Platelet abnormalities in patients with Parkinson’s disease undergoing preoperative evaluation for deep brain stimulation

Sheng-Che Chou1,4*, Chun-Hwei Tai2 & Sheng-Hong Tseng3

Normal hemostatic function is important for reduction of the risk of intracranial hemorrhage during stereotactic neurosurgery including deep brain stimulation (DBS) surgery. This study investigates the hemostatic function in patients with Parkinson’s disease (PD) undergoing preoperative evaluation for DBS, with emphasis on the number and function of platelets. In 107 PD patients, only one had abnormal activated partial prothrombin time and normal prothrombin time. Among the other 106 patients, six (5.7%) had only thrombocytopenia, seven (6.6%) only prolonged bleeding time (BT), and 14 (13.2%) only prolonged closure time (CT) of platelet function analyzer 100 (PFA-100). Totally, 34 of the 106 patients (32.1%) had at least one of three kinds of platelet abnormalities. No factor was found to be associated with the occurrence of platelet abnormalities except that abnormal platelet group and prolonged BT subgroup had more patients using selegiline and lower UPDRS-III motor subscore with medication off than normal platelet group (p < 0.05). The use of selegiline was significantly correlated with prolonged BT (p = 0.0041) and platelet abnormality (p = 0.0197). Therefore, it is important to have detailed evaluation of the hemostatic function for PD patients undergoing preoperative evaluation for DBS, especially the platelet number and function.

Parkinson’s disease (PD) is a degenerative disorder of the central nervous system that presents impairment of motor functions. In recent years, deep brain stimulation (DBS) has become a widely accepted treatment method for PD patients1. The DBS surgery, a kind of stereotactic surgery, always harbors the risk of intracranial hemorrhage (ICH) during surgery2–4. In DBS surgery, DBS electrodes are implanted to the targets deep in the brain and intraoperative microelectrode recording is often adopted to identify the locations of the targets. All these procedures need repeated insertion of the equipment into the brain, and carry the risk of vascular injury and ICH. Although the risk of ICH can be minimized by well-controlled blood pressure, meticulous surgical techniques, and careful trajectory planning, the incidence of ICH caused by DBS surgery has been found to range from 0.8 to 5.3%3–9.

Hemostasis for the ICH that is bleeding during DBS surgery mainly depends on the clotting and coagulation functions of patients. Therefore, preoperative evaluation of hemostatic function is mandatory and any abnormalities of hemostatic function should be corrected either before or during the surgery. In the literature, coagulopathy9, thrombocytopenia9,10–12, or platelets dysfunction13 in PD patients had been mentioned in several reports. However, it is still unclear whether the PD patients have hemostatic dysfunction, especially the patients having received medical treatment for more than 5 years and being considered for candidate of DBS surgery. This article investigates the hemostatic function in patients with PD undergoing preoperative evaluation for DBS, with emphasis on the number and function of platelets.

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Methods
The PD patients undergoing preoperative evaluation for DBS surgery from January 2015 to December 2017 were investigated. This study was approved by the Research Ethics Committee of National Taiwan University Hospital (201909010RIND) and all methods were carried out in accordance with relevant guidelines and regulations. Patients with the diagnosis of PD for more than five years and with at least one of the following conditions-marked motor fluctuation, severe levodopa-induced dyskinesia, and intractable tremor—were included for preoperative evaluation. Patients with diagnosis of atypical parkinsonism, poor response to levodopa treatment, dementia, depression, psychiatric symptoms at low dosage of levodopa treatment, or systemic illness that influenced the perioperative safety of the patient were excluded from evaluation. In addition, patients having hematological disorder, renal insufficiency, liver cirrhosis, being treated with antiplatelet or anticoagulation agents, or nonsteroidal anti-inflammatory drugs were excluded from this study.

The age, sex, duration of symptoms, Hoehn and Yahr stage with medication off and on periods, PD medications, levodopa dosage, and LEDD between the normal and thrombocytopenia, prolonged BT, prolonged CT of PFA-100 or abnormal platelet groups was analyzed by Chi-square tests or Fisher’s exact tests for dichotomous variables, and independent-samples t-tests for continuous variables. In the univariate logistic regression analysis, comparisons between each group’s variables were made. Multivariate analysis was conducted by fitting a logistic regression model to identify risk factors of platelet abnormalities. The statistical analysis was performed with Statistical Analysis Software (version 9.4). The statistical significance was accepted as \( p < 0.05 \).

Ethics declarations. This study was approved by the Research Ethics Committee of National Taiwan University Hospital (201909010RIND).

