged 48-73 years, showed classical GBS clinical onset – limb weakness, sensory deficits, hypoareflexia – and three of them were admitted in intensive care unit (ICU) for ventilator support.

Results. The cerebrospinal fluid showing albumin-cytological dissociation was performed in two cases. Nerve conduction studies supported the diagnosis in all cases. Interstitial pneumonia was documented by chest X-rays or CT scans in all cases: they were treated with intravenous immunoglobulin (IVIg) and the drugs used for COVID-19 infection.

Conclusions. Although the mechanism of GBS onset is still unclear in COVID-19, fatal cases may be more frequent than other virus-related GBS, so that strictly monitoring in high-risk patients could dramatically decrease the mortality of GBS.

Key words

- COVID-19
- Guillain-Barré syndrome
- mortality

INTRODUCTION

Guillain-Barré syndrome (GBS) is an acute acquired immune-mediated polyradiculoneuropathy [1], more frequent in males, with about 100,000 cases every year worldwide [2], diagnosed according to clinical findings and classified in several variants, such as acute inflammatory demyelinating polyradiculoneuropathy (AIDP), acute motor axonal neuropathy (AMAN) and acute motor sensory axonal neuropathy (AMSAN). Mortality rates in Europe and North America vary between 3% and 7% [2]. The etiology can be traced back to a viral illness in half of the cases, the onset typically occurs in one to two weeks after a Campylobacter jejuni, HIV, Influenza A virus, Cytomegalovirus, Mycoplasma Pneumoniae, Haemophilus Influenzae infection or Arbovirus infection such as Zika and Chikungunya virus. The incidence rate of GBS in USA and Europe increases with age (0.6 per 100,000 per year in children and 2.7 per 100,000 per year in >80-year-old people) [2].

Between February 2020 and May 2022, COVID-19 has caused about 6 million deaths worldwide [3]. Most of these deaths were due to respiratory complications caused by SARS-CoV-2 infection, but non-respiratory complications, including cardiac, renal, and neurological are also commonly identified in persons dying of COVID-19 [4]. Recent studies demonstrated the occurrence of GBS in patients with SARS-CoV-2 infection [5-9]. GBS can therefore represent a complication related to SARS-CoV-2 which can contribute to COVID-19 mortality. We described a series of 4 cases of

Address for correspondence: Elisa Colaizzo, Dipartimento di Neuroscienze, Istituto Superiore di Sanità, Viale Regina Elena 229, 00161 Rome, Italy. E-mail: elisa.colaizzo@iss.it.

patients dying of GBS occurring after SARS-CoV-2 infection observed in a survey of 8,436 patients dying of COVID-19 in Italy.

MATERIALS AND METHODS

Study population and data collection

Data were obtained from the Italian National Institute of Health (Istituto Superiore di Sanità, ISS) Integrated Surveillance System [4, 10]. COVID-19-related deaths were defined as those occurring in patients who tested positive for SARS-CoV-2, independent of pre-existing comorbidities possibly contributing to death. Medical charts and death certificates of patients dying in the hospital were sent to the Italian National Institute of Health by all the regions and autonomous provinces of Italy. At Italian National Institute of Health COVID-19 Mortality Group, medical charts were reviewed by medical researchers to collect detailed information. Beyond data on demographic characteristics (region of residence, gender, age) and COVID-19 related data symptoms (fever, dyspnea, cough, diarrhea, and hemoptysis), chest X-rays or CT chest scans, pharmacological treatments (antibiotics, antivirals, monoclonal antibodies, corticosteroids), need of respiratory assistance, admission to intensive care, results of repeated SARS-CoV-2 testing, pre-existing comorbidities (diagnosed before hospital admission based on anamnestic data), hospital complications with relative additional notes and death data were collected.

Medical charts of 8,436 COVID-19 related deaths occurring between February 21st 2020 and January 10th, 2022, were reviewed to extract the list of cases of GBS occurring after SARS-CoV-2 infection. GBS was identified if the diagnosis was reported in the medical chart or death certificate. Medical charts of patients experiencing GBS were further reviewed by neurologists at INIH to collect GBS specific data: clinical features (limb weakness, hypoareflexia, sensory disturbances), results of cerebrospinal fluid (CSF) analysis (albumin-cytological dissociation), nerve conduction studies, and therapy for GBS. Lag time between dates of onset of COVID-19 symptoms and GBS disease (symptom onset and diagnosis) have been obtained for GBS cases occurring post COVID-19 infection. Summary statistics data obtained: categorical variables are summarized by frequencies, and continuous variables by mean and standard deviation (SD).

