Since January 2020 Elsevier has created a COVID-19 resource centre with free information in English and Mandarin on the novel coronavirus COVID-19. The COVID-19 resource centre is hosted on Elsevier Connect, the company's public news and information website.

Elsevier hereby grants permission to make all its COVID-19-related research that is available on the COVID-19 resource centre - including this research content - immediately available in PubMed Central and other publicly funded repositories, such as the WHO COVID database with rights for unrestricted research re-use and analyses in any form or by any means with acknowledgement of the original source. These permissions are granted for free by Elsevier for as long as the COVID-19 resource centre remains active.
Short communication

Analysis of nationwide multimodal complex treatment and drug pump therapy in Parkinson’s disease in times of COVID-19 pandemic in Germany

Daniel Richter a, Raphael Scherbaum a, Dirk Bartig b, Ralf Gold a,b,c, Christos Krogias a,b, Lars Tönges a,b,c,*

a Department of Neurology, St. Josef-Hospital Bochum, Ruhr University Bochum, Germany
b Medical Faculty, Ruhr University Bochum, Germany
c Center for Protein Diagnostics (ProDi), Ruhr University Bochum, Bochum, Germany

ARTICLE INFO

Keywords:
Parkinson’s disease
Health services
Inpatient
Multimodal care

ABSTRACT

Introduction: During the first peak phase of the COVID-19 pandemic, the German Ministry of Health recommended that elective treatments should be postponed to increase hospital capacities. This has also compromised the capacity for application of specialized Parkinson’s disease (PD) therapies to an unknown extent.

Methods: We conducted a nationwide cross-sectional study using administrative database of all hospitalized patients with main diagnosis of PD receiving multimodal complex treatment (PD-MCT), initial setup of levodopa/carbidopa intestinal gel (LCIG) or continuous subcutaneous apomorphine infusion (CSAI) in Germany. We compared case numbers and clinical characteristics of the pandemic (March 16th - May 15th, 2020) and post-lockdown (July 16th - September 15th, 2020) period with the pre-pandemic (January 16th - March 15th, 2020) and historical control period (March 16th - May 15th, 2019).

Results: We identified a strong decline for PD-MCT (-62.8%) and for the application of drug pump-based therapies (-69.4%) during the first peak phase of the pandemic as compared to the pre-pandemic period while specialized PD treatment procedures increased again in the post-lockdown phase. Advanced disease was a marker for PD-MCT patients during the pandemic period.

Conclusion: Besides the marked decline in specialized PD treatments during the first peak phase of the COVID-19 pandemic, we found recuperative effects for these procedures in the post-lockdown period without reaching pre-pandemic levels. Strengthening treatment capacities for PD patients, even in the event of a persistent pandemic, is urgently needed in order to maintain the quality of care.

1. Introduction

On March 16th, the German Ministry of Health recommended that elective treatments, such as deferrable surgeries, should be postponed to increase hospital capacities for the expected rising numbers of coronavirus disease 2019 (COVID-19) patients. Shortly afterwards, the German government introduced strict hygiene and lockdown measures for strong social distancing to control the spread of COVID-19. As a result, the number of new infections decreased from mid-April on. On May 6th, the rules of the social distancing and economic lockdown were slowly relaxed because of the subsequent decrease in the rate of new infections.

While treatment postponements successfully improved overall hospital treatment capacities, it has been argued that these measures could have delayed treatment of patients who were in need of specialized treatment procedures on a regular basis, such as the multimodal complex treatment (PD-MCT) for Parkinson’s disease (PD) patients. In Germany, PD-MCT is performed in a multiprofessional setting on specialized inpatient units. The PD-MCT includes a constant and careful anti-parkinsonian drug titration by physicians with special expertise for PD and the application of activating therapies in a multidisciplinary team which involves different professions such as physiotherapists, occupational therapists and speech therapists as well as other para-medical disciplines. The effectiveness of PD-MCT for the clinical improvement of symptoms has been examined and demonstrated previously [1–5]. Over the last years, PD-MCT has been increasingly applied [6].

Another important and effective [7,8] therapy option for PD patients with motor fluctuations is a drug pump-based therapy (DPT) with...
levodopa/carbidopa intestinal gel (LCIG) or a continuous subcutaneous apomorphine infusion (CSAI). For the implementation of these advanced therapies, a specialized clinical setting is needed, too.