Consent to participate. Informed consent was not needed from all patients included in the study according to the approval of Research Ethics Committee of National Taiwan University Hospital.

Results
During the study period, there were 112 patients with PD undergoing preoperative evaluation for DBS surgery. Five patients treated with antiplatelet or anticoagulant agents were excluded from this study. In the remaining 107 patients, one (0.9%) patient had abnormal aPTT (37.6 s) and normal PT; however, he had prolonged BT (8.5 min) and normal platelet count and CT of PFA-100. The other 106 patients (99.1%) had normal PT and aPTT, and they were subjected to the analysis of platelet abnormality, excluding the patient with abnormal aPTT.

Table 1 shows the demographic data of the 106 patients with Parkinson’s disease. Among these patients, 51 (48.1%) were females and 55 (51.9%) were males. The age ranged from 35 to 77 (mean ± standard deviation, 62.5 ± 7.4) years old. The duration of symptoms in these patients ranged from 5 to 37 (11.7 ± 5.4) years. The Hoehn and Yahr stage ranged from stage 2 to 5 (3.6 ± 0.6) with medication off, and stage 1 to 5 (2.5 ± 0.6) with medication on. The UPDRS-III motor subscore ranged from 16 to 95 (41.4 ± 12.5) with medication off, and 3 to 40 (18.7 ± 8.7) with medication on. All 106 patients had normal PT (10.3 ± 0.5 s) and aPTT (27.6 ± 2.0 s). PD medications received by these patients included levodopa/benserazide, entacapone, amantadine, carbidopa/levodopa, pramipexole, ropinirole, biperiden, rotigotine, selegiline, trihexyphenidyl, and azilect. The levodopa dosage ranged from 150 to 2400 mg/day (865.7 ± 383.8 mg/day). The LEDD ranged from 165 to 2805 mg/day (1341.4 ± 501.0 mg/day).

Figure 1 shows the number and percentage of patients having thrombocytopenia, abnormal CT of PFA-100 and/or prolonged bleeding time in these 106 PD patients. Totally 34 patients (32.1%) had at least one of these three kinds of platelet abnormalities. Ten patients (9.4%) had thrombocytopenia, 12 (11.3%) prolonged BT, and 19 (17.9%) prolonged CT of PFA-100. In these patients, six (5.7%) had only thrombocytopenia, seven (6.6%) only prolonged BT, and 14 (13.2%) only prolonged CT of PFA-100. Two patients (1.9%) had both thrombocytopenia and prolonged BT, two (1.9%) had both thrombocytopenia and prolonged CT of PFA-100, and three (2.8%) had both prolonged BT and prolonged CT of PFA-100.

The 106 patients can be divided into two groups: normal platelet (72 patients, 67.9%) and abnormal platelet (34 patients, 32.1%) groups. The abnormal platelet group was further divided into 3 subgroups: thrombocytopenia (10 patients, 9.4%), prolonged BT (12 patients, 11.3%), and prolonged CT of PFA-100 (19 patients, 17.9%). The difference of age, sex, duration of symptoms, Hoehn and Yahr stage, UPDRS-III motor subscore, levodopa dosage, LEDD, and PD medication between normal platelet and abnormal platelet or each subgroup were analyzed (Table 2). There was no difference in the age, sex, Hoehn & Yahr staging, UPDRS-III motor subscore with medication on, the dose of levodopa, and LEDD between these two groups \( (p > 0.05) \), except that the UPDRS-III motor subscore with medication off was higher in the normal platelet group than in the abnormal platelet group \( (p = 0.0418) \) and prolonged BT subgroup \( (p = 0.0249) \). There was no difference in the PD drugs used by
the patients between these two groups, except that the abnormal platelet group had more patients using selegiline than the normal platelet group ($p = 0.0290$), and the prolonged BT subgroup also had more patients using selegiline than the normal platelet group ($p = 0.0070$). In the univariate logistic regression analysis (Table 3), we found that use of selegiline was significantly associated with prolonged BT ($p = 0.0041$, OR 11.500) and abnormal platelet ($p = 0.0315$, OR 4.929). The UPDRS-III motor subscore with medication off was also significantly

