Original Research Article

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Study on the Causes, Consequences and Predictors of Motor Exacerbations in Idiopathic Parkinson's Disease

N. Praveen Chander[1], S. Robert Wilson[2]

Abstract

Introduction: Patients with Parkinson's disease have episodes of worsening of motor and nonmotor symptoms. Such exacerbations can be mistaken as intrinsic worsening of the disease per se, leading to unnecessary dose adjustments. Whereas in reality, these are due to secondary causes. In spite of the clinical significance and social impact of motor exacerbations, there is little research work available from the literature. *Aim:* To study on the causes, consequences and predictors of motor exacerbations in Idiopathic Parkinson's disease. *Materials and Methods: Place of study;* Institute of Neurology, Madras Medical College & Rajiv Gandhi Government General Hospital, Chennai. *Study design and duration;* Between August 2012 and December 2014, prospective observational study. *Results:* The study group consisted of 87 subjects which includes 28 females. The Exacerbations group had a later age of onset and longer duration. The mean UPDRS ADL for exacerbations group is 27.2 whereas the mean for control group is 22.6. The basic MMSE had a significant p value. Various causes for motor exacerbations were: medication errors, medical illness, psychiatric problems, alcohol, smoking, and surgical procedure. The commonest cause in our study was medication errors followed by medical illnesses. Two patients had worsening of motor features following episode of binge drinking. One patient had worsening of motor features due to surgical problem. Two patients had worsening who were having depression and anxiety. A combination of these occurred in majority of the cases. Patients presenting with worsening of tremor had better prognosis and they recovered almost fully. *Conclusion:* This study reveals that Medication errors, Systemic medical problems, Psychological causes, Alcohol and surgical problems can worsen the motor exacerbations. Medication errors followed by diverse medical conditions are the common causes. Motor exacerbations due to various causes is reversible in most of the cases.

Keywords: Parkinson's Disease; Motor Exacerbation; Medication Errors.

Introduction

Parkinson disease (PD) is an extensively studied neurodegenerative disorder [1]. James Parkinson was the first to identify this clinical constellation of symptoms in his paper called "The Shaking Palsy". Parkinson's disease can affect many aspects of the patient's health and daily life [2]. Parkinson's disease (PD) has a cumulative effect on patients, their family members, the healthcare and social care systems [3]. Regardless of the insidious course of Parkinson Disease, it is not infrequent for patients to have episodes of worsening of their motor and 3 nonmotor symptoms. Such exacerbations can be mistaken as intrinsic worsening of the disease per se, leading to unnecessary dose adjustments. Whereas in reality these are due to secondary causes. These causes have to be identified and treated aptly. The smooth course of the well controlled disease encounters many obstacles in addition to the worsening of the disease per se. These various factors which astray the disease control has to be studied and analysed. In spite of the clinical significance and social impact of motor exacerbations in PD, there is only little research work available from the literature.

Aim

To study on the causes, consequences and predictors of motor exacerbations in Idiopathic Parkinson's disease in our centre.

Author's Affiliation: [1]DM Neurology, Department of Neurology, Global Hospitals, Perumbakkam, Chennai, Tamil Nadu 600100, India. [2]DM Neurology, Department of Neurology, SRM Medical College Hospital, Potheri, Chennai, Tamil Nadu 603203, India.

Corresponding Author: S. Robert Wilson, DM Neurology, Department of Neurology, SRM Medical College Hospital, Potheri, Chennai, Tamil Nadu 603203, India.
E-mail: jasonrobby09@gmail.com
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Materials and Methods

Place of study

The study was conducted at the Movement disorders Clinic, Institute of Neurology at Madras Medical College & Rajiv Gandhi Government General Hospital, (RGGGH), Chennai, Tamilnadu. The study population includes patients who are attending the Movement disorder Clinic. Institutional ethical committee approval was obtained on 05-03-2013 No: 12032013 for the study.

Study Design and Duration

The study design was a longitudinal study, which was conducted between August 2012 and December 2014. 87 consecutive Parkinson's patients who satisfied our inclusion and exclusion criteria were selected randomly for the study after obtaining informed consent from them.

Inclusion Criteria

1. Parkinson disease (PD) patients as per UK Parkinson society Brain Bank Criteria who are on anti- Parkinsonism drugs for more than a year were included in the study.
2. Those patients with proper treatment records.

