Journal of the Neurological Sciences xxx (xxxx) xxx–xxx

Contents lists available at ScienceDirect

Journal of the Neurological Sciences

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

The nosology of tardive syndromes

Karen Frei[a], Daniel D. Truong[b,c,*], Stanley Fahn[d], Joseph Jankovic[e], Robert A. Hauser[f]

[a] Department of Neurology, Loma Linda University Medical Center, Loma Linda, CA, United States
[b] The Truong Neurosciences Institute, Fountain Valley, CA, United States
[c] Department of Neurology, University of California, Riverside, Riverside, CA, United States
[d] Neurological Institute, Department of Neurology, Columbia University Medical Center, New York, NY, United States
[e] Parkinson's Disease Center and Movement Disorders Clinic, Department of Neurology, Baylor College of Medicine, Houston, TX, United States
[f] Parkinson's Disease and Movement Disorders Center, Departments of Neurology, Molecular Pharmacology and Physiology, University of South Florida, Tampa, FL 33613, United States

ARTICLE INFO

Keywords:
Tardive syndrome
Tardive dyskinesia
Tardive dystonia
Tardive tremors
Tardive akathisia
Tardive tourettism
Tardive pain
Tardive parkinsonism
Extrapyramidal syndrome

ABSTRACT

Since the original description of side effects of neuroleptics, different terminologies and definitions for tardive dyskinesia (TD) and tardive syndrome (TS) have been used by different authors, and often these two terms have been used interchangeably. This paper proposes a nosology designed to define and clarify various terms and phenomenologies within the TS spectrum.

We propose to use the term tardive dyskinesia to refer to the original description of repetitive and complex oral-buccal-lingual (OBL) movements, as well as to the analogous repetitive movements that can appear in the limbs, trunk, or pelvis. The repetitive, relatively rhythmic nature of the movements is the common denominator of this phenomenologic category.

The term tardive syndrome refers to the spectrum of all persistent hyperkinetic, hypokinetic and sensory phenomenologies resulting from chronic dopamine receptor blocking agents (DRBA) exposure. Thus, TS is an umbrella term.

When dystonia is the main feature of TS it is considered to be tardive dystonia (TDyst). Retrocollis appears to be the predominant form of cervical dystonia in this condition. Cranial dystonias, particularly oromandibular dystonia, are also common forms of TDyst. Tardive akathisia refers to the inability to remain still with an urge to move, giving the appearance of restlessness. It is a sensory phenomenon and a common and disabling form of TS. Unlike acute akathisia, tardive akathisia tends to occur late and persists after the drug is withdrawn. In tardive tourettism, the patient exhibits the features of Tourette syndrome with complex motor and phonic tics associated with premonitory urge and relief of tension after performing the tic behavior. Tardive tremor differs from the resting tremor seen in drug-induced parkinsonism in that it is mainly a postural and kinetic greater than resting tremor. Tardive pain has been reported in association with chronic use of DRBA's. The pain involved the mouth, tongue and the genital region. The patients tended to obsess over the pain and usually had some other form of motor tardive syndrome, either tardive dyskinesia, tardive akathisia or tardive dystonia. The term tardive parkinsonism has been proposed for those drug induced parkinsonism patients who have persistent symptoms following discontinuation of the DRBA. However, there is a strong possibility that the DRBA may have simply unmasked subclinical parkinsonism or that there is coincident Parkinson disease developing during the period the patient is taking the DRBA.

1. Introduction

Different terminologies and definitions for *tardive dyskinesia* (TD) and *tardive syndrome* (TS) have been used by different authors, and often these two terms have been used interchangeably. Unless an author defines these terms in her/his writing, the reader is left uncertain which specific abnormal movement phenomenology the author is referring to. To avoid this ambiguity we propose a nosology designed to define and clarify various terms and phenomenologies within the TS spectrum.

The reason for the ambiguity and confusion is largely attributable to the history of awareness by the medical community of TS and other movement and sensory disorders caused by exposure to dopamine receptor blocking agents (DRBAs), also known as neuroleptics, used

* Corresponding author at: The Truong Neurosciences Institute, Fountain Valley, CA, United States.
E-mail address: dtruong@pmdi.org (D.D. Truong).

https://doi.org/10.1016/j.jns.2018.02.008
Received 22 January 2018; Received in revised form 30 January 2018; Accepted 2 February 2018

chiefly to treat psychosis (antipsychotic drugs) or various gastrointestinal disorders such as nausea (anti-emetics), cough (anti-tussives) and gastroparesis (promotility drugs). It should be noted that various conditions and drugs other than DRBAs can cause abnormal movements that resemble specific tardive disorders [1].

The term “tardive dyskinesia” (TD) was initially coined [2] to describe patients with rhythmic, repetitive (stereotypic), persistent movements after long exposure to antipsychotic drugs. Over time, other phenomenological types of persistent movements after exposure to these drugs were described [3–5]. At the same time, the specialty of movement disorders evolved and those specialists recognized distinctions among the different phenomenologies induced by the antipsychotic agents and began applying specific terminologies for them. To group all of these persistent movement disorders together (i.e., the abnormal movements persist after the causative drug has been withdrawn), an umbrella term, “tardive syndrome,” began to be used. Furthermore, it is this growth of knowledge of various movement phenomenologies within the encompassing TS that requires a nosology to categorize these various distinct phenomenologies to avoid ambiguity, misunderstanding and confusion. These phenomenological distinctions become critical because treatment choices can be specific depending on the type of TS the patient has.