### Table 1. Demography of patients with Parkinson's disease.

| Characteristics                  | PD patients (n = 106) |
|----------------------------------|-----------------------|
| Age (years)                      | 35–77 (62.5 ± 7.4)    |
| Sex (Female : Male)              | 51:55                 |
| Duration of symptoms (years)     | 5–37 (11.7 ± 5.4)     |
| Hoehn and Yahr stage             |                       |
| Off                              | 2–5 (3.6 ± 0.6)       |
| On                               | 1–5 (2.5 ± 0.7)       |
| UPDRS-III                        |                       |
| Off                              | 16–95 (41.4 ± 12.5)   |
| On                               | 3–40 (18.7 ± 8.7)     |
| PT (second)                      | 9.3–11.5 (10.3 ± 0.5) |
| aPTT (second)                    | 22.2–32.6 (27.6 ± 2.0)|
| Levodopa (mg/day)                | 150–2400 (865.7 ± 383.8) |
| LEDD (mg/day)                    | 165–2805 (1341.4 ± 501.0) |
| PD medications                   |                       |
| Levodopa/benserazide             | 74 (69.8%)            |
| Entacapone                       | 56 (52.8%)            |
| Amantadine                       | 56 (52.8%)            |
| Carbidoma/levodopa               | 48 (45.3%)            |
| Pramipexole                      | 45 (42.5%)            |
| Ropinirole                       | 32 (30.2%)            |
| Biperiden                        | 23 (21.7%)            |
| Rotigotine                       | 14 (13.2%)            |
| Selegiline                       | 9 (8.5%)              |

Figure 1. The number and percentage of patients with thrombocytopenia, prolonged closure time of platelet function analyzer 100 (CT of PFA-100), and/or prolonged bleeding time (BT) in 106 patients with Parkinson’s disease.

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associated with abnormal platelet (p = 0.0464, OR 0.960). In the multivariate analysis (Table 4), lower UPDRS-III motor subscore with medication off (p = 0.0316, OR 0.954) and use of selegiline (p = 0.0197, OR 0.609) were significantly associated with platelet abnormality when the other variables were controlled.

**Discussion**

The hemostatic function depends on both coagulation and clotting systems. The association between PD and coagulation abnormalities had been noted previously. A study found that the 160 patients taking PD medications had higher average values of PT and plasma levels of prothrombin fragment 1+2, D-dimer, plasmin-α2 antiplasmin complex, thrombomodulin and E-selectin than the 110 patients without any medication or the 159 in this study. Furthermore, abnormalities in coagulation functions are more prominent in patients with more severe disease conditions (higher Hoehn and Yahr stage) and longer histories of illness and medical therapy. These results suggest the coagulation abnormalities in PD patients are related to the duration and severity of PD, treatment with antiparkinsonian agents, multiplicity of PD drugs, and duration of treatment. However, our study found that 106 of the 107 PD patients (99.1%) had normal coagulation functions and only one patient (0.9%) had prolonged aPTT, which suggests that most PD patients had normal coagulation function. In previous study, the age of the patients treated with antiparkinsonian agents was 59.7 ± 14.0 years old, the duration of disease/therapy duration was 4.8 ± 2.4/4.0 ± 5.4 years, and the Hoehn and Yahr stage was 3.1 ± 0.9. However, the age of our patients was 62.5 ± 7.4 years old, the duration of disease was 11.7 ± 5.4 years, and the Hoehn and Yahr stage at medication off condition was 3.6 ± 0.6. These data, being similar to or higher than those in previous studies, do not support the view that patients with more severe disease, longer histories of illness and medical therapy are associated with coagulation abnormalities. The inconsistency between our results and the previous report is unclear and deserves further investigation. Although the prevalence of abnormal PT or aPTT (0.9%) is very low in our study, it is still necessary to have PT/aPTTT test in preoperative evaluation, because they can be affected by medical disease or medication other than PD drugs.

In addition to the coagulation system, the clotting system, especially the quantity and quality of platelets, is also the major component of hemostatic function. In this study, we examined the platelet number and function, and found that 32.1% (34/106) of PD patients had at least one of three kinds of platelet abnormalities (thrombocytopenia, prolonged BT and/or prolonged CT of PFA-100). Platelets have been found to have similar structural, functional and biochemical characteristics to the neurons in a variety of neurodegenerative disorders (NDDs)
Table 3. Univariate analysis of the factors affecting platelet count and function in PD patients. PD, Parkinson’s disease; BT, bleeding time; CT, closure time; PFA-100, Platelet Function Analyzer-100; OR, odds ratio; CI, confidence interval; UPDRS, Unified Parkinson’s Disease Rating Scale; LEDD, levodopa equivalent daily dose. *Statistically significant.