RESULTS

As at date of 10th January 2022, in Italy, among 8,436 medical charts of COVID-19 related deaths referred to the COVID-19 mortality database at Italian National Institute of Health four patients with a history of GBS: 2 females, 2 males, mean age ± SD: 62.7±11 (73-48) were identified (prevalence of SARS-CoV-2 related GBS among patients dying of COVID-19=0.05%). Demographic and COVID-19 clinical characteristics of these patients, as well the GBS symptoms at the onset are reported in the *Table 1*. Fever and dyspnea were reported at hospitalization 4/4 and 3/4, respectively. All patients had pneumonia documented by chest X-rays or CT chest scans, mainly requiring respiratory as-

Table 1
Demographic and clinical characteristics of patients dying of SARS-CoV-2 related Guillain-Barré syndrome (GBS)

Number of patients (n)	**4**
Gender	
Female	2
Male	2
Age (years)* mean (SD)	62.7 (11.6)
COVID-19 symptom at hospitalization (n)	
Fever	4
Cough	1
Dyspnea	3
Diarrhea	1
Pneumonia (n)	**4**
Respiratory assistance	
No	0
Yes	
Mechanical ventilation	2
High flow oxygen	0
cPAP	1
NA	1
Admission to intensive care	
No	1
Yes	3
COVID-19 swab testing swabs at death (n)	
Positive	3
Negative	1
Acute respiratory failure	4
Brain damage	2
Superinfections	2
Shock	2
Others	0
Complication during hospitalization (n)	
Brain damage	2
Superinfections	2
Shock	2
Others	0
COVID-19 related therapy (n)	
Antibiotics	4
Antiviral	3
Corticosteroids	3
Monoclonal antibody	2
Onset of GBS symptoms	
Tetraparesis	
Yes	3
No	0
NA	1

Continues

Table 1
Continued

Number of patients (n)	**4**
Onset of GBS symptoms *(continued)*	
Paresthesia	
Yes	1
No	1
NA	2
Facial palsy	
Yes	0
No	2
NA	2
Electrodiagnostic patterns (VCN/EMG)	
Axonal damage	
Yes	2
No	2
Demyelination damage	
Yes	4
No	0
CFS analyzed	2
Albuminocytologic dissociation	2
Therapy for GBS	
Intravenous immunoglobulines	4

*Age at death in GBS patients diagnosed during COVID-19 disease onset: 48, 59, 71, 73.

sistance (2 mechanical ventilation, and 1 cPAP), and admission in intensive care (3/4). Complications during hospitalization were brain damage (2/4), superinfections (2/4), and shock (2/4). All patients received antibiotics, mainly in combination with corticosteroids (3/4) and antivirals (3/4). Two patients also received monoclonal antibody (tocilizumab). Only one patient tested negative to SARS-CoV-2 before dying.

GBS generally presented with muscle weakness (three patients) and less frequently with paresthesia (one patient). Electrophysiological studies were suggested for GBS showing demyelinating changes in all cases: also, only one patient showed axonal nerve damage. In patients with available lumbar puncture (two patients) albumin-cytological dissociation was reported. All patients were treated with intravenous immunoglobulin.

In the *Figure 1*, lag time of onset of GBS symptoms, diagnosis, and death after onset of COVID-19 symptoms are shown: since COVID-19 onset, one patient developed GBS after three days, one patient after 29 days and two patients after 31 days. For these patients, death occurred after 8, 74, 63 and 73 days after COVID-19 onset, respectively.

DISCUSSION

We described 4 cases of patients dying of SARS-CoV-2 related GBS identified in a sample of 8,436 COVID-19 related deaths. Based on these data it can be estimated that 0.05% of all COVID-19 deaths are associated with SARS-CoV-2 related GBS. Limited data on characteristics of fatal SARS-CoV-2 related GBS are available so far [4]. The four cases we described were older when compared to an international COVID-19 related GBS cohort (61 *vs* 56) and with an Italian one (61 *vs* 59) [3, 11]. Furthermore, their age was increased if compared to pre-pandemic cases (age of greatest incidence was 30-50 years) [12]. The most frequently described causes of death in GBS are respiratory failure, pneumonia, cardiac arrest, and autonomic dysfunction [4]. As reported, we also observed in all four our cases pneumonia and respiratory failure. Considering neurophysiological features, in all our patients demyelinating findings were detected as generally reported in COVID-19 related GBS [3]. Although axonal form as AMAN or ASMAN are generally associated with a poor prognosis, only two of our patients had a mixed form, demyelinating and axonal, the other two had only demyelinating as in COVID-19 related GBS demyelinating form may be severe or fatal. Severe forms of GBS described are associated with COVID-19 [6].