Exclusion Criteria

Parkinson's plus patients,Patients with very poor drug compliance, Patients with Dopamine receptor blocking agents, Patients whose MMSE<10 were excluded from the study, Patients with a pre-existing psychiatric illness, Patients who were unwilling for hospital admission and evaluation if necessary, Patients who were refractory to Anti Parkinson drug, Burnt out cases of PD, Patients whose life expectancy was < 1 year.

Methods of Data Collection

The data were collected in the proforma specifically designed for the study. The data includedthe following.

Demographic data: Patient name, age, sex, address, occupation and average monthly income were obtained.

Disease data: Age of onset and duration of the disease, main symptomatology at the onset, other clinical features, and co morbid illness were obtained. Further any new symptoms encountered by the patient were also noted. Symptom free period was also noted. The details were also counter checked with the attenders.

Treatment data: Treatment details including names of the drugs used, starting and maximum dosages, duration of treatment, details regarding compliance, adverse effects an intake of other medications were recorded. Further use any other offending drugs, antipsychotics was also noted.

Investigation data: Details of investigations done and their findings were recorded, which included CT Brain, MRI Brain and CSF analysis, complete hemogram, blood biochemistry and other relevant investigations. Further all patients were subsequently evaluated using the 4 Unified Parkinson's Disease Rating Scale (UPDRS), the Hoehn and Yahr (H&Y) stage, and the Korean version of the Schwab and England activities of daily living. Further MMSE scoring, Hamilton Anxiety Inventory, Hamilton Depression Inventory were also completed.

Methods of Data Analysis

All the collected data were entered into Microsoft Windows 2010 excel spreadsheet and analyzed with the help of Microsoft excel and SPSS software. Comprehensive reviews of all the clinical visits or telephonic encounters were also analyzed for the entire study period. Motor exacerbations were noted as given by the patient himself or by the care takers. It includes worsening of motor functions in at least one of the motor domains (bradykinesia, tremors, rigidity or Gait disturbances and falls). Appropriate patients were admitted and evaluated. The cause if identified was also treated accordingly. The clinical causes, duration and outcome were recorded. Statistical parameters (mean, SD, median, frequency, percentage) were calculated and baseline characteristics were compared between the study (patients with exacerbations) group and the control group (Patients without exacerbations). Univariate analysis was done using the 2-sample t test (Mann Whitney test) for continuous variables and the Fisher exact test for categorical variables. Analysis was done in SPSS Version 18.0 and SAS version 9.

Results

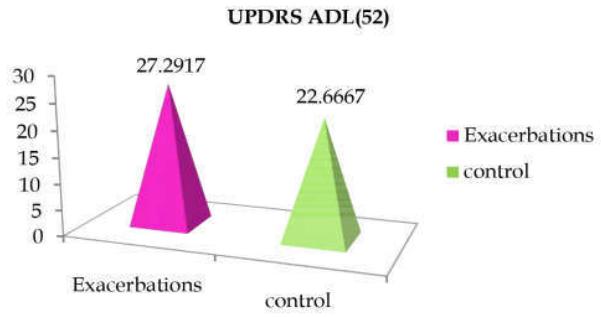
The study group population consisted of 87 subjects which includes 28 females. No one below 30 yrs was present in the group. The study population has a mean age of 63.59 years (range, 37 to 81.0 y), and the median disease duration of 3.6 years (ranges

from 1 to 13 y). During the 28 months study period, among the 87 individuals, 24 patients had motor exacerbations. {24 of 87 of the total patients (27.58 %) in the cohort (Table 1).

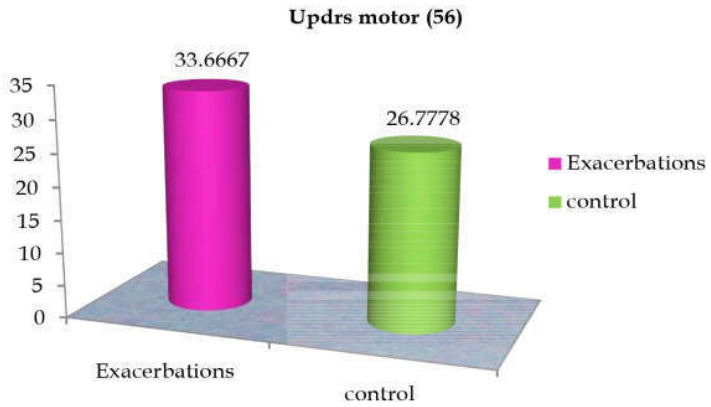
Mean age of people in the control group was 62.6984. Iin contrary the Exacerbations group had a relatively later age of onset (Mean 61.7292, SD- 2.17 in relation with a mean value of 59.15 in the Control group with asignificant p'value 0.012.The duration of illness is also slightly more with exacerbations group. The mean value for the same is 4.2292 years with a SD of 1.22. Whereas the Mean is 3.3175 years for the control group. (Significant p value – 0.004).

