Parkinsonism and Related Disorders 20 (2014) 1325–1328

Contents lists available at ScienceDirect

Parkinsonism and Related Disorders

journal homepage: www.elsevier.com/locate/parkreldis

Point of view

Viewpoint: Challenges in our understanding of neuroleptic induced parkinsonism

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ARTICLE INFO

Article history:
Received 23 July 2014
Received in revised form
27 September 2014
Accepted 28 September 2014

Keywords:
Neuroleptic parkinsonism
Secondary parkinsonism
Simpson Angus Scale
Parkinsonian gait
Extrapyramidal side effects
Stigma

ABSTRACT

Parkinsonism remains a common and often overlooked adverse effect of almost all neuroleptic drugs, including the "atypical," or "second generation" antipsychotics. While neuroleptic induced parkinsonism (NIP) is often thought to be well understood in terms of its clinical course, pathophysiology, and treatment, this is clearly not the case, and almost all our current beliefs are based on data published decades ago of dubious merit, and recent studies which are confounded by design conflicts. This article attempts to highlight gaps in our knowledge. While there are data on the stigma associated with idiopathic Parkinson's disease, there are none on NIP, where the problem is most likely much greater. The natural course of NIP remains unknown, including the question of whether this is a risk factor for the later development of tardive dyskinesia. While treatment with anticholinergics or amantadine is the norm, there are weak and conflicting data on whether these have much value. Why quetiapine and clozapine do not worsen motor function in people with idiopathic PD, while all other neuroleptic do, remains uncertain. Neuroleptics are among the most widely prescribed medications in the United States, with 20% of nursing home residents taking them, with an increasing use for treating depression as well as psychosis, underscoring the importance of understanding NIP, the most important adverse motor effect of this class of drugs.

"The emergence of parkinsonism during chlorpromazine and reserpine therapy constitutes undoubtedly one of the most fascinating developments in psychiatric therapy." [1].

1. Introduction

Parkinsonism is undoubtedly the single most important drug induced movement disorder in the elderly. It impairs gait, leading to reduced independence, increased need for nursing home placement and risk of falls [2]. Although many physicians consider tardive dyskinesia (TD) the most serious drug induced movement problem because the movement may be severe and permanent, the use of antipsychotics in the elderly in the U.S. is so widespread and the parkinsonian effects so commonly reduce physical function, an uncommon problem with TD, that there is little comparison. About 20% of Americans in nursing homes take antipsychotic drugs [3].

2. Defining neuroleptic induced parkinsonism (NIP)

Parkinson syndrome, or parkinsonism, is defined by the 1992 U.K. Brain bank criteria as a bradykinetic disorder that also includes one of the three criteria: rigidity, rest tremor or postural instability [4]. Most studies on NIP were published in the 1960's and 70's, prior to the development of a universally accepted definition of parkinsonism. Parkinsonism was, nevertheless, recognized immediately and was considered by some to be a marker of antipsychotic response [5]. The early papers were confounded by their difficulty in defining as well as in measuring parkinsonism. In 1968 the Simpson Angus Scale [6] was published, becoming the standard measurement instrument for NIP, and is still in use. Although it has been validated in several publications, it does not meet simple face validity by neurological standards, lacking any measure of bradykinesia, the fundamental sign of parkinsonism. It is also overly reliant on rigidity, with 6 of the 10 items measuring rigidity (neck, arms, shoulders, elbows, wrists, legs), in addition to which the instructions for measuring rigidity are challenging to use (e.g. assess neck rigidity by having the patient lie supine and dropping the head onto a pillow). The use of glabella reflex, which has subsequently been recognized as an unreliable measure of pathology [7,8], and

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http://dx.doi.org/10.1016/j.parkreldis.2014.09.030
1353-8020/

pooled saliva in the mouth, in patients taking drugs that reduce saliva production, round out the confounding aspects of this rating instrument.

3. Recognizing parkinsonism

Few studies have assessed how often parkinsonism is recognized by treating physicians so that the prevalence of NIP is uncertain. Prevalence figures vary from 0.3% [9] to 66% [10]. TD and parkinsonism were found to be missed by psychiatry residents quite frequently [11] in an era in which psychiatry residents were likely better educated on neuroleptic movement disorders than they are today. With a brief training course, recognition improved [12]. In a nursing home, as well as on a teaching medical service, parkinsonism, not necessarily neuroleptic induced, was not recognized in about half the cases [13,14].