| Variable                  | Thrombocytopenia | Prolonged BT | Prolonged CT of PFA-100 | Abnormal platelet |
|---------------------------|------------------|--------------|-------------------------|------------------|
|                           | p value          | p value      | p value                 | p value          |
|                          | OR 95% CI        | OR 95% CI    | OR 95% CI               | OR 95% CI        |
| Age                       | 1.058 0.952, 1.175 | 1.009 0.928, 1.096 | 0.8406                  | 0.980 0.917, 1.048 | 0.5570                  | 0.990 0.937, 1.046 | 0.7211                  |
| Sex                        | 0.264 0.052, 1.332 | 1.057 0.311, 3.589 | 0.9290                  | 1.175 0.427, 3.232 | 0.7553                  | 0.940 0.415, 2.127 | 0.8813                  |
| Duration of symptoms       | 0.858 0.712, 1.033 | 1.008 0.906, 1.123 | 0.8788                  | 0.915 0.810, 1.033 | 0.1508                  | 0.930 0.850, 1.018 | 0.1170                  |
| Hoehn and Yahr stage       | Off 0.606 0.204, 1.798 | 0.603 0.219, 1.661 | 0.3278                  | 0.742 0.314, 1.755 | 0.4969                  | 0.631 0.308, 1.291 | 0.2072                  |
|                           | On 0.724 0.265, 1.981 | 0.615 0.238, 1.590 | 0.3153                  | 0.613 0.288,1.305 | 0.2044                  | 0.554 0.288, 1.064 | 0.0760                  |
| UPDRS-III                  | Off 0.983 0.927, 1.042 | 0.943 0.877, 1.014 | 0.1135                  | 0.970 0.926, 1.017 | 0.2068                  | 0.960 0.923, 0.999 | 0.0464                  |
|                           | On 0.992 0.917, 1.073 | 1.010 0.941, 1.085 | 0.7810                  | 0.960 0.902, 1.021 | 0.1902                  | 0.960 0.913, 1.009 | 0.1069                  |
| Levodopa dosage            | 1.001 1.000, 1.003 | 1.000 0.998, 1.001 | 0.6559                  | 1.000 0.998, 1.001 | 0.8943                  | 1.000 0.999, 1.001 | 0.7485                  |
|                           | LEDD 0.999 0.999, 1.002 | 0.999 0.999, 1.001 | 0.9347                  | 1.000 0.999, 1.001 | 0.6157                  | 1.000 1.000, 1.001 | 0.4339                  |
| PD medications             | Levodopa/ benserazide 0.897 0.211, 3.816 0.8835 | 0.538 0.153, 1.895 | 0.3349                  | 0.833 0.278, 2.494 | 0.7444                  | 0.705 0.295, 1.687 | 0.4324                  |
|                           | Amantadine 0.596 0.155, 2.294 0.4522 | 0.895 0.263, 3.038 | 0.8585                  | 0.994 0.361, 2.736 | 0.9099                  | 1.007 0.445, 2.279 | 0.9875                  |
|                           | Entacapone 0.596 0.155, 2.294 0.4522 | 1.789 0.494, 6.477 | 0.3753                  | 0.994 0.361, 2.736 | 0.9099                  | 1.007 0.445, 2.279 | 0.9875                  |
|                           | Carbidopa/ levodopa 0.989 0.256, 3.813 0.9866 | 2.076 0.600, 7.177 | 0.2485                  | 1.648 0.596, 4.552 | 0.3356                  | 1.668 0.733, 3.794 | 0.2223                  |
|                           | Pramipexole 1.572 0.417, 5.925 0.5043 | 0.786 0.216, 2.855 | 0.7142                  | 1.414 0.511, 3.913 | 0.5043                  | 1.397 0.613, 3.182 | 0.4263                  |
|                           | Ropinirole 1.619 0.414, 6.330 0.4885 | 1.735 0.494, 6.086 | 0.3897                  | 0.867 0.277, 2.714 | 0.8068                  | 1.161 0.482, 2.800 | 0.7388                  |
|                           | Biperiden 0.310 0.037, 2.612 0.2814 | 0.254 0.031, 2.098 | 0.2032                  | 0.744 0.219, 2.523 | 0.6349                  | 0.372 0.116, 1.195 | 0.0968                  |
|                           | Rotigotine 0.000 NA | 0.9587 | 1.109 0.213, 5.766 | 0.9020                  | 0.652 0.132, 3.230 | 0.6008                  | 0.537 0.139, 2.066 | 0.3654                  |
|                           | Selegiline 0.000 NA | 0.9787 | 11.500 2.173, 60.865 | 0.0041*                  | 4.313 0.796, 23.376 | 0.0901                  | 4.929 1.152, 21.091 | 0.0315*                  |

Table 4. Multivariate analysis of the factors between normal and abnormal platelet groups in PD patients. PD, Parkinson’s disease; UPDRS, Unified Parkinson’s Disease Rating Scale. *Statistically significant. (p < 0.05).
abnormalities persist longer after levodopa is withdrawn. In addition, the thrombocytopenia in a patient did not recur when purified levodopa was used to treat PD symptoms, which indicates the thrombocytopenia is not due to direct allergy to levodopa in this patient. Our patients did not receive immunological examination, thus, we have no comments about the autoimmune reaction.