Table 1:

Characteristics	Subjects with clinical excarberatons (n=24)	Subjects without clinical excarberations (n=63)
Total number of patients studied (87)	24	63
Demographical statistics		
Age in years (mean +-SD)	65.958	62.698
Age of onset of PD in years	61.729	59.158
Duration of the disease	4.229	3.317
Male: Female ratio	M = 17 f=7	M:42 F: 21
Family history of PD	2	5
Motor scoring		
UPDRS ADL 52	27.29	22.66
UPDRS Motor Scoring 56	33.66	26.77
Modified Hoehn and Yahr 5	2.52	2.26
Schwab& England 100%	74.58	74.6
Non motor score		
MMSE	19.12 (459)	23.5 (1116)
Hamilton Anxiety score	16.62 (399)	16.8 (1059)
Number of Anxious patients	1 (24)	14 (64)
Hamilton depressive score	7.29 (175)	8.57 (540)
Number of depressed patients	1 (24)	10 (64)
Medications		
On levo dopa	21	60
On trihexiphenydyl	22	58
On bromocriptine	6	9



Graph 1:



Graph 2:

The UPDRS ADLscoring mean value for the exacerbations group is 27.2917 with a SD of 8.45 whereas the mean for the control group is slightly lower value of 22.6667. This has a significant p value of 0.013. The UPDS motor scale in the exacerbations group has a mean of 33.6667 with SD of 7.83341; the meanvalue for the control group is 26.7778 with a positive p value of 0.0001.

The other prognostic scoring systems like Hoehn and Yahr did have a significant p value (0.005). The mean is more or less similar in both the groups. (Exacerbations group – Mean – 2.5208, SD -0.243; Control group Mean – 2.26, p value - 0.005). The basic MMSE had a significant p value in our study. The mean MMSE score for the exacerbations group is 19.125 with a SD of 4.62; the mean MMSE in the group without motor exacerbations is 23.15. The p value is 0.0001 which is significant.

The various causes for motor exacerbations were: medication problems, medical illness, psychiatric problems, alcohol and smoking, and surgical procedure in our study. One patient had worsening for which the exact cause could not be determined.

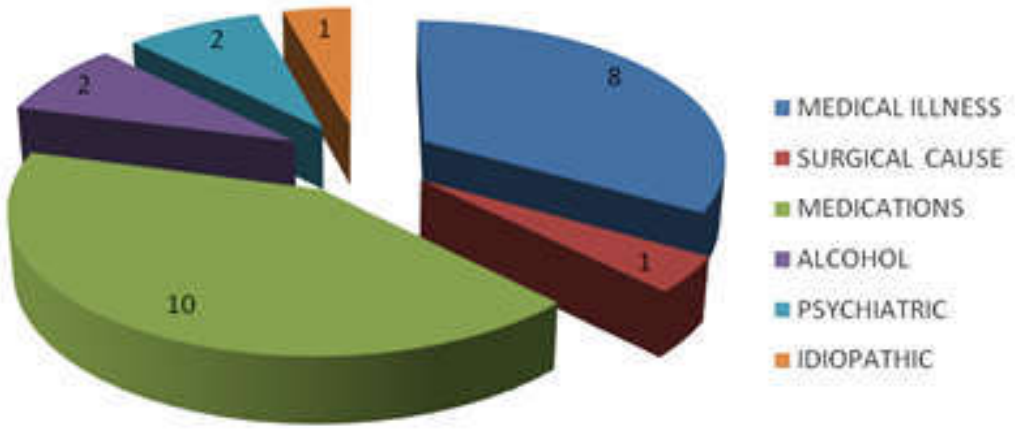
The commonest cause in our study was the medication problems which included medication errors, poor adherence and other problems related to medicines. Drug induced dyskinesias were carefully diagnosed and were not included in the exacerbations. This was schemed like this, because Drug induced dyskinesias, by itself is a separate entity which has been studied extensively at a large scale. Our study was mainly concentrating on the other causes of clinical worsening. 10 out of 24 with a percentage of 41.66. The main medication error leading to exacerbations is poor drug compliance. The other causes are inappropriate drug intake by the patients themselves, wrong medication itself and other drugs taken from outside by patient themselves. Other medications refer to alternative drugs which include Indigenous medicine also. Certain patients titrate their anti-Parkinson drugs on their own, leading to inappropriate consumption. Thus exacerbations can occur, which are unnecessary for that particular situation.