All our GBS patients were treated with intravenous immunoglobulin and with COVID-19 therapy, the cases were very severe and unfortunately the use of intravenous immunoglobulins, the treatment of choice for GBS, have not had effect. No patients with fatal GBS were vaccinated. The GBS patients were cases that date back to before the vaccination in Italy and one case when vaccination was available knowing that the vaccine campaign in Italy had started. GBS is considered a post-infectious neuropathy, developing 2-4 weeks after an acute infection [13]. The absence of SARS-CoV-2 RNA in CSF and the consideration that COVID-19

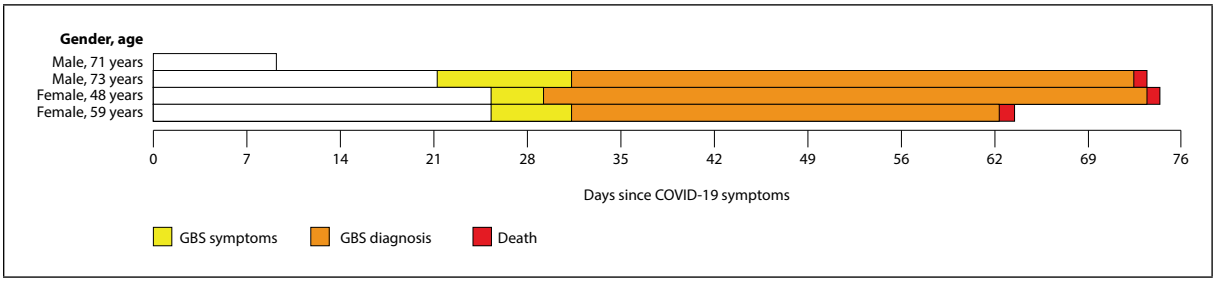

Figure 1
Lag time of onset of Guillain-Barré Syndrome (GBS) symptoms, diagnosis, and death after COVID-19 onset.

can initially be asymptomatic, which makes the latency duration longer than thought, [11] may suggest a prominent post-infectious immune-mediated mechanism rather than direct neuronal damage or a para-infectious one [14].

In our study GBS may be considered a para-infectious event, it occurred in one case 3 days after COVID-19 onset, in other patients after 29 days and in the other two patients after 31 days. Similar cases with para-infective disease caused by Borrelia Burgdorferi, Brucella and West Nile virus have been reported in different countries, because of the effect of the agent or an hyperimmune response [12]. It is probable that COVID-19-related respiratory impairment has determined the severity of the disease course [4] and respiratory failure due to GBS may get fast worse [15, 16].

The main limitation of this study relates to the fact that we only described cases of SARS-CoV-2 associated with GBS resulting in patients' death and therefore we cannot estimate the frequency of GBS in COVID-19 patients, nor the mortality associated with this condition, as we have not access to information/data of GBS diagnoses post COVID not followed by death. In addition, we based our analysis on a retrospective assessment of medical charts and an underestimation of GBS cases is possible. At last, our study was limited to cases occurred in 2020 and 2021, before new antiviral treatments became available on the market.

Although the mechanism of GBS onset is still unclear in COVID-19, fatal cases may be more frequent than other virus-related GBS [15, 16]. Clinician should be aware to promptly diagnose and treat this condition to understand if strictly monitoring patients with a high-risk profile could dramatically decrease the mortality of GBS.

The Italian National Institute of Health COVID-19 Mortality Group

The members of the Italian National Institute of Health COVID-19 Mortality Group are:

Luigi Palmieri, Elvira Agazio, Pierfrancesco Barbariol, Antonino Bella, Eva Benelli, Luigi Bertinato, Matilde Bocci, Stefano Boros, Marco Bressi, Giovanni Calcagnini, Federica Censi, Alessandra Ciervo, Elisa Colaizzo, Cecilia Damiano, Martina Del Manso, Corrado Di Benedetto, Chiara Donfrancesco, Massimo Fabiani, Francesco Facchiano, Marco Floridia, Fabio Galati, Marina Giuliano, Tiziana Grisetti, Cecilia Guastadisegni, Cinzia Lo Noce, Pietro Maiozzi, Valerio Manno, Margherita Martini, Alberto Mateo Urdiales, Eugenio Mattei, Claudia Meduri, Paola Meli, Giada Minelli, Graziano Onder, Daniele Petrone, Patrizio Pezzotti, Flavia Pricci, Ornella Punzo, Flavia Riccardo, Chiara Sacco, Paolo Salerno, Debora Serra, Matteo Spuri, Marco Tallon, Manuela Tamburo De Bella, Dorina Tiple, Brigid Unim, Luana Vaianella, Maria Fenicia Vescio, Liliana Elena Weimer, Silvio Brusaferro.

Conflict of interest statement

There are no potential conflicts of interest or any financial or personal relationships with other people or organizations that could inappropriately bias conduct and findings of this study.

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