We sought to investigate the use and the clinical characteristics of PD patients who received stationary multimodal PD-MCT in Germany during and after the first peak phase of the COVID-19 pandemic and compare the data to the pre-pandemic period, as well as to a historical control period. We further quantify the application of LCIG or CSAI implementation during the predefined time periods. This study represents a nationwide analysis of these specialized PD therapies during and after the first peak phase of the COVID-19 pandemic with full coverage of all hospitalized patients in Germany.

2. Methods

We analyzed case numbers and clinical characteristics of all patients
with PD receiving PD-MCT or the initial setup of a DPT before (January 16th - March 15th, 2020; pre-pandemic period), during (March 16th - May 15th, 2020; pandemic period) and after (July 16th - September 15th, 2020; post-lockdown period) the first peak of the COVID-19 pandemic on a nationwide level. We also compared the data with the corresponding time period in 2019 (March 16th - May 15th, 2019; historical control period). Data acquisition was done using the high-quality validated administrative diagnosis related group (DRG) database (Data transmission according to §21 KHEntgG and §24 para. 2 KHG; official data on file: Institut für das Entgeltsystem im Krankenhaus, InEK, www.g-drg.de).

In Germany, all in-patient PD cases are encoded according to ICD-10-GM and relevant operating and procedure keys (OPS-301 codes) issued by the German Federal Institute for Drugs and Medical Devices (BfArM). We extracted all cases with the ICD-10 main diagnosis code G20.- in combination with the OPS code for PD-MCT (8-97d.-). We calculated baseline characteristics for all hospitalized PD patients receiving PD-MCT and determined frequencies and percentages of each characteristic of interest for categorical variables and means and SDs for continuous variables. We conducted a multiple logistic regression analysis to determine if disease severity or the presence of motor fluctuations were independent predictors for PD-MCT patients (a) during the pandemic period and (b) during the post-lockdown period. Thus, we calculated the corresponding odds ratios (OR).

Furthermore, we determined the number of PD patients who received the initial setup of a DPT with apomorphine or levodopa/carbidopa intestinal gel during the predefined time periods by extracting all PD cases (G20.-) with the combination of the OPS code 8-97e.0 or 8-972.2, respectively.

Statistical differences in categorical variables between patients were calculated using chi-squared test ($\chi^2$) and for continuous variables using $t$-test. Multiple logistic regression analysis was conducted with SPSS 27.0 for Mac. $P < 0.05$ was defined as level of statistical significance.

For this study, no informed consent or ethical approval was required because we used secondary data provided by the InEK in compliance with the German data protection regulations and the latest Good Practice in Secondary Data Analysis recommendations (version 2; 2008). The data that support the findings of this study are available from the corresponding author upon reasonable request.

### 3. Results

#### 3.1. Case number development of PD-MCT

The use of PD-MCT dropped sharply during the pandemic period ($n = 1053$) compared to the pre-pandemic ($n = 2830$) and historical control period ($n = 2443$). In the post-lockdown period ($n = 2523$), case numbers almost recovered to pre-pandemic levels.

#### 3.2. Demographics of pandemic and post-lockdown PD-MCT patients

Mean age and gender distribution of PD-MCT patients were similar between the pandemic (mean age: 72.5±7.9 years; F/M: 39.4%/60.6%), pre-pandemic (mean age: 73.0±8.1 years; F/M: 39.0%/61.0%) and historical control period (mean age: 72.9±8.0 years; F/M: 39.8%/60.2%). Post-lockdown PD-MCT patients (mean age: 73.4±8.3 years; F/M: 40.1%/59.9%) were slightly older as compared to the historical control PD-MCT cases ($p = 0.031$) but there was no difference in gender distribution (Table 1).

#### 3.3. Clinical characteristics of pandemic PD-MCT patients

Regarding clinical characteristics of PD-MCT patients during the pandemic period, we found differences in the disease severity, measured by the Hoehn and Yahr (HY) scale, with significantly more patients in HY stage 5 during the pandemic period (10.8%, Table 1) as compared to the other time periods. HY stage 3–4 was present in 80.0% and HY stage 0–2 applied for 7.4% of the PD-MCT patients during the pandemic period. The presence of motor fluctuations was common in PD-MCT patients and was not significantly different between the pandemic