Platelet function is also important for the hemostasis. The data in the literature in PD patients are variable. A study reported that 10 PD patients had no change of bleeding time and platelet aggregation with ADP, epinephrine, and collagen at different dilution. However, in another study about 25 PD patients, none had thrombocytopenia, but the platelet aggregation induced by ADP and epinephrine was significantly decreased (32% and 60%, respectively), while collagen-induced aggregation was unchanged, as compared with 25 control subjects. In this report, we used two methods (BT and CT of PFA-100) to investigate the platelet function and found that 28 patients (26.4%) showed abnormality in either BT test or CT of PFA-100. PFA-100 is one of the clinically available tests based on platelet adhesion under shear stress. Isolated prolonged Col/EP1 closure time is possibly due to use of acetylsalicylic acid, or platelet dysfunction. Both prolonged Col/EP1 and Col/ADP CTs are possibly due to von Willebrand disease, Glanzmann thrombasthenia, Bernard-Soulier syndrome, Grey platelet syndrome, or other diseases. Some other conditions, such as bone marrow disorders, congenital or acquired platelet disorders, and drug-induced platelet disorders, can also contribute to prolonged CT of PFA-100.

Our patients showed no such diseases or conditions mentioned above, and we found 17.9% patients had prolonged CT of PFA-100. In addition to PFA-100 test, BT test using Ivy or Duke Method has long been used for evaluating the platelet function, but the results of BT can be confounded by many factors, such as age, sex, direction of incision, vigorous exercise, variations in cuff pressure, excessive wiping the incision, excessive anxiety, and cold applied to adjacent skin. Therefore, this test has been suggested not to be adopted as a routine preoperative test for patients without history of bleeding disorder by the College of American Pathologists and American Society of Clinical Pathologists since 1998. Both prolonged Col/EPI and Col/ADP CTs are possibly due to von Willebrand disease, Glanzmann thrombasthenia, Bernard-Soulier syndrome, Grey platelet syndrome, or other diseases. Some other conditions, such as bone marrow disorders, congenital or acquired platelet disorders, and drug-induced platelet disorders, can also contribute to prolonged CT of PFA-100.

In conclusion, this study revealed that about one third of PD patients were associated with thrombocytopenia and/or platelet dysfunction, which suggests platelet abnormalities may occur in PD patients even though the patients do not have history of hematological disorders, taking antiplatelet or anticoagulation drugs, or other diseases that may impair the clotting or coagulation functions. Therefore, it is important to have a detailed preoperative evaluation of the platelet number and function before DBS surgery for PD patients. This study investigated PD patients undergoing preoperative evaluation for DBS surgery and selection bias might have occurred, because patients with early or late stage PD might not be included in this study population. Further study and larger study populations are necessary to clarify the relationship between platelet abnormalities and PD.

In conclusion, this study revealed that about one third of PD patients were associated with thrombocytopenia and/or platelet dysfunction, which suggests platelet abnormalities may occur in PD patients even though the patients do not have history of hematological disorders, taking antiplatelet or anticoagulation drugs, or other diseases that may impair the clotting or coagulation functions. Therefore, it is important to have a detailed preoperative evaluation of the platelet number and function before DBS surgery for PD patients. This study showed that CT of PFA-100 had the highest sensitivity to reveal the platelet abnormality among the three parameters. However, not all the platelet abnormalities in PD patients could be identified by any single test, thus we suggest the evaluation should include as much tests as the hospital can provide to increase the detection rate of platelet abnormalities. Whenever there are platelet abnormalities, either the surgery should be postponed or some management such as platelet transfusion should be performed before or during the surgery.
Data availability
The datasets generated during and analyzed during the current study are available from the corresponding author on reasonable request.

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Author contributions
Conception and design of study: S.-H.T., C.-H.T. Acquisition of data: S.-C.C. Analysis and interpretation of data: S.-C.C. Drafting the manuscript: S.-H.T., S.-C.C. Revising the manuscript critically for important intellectual content: All authors. Approval of the version of the manuscript to be published: All authors.

Competing interests
The authors declare no competing interests.