There are two essential ingredients for all the categories within the umbrella TS, and both must be present. 1) These abnormal movements are due to exposure to DRBAs. If there is no history of such exposure to a DRBA, the clinician should search pharmacy, medical, or hospital records for any evidence of exposure to DRBAs before considering another diagnosis. 2) The other essential feature of TS is not that they appear late after prolonged exposure to the DRBA, but that the movement disorder persists and will continue, and often worsen, after the offending drug is withdrawn. The observation of persistence was unexpected [6] and soon became a key feature distinguishing the oral-buccal-lingual (O-B-L) dyskinesias from the acute oral dystonias that fade away after the drug is stopped. Besides acute dystonic reactions, other reversible movement disorders recognized include drug-induced parkinsonism and acute akathisia. Because these disorders typically resolve over time after withdrawal of the DRBA, they fall outside the TS spectrum, and thus persistence of the movement disorder became recognized as an important complication of the DRBAs.

The long duration of DRBA exposure before the persistent dyskinesias developed was also a major factor in coining the name “tardive” [2]. But the experience of clinicians over the half-century since this labeling has led to the recognition that persistent dyskinesias can also develop quite soon, even days, after the DRBA was started, even though the longer the exposure the greater the risk of developing the condition.

For some reason, the term ‘tardive’ dyskinesia [2] was adopted, rather than the term “persistent” dyskinesia [6]. Although today's clinicians recognize the importance of the persistent, even irreversible, nature of TS, the name ‘tardive’ is now deeply ingrained and there is no attempt to change it.

2. Extrapyramidal syndrome (EPS)

The term EPS has been commonly used, particularly by psychiatrists, to refer to DRBA-induced motor side effects, including acute dystonia, akathisia, and parkinsonism, as well as TS. In addition, other movement disorders such as Parkinson disease have been wrongly called EPS. Thus, the term EPS lacks clinical precision and clarity.

Wilson [7] in his awesome 1912 description of progressive hepatolenticular degeneration used the term extrapyramidal motor system as the source of the symptoms of that disease, plus those of Parkinson disease, athetosis, chorea and hypertonia. The extrapyramidal motor system referred to the basal ganglia and to anatomical pathways other than the cortico-spinal (pyramidal) tract [7]. Unfortunately, it is not an accurate term because there are several other extrapyramidal pathways besides those emanating from the basal ganglia and because the major outflow of the basal ganglia is via the thalamus to the cerebral cortex and from there the descending pyramidal system [8]. The Editor-in-Chief of the journal *Movement Disorders* will no longer accept the term extrapyramidal in the journal [9].

The term EPS should be avoided due to lack of clarity. In place of the term EPS, a more precise nomenclature has been advised. We will use the term tardive syndrome (TS) to refer to the spectrum of all persistent hyperkinetic, hypokinetic and sensory phenomenologies resulting from chronic DRBA exposure. The tardive syndromes must be differentiated from acute onset DRBA-induced motor syndromes including acute dystonia, akathisia, neuroleptic-malignant syndrome and drug-induced parkinsonism.

3. Historical aspects

Reserpine (subsequently found to be a dopamine depletor) and chlorpromazine (now recognized to act as a dopamine receptor blocker) were introduced in Europe in the early 1950s to treat psychosis and other agitated states. Adverse neurologic effects caused by antipsychotic drugs were noted shortly after they became available, particularly drug-induced parkinsonism, akathisia and acute dystonic reactions. In 1954 these drugs were reported to induce parkinsonism and akathisia in some of the patients [10]. Other antipsychotic drugs were introduced and found to have similar adverse effects. Delay and Deniker [11–13] introduced the term “neuroleptic” to describe the calming effect of these drugs, but with the liability of causing drug-induced parkinsonism, which was considered a part of the definition of a neuroleptic.

One of the earliest reports in the U.S. of drug-induced parkinsonism from chlorpromazine was in 1956 when Hall and colleagues [14] reported that 36 of 90 patients receiving the drug for up to 2 months developed the disorder; in all but six the adverse effect resolved within one month of being withdrawn from the drug. In that same year, Cohen [15] described two cases of acute dystonic reaction out of 1400 patients treated with chlorpromazine. He called them transient tonic spasms, but remarked that the movements resembled those seen in dystonia musculorum deformans. In the same report, Cohen [15] observed drug-induced parkinsonism in 4% of his cases. In a major review of the complications of neuroleptics in 1957, Hollister [16] mentioned Cohen's two cases, calling them transient episodes of tonic spasms, and Hollister apparently found no similar cases in the literature, although Kulenkampff and Tarnow [17] in German in 1956 reported similar dystonic reactions. Referring to the publication of Cohen's paper and Hollister's review, Shanon and colleagues [18] immediately wrote a one-page paper in 1957 reporting acute dystonic reactions in seven of 560 patients taking perphenazine. All seven were under the age of 23 years.

The year 1957 also saw the publication of the first description of stereotypic facial movements in a half-page letter in January 1957 by Schônecker [19]. He described a new phenomenological movement disorder of orobuccal and lingual (O-B-L) movements in 3 patients. In contrast to those drug-induced movement phenomenologies described by others earlier, Schônecker's patients developed theirs after they had been taking the antipsychotic for a longer period of time. He also noted that these O-B-L movements persisted after the medication had been discontinued and were still present at the time he submitted his paper. However, this report appeared to go unnoticed for several years; perhaps because it was positioned on a page between two papers, one that ended at the top of the same page, and the other beginning below Schônecker's. It is only this bottom paper on the same page that is cited in PubMed for that page in the journal, and not Schônecker's. The first reference we found to Schônecker's. paper was by Crane in his 1968 review of TD [20].

Schônecker published another paper [21] in the same journal later