### Table 1

|                     | Historical control patients | Pre-pandemic patients | Pandemic patients | Post-lockdown patients | P Value for pandemic period | P Value for post-lockdown period |
|---------------------|----------------------------|-----------------------|------------------|------------------------|-----------------------------|---------------------------------|
| N                   | 2443                       | 2830                  | 1053             | 2523                   | 0.085                       | 0.075                           |
| Age (years) mean ± SD | 72.9 ± 8.0                | 73.0 ± 8.1            | 72.5 ± 7.9       | 73.4 ± 8.3             | 0.174                       | 0.003                           |
| Gender (Male), n (%) | 1471 (60.2%)               | 1725 (61.0)           | 638 (60.6)       | 1512 (59.9)            | 0.836                       | 0.444                           |
| Disease severity, n (%) |                       |                       |                  |                        |                             |                                 |
| HY 0 - 2            | 217 (8.9)                  | 250 (8.8)             | 78 (7.4)         | 230 (9.1)              | 0.140                       | 0.719                           |
| HY 3 - 4            | 1967 (80.5)                | 2303 (81.4)           | 842 (80.0)       | 2049 (81.2)            | 0.324                       | 0.877                           |
| HY 5                | 210 (8.6)                  | 226 (8.0)             | 114 (10.8)       | 203 (8.0)              | 0.009                       | 0.936                           |
| Not further specified | 49 (2.0)                  | 51 (1.8)              | 19 (1.8)         | 41 (1.6)               | 0.996                       | 0.618                           |
| Presence of motor fluctuations n (%) | 1691 (69.2)               | 1953 (69.0)           | 745 (70.8)       | 1831 (72.6)            | 0.292                       | 0.004                           |

*P Value for the comparison between pre-pandemic and pandemic patients. $\dagger$ P Value for the comparison between historical controls and pandemic patients. $\ddagger$ P Value for the comparison between post-lockdown and pandemic patients. $\langle$ P Value for the comparison between post-lockdown patients and historical control patients. Abbreviations: SD, standard deviation; HY, Hoehn and Yahr scale.
period (70.8%) and the pre-pandemic (69.0%, $p = 0.292$) or historical control period (69.2%, $p = 0.363$, Table 1). Regression analysis revealed that HY stage 5 was a predictor for PD-MCT treatment during the pandemic period (adjusted OR for HY5: 1.591, CI 1.169–2.167, $p = 0.003$; for HY 3–4: 1.190, CI 0.931–1.520, $p = 0.166$; for the presence of motor fluctuations: 1.008, CI 0.873–1.165, $p = 0.911$).

3.4. Clinical characteristics of post-lockdown PD-MCT patients

We found no differences regarding the disease severity of PD patients receiving PD-MCT in the post-lockdown period in comparison to the pre-pandemic and historical control periods. 8.0% of the post-lockdown PD-MCT patients were in HY stage 5, 81.2% were in HY stage 3–4 and 9.1% were in HY stage 0–2 (Table 1). The presence of motor fluctuations was significantly more frequent during the post-lockdown period (72.6%) as compared to the pre-pandemic period (69.0%, $p = 0.004$) and historical control period (69.2%, $p = 0.009$). The presence of motor fluctuation was a predictor for PD-MCT treatment during the post-lockdown period (adjusted OR 1.179, CI 1.052–1.309, $p = 0.002$; for HY5: 0.845, CI 0.676–1.058, $p = 0.142$; for HY 3–4: 0.931, CI 0.791–1.096, $p = 0.391$).

3.5. Case number development of LCIG and CSAI

Only patients in HY stadium 3 to 5 and the presence of motor fluctuations received DPT during the predefined time periods. The initial setup of LCIG and CSAI also dropped during the pandemic period ($n = 26$) in comparison to the pre-pandemic ($n = 85$) and historical control period ($n = 69$). In the post-lockdown period, we found an increase of the application with incomplete recovery as compared to the pre-pandemic levels ($n = 53$, Fig. 1).

4. Discussion

In this nationwide analysis of administrative data in Germany, we found a profound decline of PD-MCT procedures as well as for the application of LCIG and CSAI in PD patients during the first peak phase of the COVID-19 pandemic, when massive social distancing and lockdown measures were applied. Analysis of the post-peak phase of the COVID-19 pandemic revealed again an increase in the numbers of specialized PD treatments without full recovery to pre-pandemic levels.