4. Recognizing stigma

The effect of bodily appearance has been studied to a very limited degree in idiopathic Parkinson's disease (IPD), but not at all in patients with NIP. Since the features of a masked face in older patients produce a negative perception, even among physicians [15] one can only guess at what the perception of a masked facial expression is among peers and family in young adults. In addition, the studies in IPD have been limited to facial expression. If tremor and stooped posture also occur, it is highly likely that a further deleterious perception develops. A study reported that observers found patients with IPD to be "cold, withdrawn, unintelligent and moody," in addition to being perceived as relating poorly to the interviewer [16]. A study of U.S. adults who only saw videos of faces with variable degrees of masking predicted increased "neuroticism" with increased masking [17]. Another study of attitudes of 284 physicians from the U.S. or Taiwan viewing videotapes of Caucasians and Taiwanese, with a masked facial expression from IPD, found that the patients with the greater masking were more likely to be deemed depressed, less sociable, less socially supportive and less cognitively intact, based simply on their facial appearance [18]. Recognition of this as an additional iatrogenic burden to neuroleptic treated patients, should increase the impetus to recognize NIP.

5. The clinical syndrome

Parkinsonism is generally subacute in onset, but how quickly it develops varies with the drug, its dose and its mode of administration. Early studies differ in reporting how quickly it develops, from a week [1] to two months [19]. Older people are at greater risk, presumably due to the loss of substantia nigra cells with age Women are affected more than men [19], which is counter-intuitive, since men have a higher incidence of IPD than women. Therefore "unmasking" latent IPD is not a plausible explanation for this gender discrepancy. Why NIP should often be asymmetric is unexplained [20,21]. There are no data to suggest that normal adults have asymmetric distributions of their nigral neurons or their dopamine receptors. Why NIP has less tremor than IPD is another unexplained observation, as is why some have tremor and others do not. Perhaps more interesting is the frequent observation made in the 70's that NIP usually resolved without treatment [22,23] despite continued use of the neuroleptic.

The duration of NIP after drug discontinuation has long been known to be highly variable. While there are isolated reports of NIP persisting as long as 18 months [24], there is one report of it lasting seven years [25], raising the question of whether some patients rendered parkinsonian from neuroleptics may remain permanently parkinsonian, without progression. Whether chronic use of neuroleptics may cause morphological changes in the brain is unknown. The neuropathology of NIP is limited to two autopsy reports [26], in which no abnormalities were identified.

6. Pathophysiology

Longstanding dogma holds that drugs that reduce dopamine D2 receptor stimulation may result in parkinsonism [22]. All current antipsychotics, also known as neuroleptics, share the property of blocking dopamine D2 receptors, but not all cause parkinsonism. The "atypical" antipsychotics with only two exceptions, all cause parkinsonism [27]. Double blind, placebo controlled trials have shown that quetiapine and clozapine do not worsen parkinsonism in people with IPD, as assessed by PD experts [28]. There are two proposed explanations for this. One proposes the benefit of 5HT2a activity [29] and the other that D2 binding is too brief to cause parkinsonism [30]. Neither theory is satisfactory. The addition of a pure 5HT2A antagonist, pimavanserin, to risperidone or haloperidol, was not observed to eliminate parkinsonism (ref), casting doubt on the serotonin – dopamine antagonist ratio theory [31]. The observation that parkinsonism lasts for weeks to months whereas the antipsychotic benefit of neuroleptics wears off within hours, and that the likelihood of parkinsonism is dose related suggests that "fast off" theory is also not a complete explanation. Other drugs, however, such as valproic acid, may cause parkinsonism, despite having no known direct effect on dopamine or its receptors [32]. Lithium has indirect dopamine effects [33,34], not clearly related to dopamine in the striatum, as do cinnarizine and flunarizine, all common causes of parkinsonism. These data suggest that the explanation both for parkinsonism and anti-psychotic efficacy is attributable to more than simply D2 receptor blockade. This remains a challenge that might guide development of safer antipsychotic drugs.

7. Diagnosing NIP

The "gold standard" for diagnosing IPD in a patient on a neuroleptic is to stop the neuroleptic and observe the patient for an extended period of time [35]. Whether IPD is present or not, the parkinsonism should improve as the neuroleptic effect wears off, then slowly worsen as the IPD slowly progresses. Since IPD is very variable in its progression, and normal aging includes parkinsonian signs [36] this might take more than one year [24]. In patients who must remain on neuroleptics because of their psychiatric disorder, this is not a tenable approach. While dopamine transporter (DaT) single positron emission computed tomography (SPECT) scan is widely available to distinguish IPD from essential tremor, it has not been approved in the U.S. for diagnosing NIP. Data suggest that DaT scan can likely make this distinction, but this requires confirmation [37]. Transcranial ultrasound (TCU), which can help confirm the diagnosis of IPD in the general population, is unlikely to be helpful for this problem as the abnormality in the pars compacta, an increased echogenic region, is seen in both IPD and NIP, thus obviating its utility for this question [38].

8. IPD patients on neuroleptics

There are few data on the concurrence of IPD exacerbated by neuroleptics. Publications on this topic are small series or case reports, with only a handful of diagnoses confirmed by autopsy, so its management is uncertain. The largest series reporting on schizophrenics developing presumed IPD found that quetiapine or clozapine was helpful in managing the schizophrenia and allowed the