The second common cause in the list was various medical illnesses. They were lower respiratory tract infections (RTI), urinary tract infections (UTI), dehydration, constipation and combination of these. Total number of exacerbations due to medical issues accounted to 8 out of 24 with a mean of 33.33.Two patients had worsening of motor features following episode of binge drinking (2 out of 24, 8.33 %). Careful analysis was made to rule out the immediate effects of alcoholism not to be mistaken as motor worsening.

We also had one patient (1 out of 24, 4%) who had worsening of motor features due to surgical problem. Patient was in post surgical status after undergoing appendicectomy. Patient did not have any post surgical complications.

The wound healing was normal and the point to be noted is that patient was in his usual anti Parkinson drugs, during the post operative status.

Two other patients had worsening who were having depression and anxiety (2 out of 24). One patient had clinical exacerbations for which the exact cause could not be evaluated. This patient partially recovered without any specific intervention.



Graph 3:

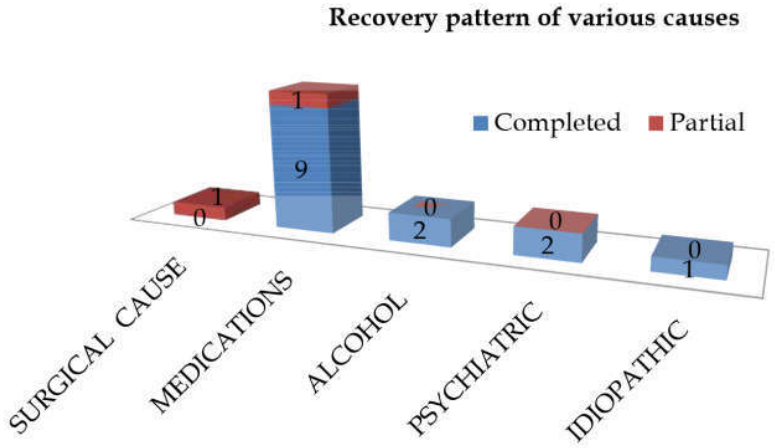
Symptom Analysis during Exacerbations

Different types of motor deteriorations included tremor disturbances alone (6 out of 24, 25%), gait disturbances alone (1 /24), akinesia, bradykinesia alone (1 each). A combination of these occurred in the majority of the cases (15 /24, 62.5%).

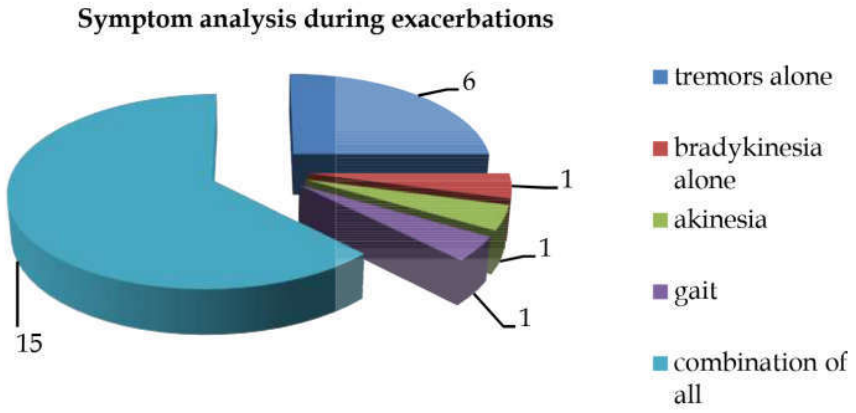
Medical and surgical illness due to various sub factors produced clinical motor exacerbations in the form of worsening of bradykinesia, tremulousness and falls. Further patients also had combination of these. Alcohol as a cause for the worsening of features produced worsening of the previously well controlled tremors. Whether the tremors are due to alcohol as such or is a worsening of Parkinsonism is debatable which is further discussed in the discussion part. Anxiety produced worsening of tremors whereas depressed patients had more of bradykinesia. In severe depression patient was almost akinetic. Gait deterioration occurred in 2 patients with no identifiable confounding factors.