PD-MCT is a highly effective treatment for motor and non-motor symptoms in PD [3,4] with a long-lasting positive effect on motor performance over at least several weeks [5]. Motor and physical activity are central treatment components of the PD-MCT. There is growing evidence, that physical exercise may even attenuate clinical symptom progression in PD [5,10]. Therefore, it is important to seek for regular PD-MCT application to optimize pharmacological and non-pharmacological treatment. The proven decline in PD-MCT procedures during the peak-phase of the pandemic affected hundreds of PD patients in Germany. We assume that this may have led to a worsening of symptoms in many PD patients affecting multiple aspects of the well-being of these patients with impact on the health-related quality of life although data on this development are not yet available. In addition to an assumable decrease in physical activity during the pandemic, the combination of these factors might mutually reinforce each other. Fortunately, we found increasing PD-MCT applications after the first peak-phase of the pandemic, indicating recuperative effects without long-lasting PD-MCT depression. Nevertheless, PD-MCT numbers remained under pre-pandemic levels.

Concerning drug pump treatment, this therapy is also highly effective [7,8], but again, a specialized clinical setting is needed to apply these therapies. It will be interesting how the health care system will intercept this deep cut in PD care, caused by the postponement of these specialized PD treatments. Future studies should investigate the impact of lockdown measures including treatment postponements on motor and non-motor symptoms, PD associated complications and quality of life for PD patients to measure harm and thus provide a common basis for policymakers and health care providers taking decisions on the persistent pandemic situation. However, as lockdown measures have proved to significantly flatten the curve of this pandemic, a promising solution could be the expansion and incorporation of telemedicine services into routine medical care to overcome the inability of health care access in times of a necessary lockdown.

Regarding the clinical characteristics of PD patients receiving PD-MCT, we found that HY stage 5 was a predictor to receive PD-MCT during the first peak phase of the pandemic. Furthermore, the presence of motor fluctuations was a marker of PD-MCT patients during the post-lockdown period. In line with this, studies on other patient populations with neurological diseases, e.g. stroke patients, also found that less patients [11] but with more severe symptoms [12] presented to hospital during the COVID-19 pandemic.

Our nationwide study has several strengths and limitations. In this study, we analyzed comprehensive data on the PD-MCT procedures for PD patients in Germany. These data are based on the documented diagnoses and procedures in the G-DRG system, the correctness of which is regularly monitored by insurance companies. Our administrative data have high quality and accuracy because registration of all PD-MCT procedure is a prerequisite to get financial compensation and the coding of operating and procedure keys are closely controlled by medical services of the medical health insurances. Thus, our data are very robust as they provide almost 100% coverage of all hospitalized patients in Germany with a very low risk of missing patients or double coding of procedures, resulting in high validity and consistency. Regarding the data from 2020, the hospitals were forced by law to submit accurate data within a short period of time, to enable the government to evaluate the adopted measures for hospitals in times of COVID-19 pandemic.

5. Conclusion

We found a marked decline in PD-MCT procedures as well as for the application of LCIG and CSAI in PD patients during the first peak phase of the COVID-19 pandemic. Post-lockdown analysis revealed recuperative effects of these specialized PD treatments without reaching pre-pandemic levels. An advanced disease was a predictor to receive PD-MCT during the first peak phase of the COVID-19 pandemic in Germany. These data might be helpful to policymakers and health care providers taking decisions on the still ongoing pandemic.

Author contributions

All authors participated in study design. DR and LT composed the manuscript. DR performed the statistical analysis. DB conducted the data abstraction. DR wrote the first draft of the manuscript. RS, RG, CK and LT participated in manuscript revision.

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.

Daniel Richter receives FoRUM grant (K136-20) of the Ruhr-University of Bochum. Raphael Scherbaum reports no disclosures. Dirk Bartig has received orders for analysis of the German Diagnosis-Related Groups system from Boehringer Ingelheim and Sanofi Aventis. RS reports no disclosures. Ralf Gold received consultation fees and speaker’s honoraria from Bayer Schering, Biogen Idec, Merckserono, Novartis, Sanofi-Aventis, and TEVA. He also acknowledges grant support from Bayer Schering, Biogen Idec, MerckSerono, Sanofi-Aventis, and TEVA.
Christos Krogias has received speaker honoraria or travel grants for scientific meetings from Bayer Vital, and Daichii Sankyo. Lars Tönges has received travel funding and/or speaker honoraria from AbbVie, Bayer, Bial, Desitin, GE, UCB, and Zambon and consulted for AbbVie, Bayer, Bial, Desitin, UCB, and Zambon.

Acknowledgments

None.