The motor exacerbations necessitated admission and 6 patients were under hospital care. (6 out of 24, 25 %), the remaining 18 patients were managed on outpatient basis (18 out of 24). Of the 6 admitted patients 5 recovered completely, 1 died due to medical sepsis. Of the 18 OP patients 14 recovered to their baseline status, 2 patients were refractory to treatment and had persistent decline in motor functioning. 2 more patients lost their follow up immediately, so their response to treatment is totally unknown.

Patients presenting with worsening of tremor component had a better prognosis and they recovered almost normal. Whereas those with combination of all the above symptoms had poor prognosis as they lack complete resolution in one symptom or the other.



Graph 4:



Graph 5:

Discussion

As per date only few studies are available in the analysis of causes, consequences and predictors of clinical worsening in Parkinson disease. Karen S Zheng et al has conducted a study in the same aspect at Department of Neuro science, Weill Cornell medical college, New York in 1912. Our study also has focussed on the same aspect. Identifying motor clinical exacerbations in Parkinson's disease are of major importance in the management of PD,especially on outpatient basis, so that unnecessary economic as well as therapeutic strain can be prevented.5Insufficient research in this aspect in the field is quite surprising where nearly one fourths of the subjects are affected. Nearly 27.85 % subjects of our cohort had clinical worsening of features. This is in accordance with previous studies in the literature. This is nearly one fourth of the study group.The mean age group of the exacerbations group was around 65.95 which were slightly more than the control group. The older the patients, more they have the motor exacerbations, the reason for which can be attributed to many factor the main being the drugcompliance factor. The age of onset of the illness was more in the group with motor exacerbations. Similarly the group had a higher duration of illness when compared to the control group. More the duration of illness more are the chances for motor exacerbations owing to various causes discussed later.Almost all the exacerbations were attributable to various specific causes.

The medication related reasons were the most common among the list. The medications related exacerbations were related to various types of errors like drug administration errors, drug intake errors (inappropriate drug intake by the patients on their own) and poor adherence as such by the patients. Whatever may be the reason, the medication errors in total top the list for these motor exacerbations. This has to be identified and dealt with appropriately especially early identification of this confounding factor can easily prevent unnecessary complications. Creating awareness on this aspect to the patient as well as the attenders plays a vital role. The consequences of the same have to be explained in detail during their visits and this helps them to understand the undue importance. During the visits the patient should be explained about the consequences of over the counter drugs.The second common cause was Medical problems which aggravated the motor features. The medical problems included a wide diversity of conditions like Respiratory tract infection, urinary tract infection, dehydration, constipation and combination of these. Respiratory infection patient presented with persistent cough with sputum. Patient was found to have worsening of tremors and bradykinesia even before starting on cough syrups or broncho dilator medications. (Certain cough syrups have anti- Parkinson effect, and brocho dilators can increase tremulousness). One patient recovered on treating the RTI where as the other had only partial relief of symptoms in spite of the betterment of the medical problem, the reason for which could not be explained. One patient had urinary tract infection with polyuria, dysuria and fever. The patient had worsening of motor features. Though this clinical exacerbation can be attributed to UTI directly, the probability of dehydration due to polyuria cannot be ruled out completely. One more case had classical features of dehydration due to inadequate fluid intake with severe sweating. This patient also had worsening of features which was completely reversible following correction of the fluid status. Patient also had mild electrolyte derangements which whether can be attributed for the worsening of the clinical features cannot be explained thoroughly. 2 patients presented with combination of symptoms, had multi system involvement who were treated with broad spectrum antibiotics and other supportive measures.

One patient had severe constipation did not pass stools for 10 days. Later the same patient had worsening of bradykinesia. Further after giving enema, patient had improvement in his general condition and also his bradykinesia. Whether this worsening can be attributed entirely to constipation is a still a question. As per a Korean study conducted by Hye young the gastro intestinal symptoms are under recognised by the patients, their care givers and even by the physicians.Early identification and appropriate intervention can prevent unnecessary GI morbidities in their lives. 2 patients had multiple medical problems leading to worsening of Parkinsonian motor features.1 among the 24 patients had anxiety due to various personal reasons, which in turn has lead to worsening of the motor features. The patient recovered only partially after treatment of the anxiety and alleviation of the underlying psychosocial stress factors.One another patient had depressive symptoms as determined by the Hamilton's depression inventory. This patient was categorised as severely depressed patient as per the Inventory. She had bradykinesia and finally became akinetic. Further she was started on anti depressants. She showed improvement after treatment. Her depression in addition to bradykinesia showed

improvement. As per literature, around 50% of the PD patients experience depressive episodes in their life time. In our study 7 patients from the control group and one from the exacerbations group had depression. Since no other reasonable cause could be made out for the sudden worsening of motor features, other than the depression, depression is considered to be the inciting event. Further improvement after treatment of depression also favours this ideology. The only case with surgery as a reason for the exacerbations has underwent appendicectomy 1 week prior. This patient was receiving his usual medications in the normal dosage.Suddenly patient started to worsen in his tremors component, which was even present earlier but was minimal. Following the surgery, the patient's tremulousnessworsened and the THP dosage has to be hiked, to take care of the symptoms. One patient had worsening of his gait. Patient's stride suddenly became severely bradykinetic and was stooping. The reason for this acute worsening could not be made out. No specific etiological cause discussed above or other additional cause could not be made out. The management in these cases was tailored according to the patients needs. The specific causes were managed accordingly. The management was planned by the corresponding treating units and was protocol based. Patients who were in need for inpatient care were admitted and managed accordingly. The other cases were prescribed drugs on outpatient basis and were followed regularly. Remission was considered only when the patients were relieved of their symptoms, if not complete recovery, at least the return to the base line was considered as remission. The study group had varied responses to treatment. 16 of the patients had complete recovery (return to their baseline status), 7 of the patients had only partial recovery, whereas 1 patient did not recover at all. He was a male with acute worsening of his gait without any specific cause. The patients anti Parkinson's drugs were escalated, but in vain. This quantification of recovery pattern is important, as it indirectly also marks the importance of prevention of the exacerbations.

From the study, it is clear that the medication errors leading to exacerbations can be reverted completely if; the error is recognised and intervened appropriately [6]. Most of the patients were receiving dopamine (levo dopa + carbi dopa), trihexiphenydyl. Few of them received bromocriptine as an adjuvant. This schema was more or less same in both the groups. Since this did not have significance (insignificant p value), the role of treating drugs in acute exacerbations is still unanswered. Most of our study results are in accordance with the previous study by Karen Benjamin et al in 2012, which was published in journal "Neurologist in May 2012". The occurrence of life - threatening consequences of delayed diagnosis underscores the need for better education of patients and attenders and the physicians about the differential diagnosis of the underlying cause [7]. Clinical predictors of motor exacerbations included several markers of advancing disease: longer disease duration, greater baseline impairment of ADLs, higher H & Y scores, an increased prevalence of motor complications, and a trend towards greater UPDRS motor impairment [8]. Nonmotor predictors of motor exacerbations included lower MMSE scores (despite the exclusion of demented patients), and a higher lifetime prevalence of psychosis, all of which are additional markers of disease severity. Psychosis, in particular, has also been associated with increased morbidity in PD. Further investigation is therefore warranted to determine the extent to which various causes of motor exacerbations may contribute to this increased morbidity.

Conclusion

This study reveals that medication errors (Anti parkinsonian), Systemic medical problems, Psychological causes like anxiety, depression, Alcohol effects and even surgical problems can worsen the motor exacerbations [9]. As medication errors top the list it is emphasised that by proper intake of the drugs in the optimal dosage with optimal compliance, proper education of the care giver, majority of the exacerbations can be prevented. Our study shows that the second most common cause for the motor worsening is the diverse medical causes. This aspect has to be taken care at an early phase itself which can reduce the unnecessary motor exacerbations. The treating Physician should anticipate these motor exacerbations to occur even in mild medical problems. Further this study has established that motor exacerbations due to various causes is reversible in most of the cases, in certain cases, the remission is incomplete only. The study also revealed that the motor exacerbations period varies from a minimum of seven days to nearly one and a half months [10]. The morbidity and turmoil during this period can be prevented, if the exacerbations are predicted at an early phase itself. "In summary, our study has shown that motor exacerbations are common in patients suffering from Parkinson disease for a longer duration of illness. Even though most of the patients make a full recoveryafter intervention, some have persistent symptoms. Foreseen recognition and hostile treatment

of the underlying causes of these motor exacerbations possibly will reduce morbidity, lessen hospitalisations, health care costs, and improve quality of life in Parkinson Disease patients. The needless dose modifications are also prevented .The redundant socio economic burden can also be prevented thereby reducing unnecessary burden to both the patients as well as the care givers.

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