References

[1] T. Müller, G. Ohm, K. Eliert, K. Mohr, S. Rotter, T. Haas, M. Kührer, S. Lütge, M. Marg, H. Rothe, Benefit on motor and non-motor behavior in a specialized unit for Parkinson’s disease, J. Neural. Transm. 124 (6) (2017) 715–720.

[2] J.H. Lyngning, N.M. de Vries, L.H.H. M Boonen, X. Koolman, M. Munneke, A.H. Zwinderman, B.R. Bloem, Effectiveness and costs of specialised physiotherapy given via ParkinsonNet: a retrospective analysis of medical claims data, Lancet Neurol. 17 (2) (2018) 153–161.

[3] D. Ferrazzoli, P. Ortelli, I. Zivi, V. Cian, M. Uva, E. Urso, M.F. Ghilardi, R. Maestri, G. Frazzitta, Efficacy of intensive multidisciplinary rehabilitation in Parkinson’s disease: a randomised controlled study, J. Neurol. Neurosurg. Psychiatry 89 (8) (2017) 828–835.

[4] R. Scherbaum, E. Hartelt, M. Kinkel, R. Gold, S. Muhlack, L. Tönges, Parkinson’s Disease Multimodal Complex Treatment improves motor symptoms, depression and quality of life, J. Neurol. 267 (4) (2020) 954–965.

[5] E. Hartelt, R. Scherbaum, M. Kinkel, R. Gold, S. Muhlack, L. Tönges, Parkinson’s disease multimodal complex treatment (PD-PD-MCT): analysis of therapeutic effects and predictors for improvement, J. Clin. Med. 9 (6) (2020) 1874.

[6] D. Richter, D. Bartig, S. Muhlack, E. Hartelt, R. Scherbaum, A.H. Katsanos, T. Müller, W. Jost, G. Eberdschoch, R. Gold, C. Krogias, L. Tönges, Dynamics of Parkinson’s disease multimodal complex treatment in Germany from 2010-2016: patient characteristics, access to treatment, and formation of regional centers, Cells 8 (2) (2019) 151.

[7] M. Auffret, F. Le Jeune, A. Maurus, S. Drapier, J.F. Houvenagel, G.H. Robert, P. Sauvage, M. Verin, Apomorphine pump in advanced Parkinson’s disease: effects on motor and nonmotor symptoms with brain metabolism correlations, J. Neurol. Sci. 372 (2017) 279–287.

[8] C.W. Olsanow, K. Kieburtz, P. Odain, A.J. Espay, D.G. Standaert, H.H. Fernandez, A. Varaganas, A.A.Ohman, K.L. Widnell, W.Z. Robission, Y. Prichett, K. Chatamra, J. Benesh, R.A. Lenz, A. Antonini, LCIG Horizon Study Group, Continuous intrajejunale infusion of levodopa-carbidopa intestinal gel for patients with advanced Parkinson’s disease: a randomized, controlled, double-blind, double-dummy study, Lancet Neurol. 13 (2) (2014) 141–149.

[9] M. Schenkman, C.G. Moore, W.M. Kohrt, D.A. Hall, A. Delitto, C.L. Comella, D.A. Josbeno, C.L. Christianen, B.D. Berman, B.M. Kluger, E.L. Melanson, S. Jain, J.A. Robichaud, C. Poon, D.M. Corcos, Effect of high-intensity treadmill exercise on motor symptoms in patients with de novo Parkinson disease, JAMA Neurol. 75 (2018), 219–218.

[10] N.M. van der Kolk, N.M. de Vries, R.P.C. Kessels, H. Joosten, A.H. Zwinderman, B. Post, B.R. Bloem, Effectiveness of home-based and remotely supervised aerobic exercise in Parkinson’s disease: a double-blind, randomised controlled trial, Lancet Neurol. 18 (2019) 998–1008.

[11] D. Richter, J. Eyding, R. Weber, D. Bartig, A. Grau, W. Hacke, C. Krogias, Analysis of nationwide stroke patient care in times of COVID-19 pandemic in Germany, Stroke 52 (2021) 716–721.

[12] M.N. Nguyen-Huynh, X.N. Tang, D.R. Vinson, A.C. Flint, J.G. Alexander, M. Meighan, M. Burnet, S. Sidney, J.G. Klingman, Acute stroke presentation, care, and outcomes in community hospitals in northern California during the COVID-19 pandemic, Stroke 51 (10) (2020) 2918–2924.