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Editorial: Hidden Gem

Hidden Gems in the Neurological Literature of Progressive Supranuclear Palsy

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This article will present a selection of highlights from publications pertaining to the Parkinsonian disorder known as progressive supranuclear palsy (PSP). In 1964, this entity was unveiled in neurological literature as a distinctive clinical syndrome and pathology. This landmark publication, written by a neurology resident, John C. Steele [1], was followed in 1972 by an expanded clinical description of PSP that he wrote in another classic (and solo) publication [2]. Thereafter, the neurological world started to take increasing notice of this seemingly rare and *de novo* disorder. In actuality, clinical and pathological features PSP had prior encounters with clinicians and neuropathologists before 1964 but without the attention received by the reporting of Steele and colleagues. Historical cases of what appears to be PSP have been documented in several publications [3–6].

Unfortunately for clinicians needing to achieve diagnostic certainty of PSP, early stages of this disorder can lack its hallmark eye movement disorder, namely, impaired volitional upward and downward gaze. This distinctive clinical feature, along with the rest of the phenotype described in the 1964 report [1], is now regarded as "classic" PSP or Richardson syndrome (PSP-RS), in contrast to other distinctive and different clinical presentations of PSP pathology [7]. Consequently, other aspects of eye movement disturbance can serve to assist in the recognition of PSP-RS, especially for its differentiation from Parkinson disease and related disorders. One of the "hidden gems" that appeared in print only a few years after the elucidation of PSP was a 1977 article by Troost and Daroff [8]. This study focused on horizontal extraocular movements and reported distinctive patterns of lateral eye excursions (seen even in some PSP-RS patients altogether lacking in impaired vertical movements). The horizontal eye movement abnormalities included reduction in peak velocity at following a moving target, hypometric lateral saccades (termed "cogwheeling" of eye movements), and defective ocular fixation due to intrusions of square wave jerks. Another finding of an atypical eye movement unique to PSP-RS was reported by Niall Quinn, who named it the *round-the-houses* sign [9]. This phenomenon can be observed in PSP patients whose range of vertical gaze is preserved. The round-the-houses sign occurs in response to a request for the patient to gaze up; the result is a single curved lateral arc. The importance of recognizing PSP's full range of impaired eye movements is underscored by the need for sensitive and reliable diagnostic capabilities at the very earliest stages of this disorder, especially if we are fortunate enough someday to have disease-modifying therapies.

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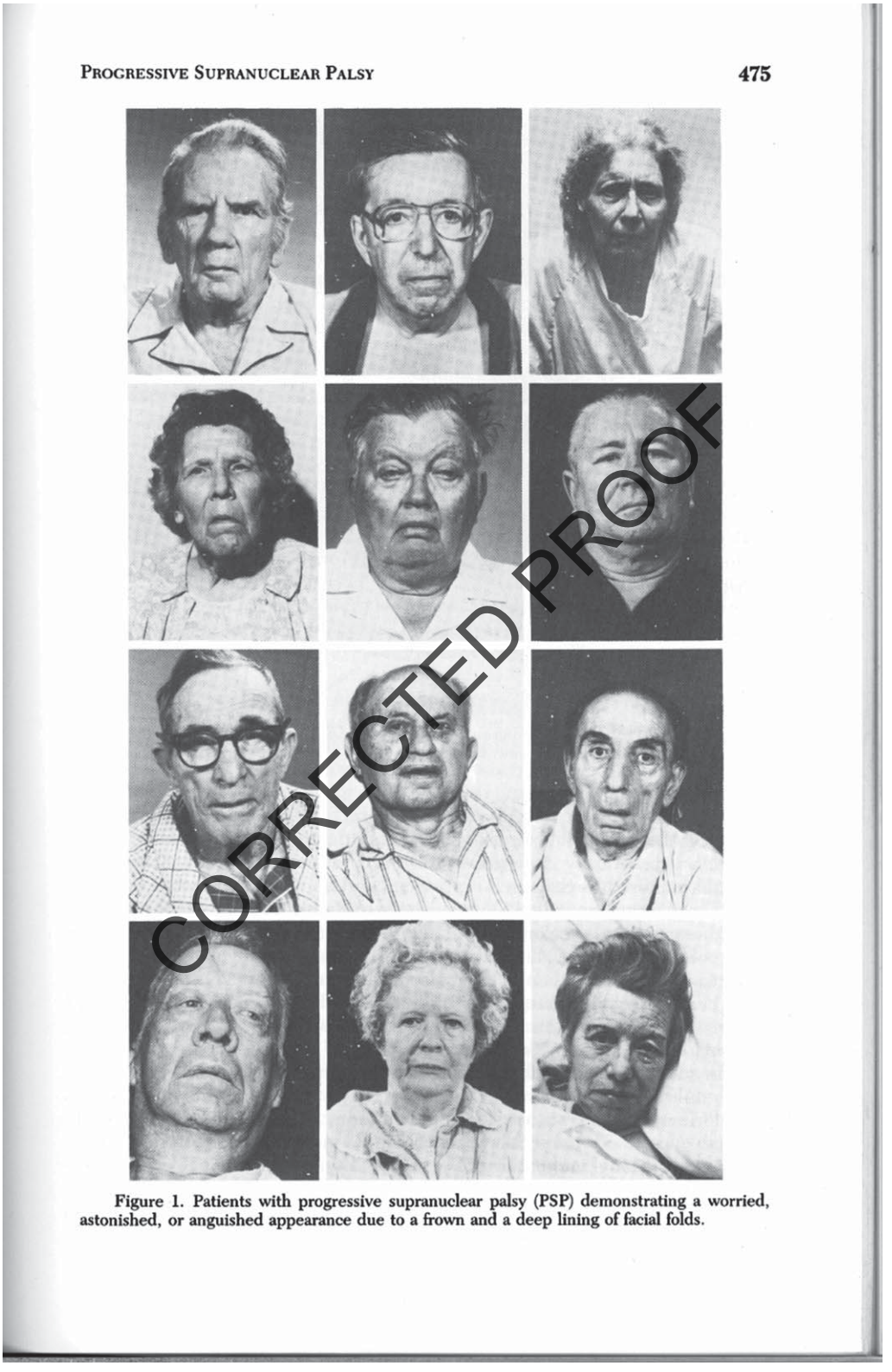

Fig. 1. A montage of the distinctive facial appearance typically observed in patients with PSP, demonstrating a worried, anguished, or astonished appearance due to a frowning appearance and a deep lining of nasolabial folds. From Jankovic [1984] (page 475); reproduced with permission.

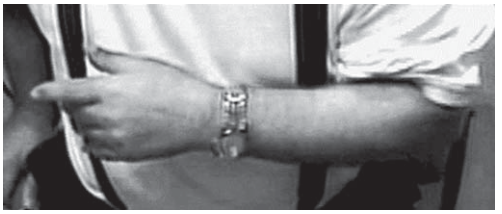

Fig. 2. An illustration of the "pointer" hand posture in PSP, as described by Barclay and Lang [1997]. This patient is under the care of the author.

Reports by other authors can be recognized as "hidden gems", characterizing other distinctive elements of PSP's diverse clinical phenotypes. For example, a classic 1984 monograph by Joseph Jankovic provides a montage of faces that nicely illustrate characteristic facial appearances commonly found in PSP sufferers (Fig. 1) [10]. These striking facial expressions, which seemingly convey worry, astonishment, or anguish, differ greatly from the more placid and masked physiognomy encountered in Parkinson's disease. Other reports have emphasized additional clinical features of PSP, also helpful for differentiating PSP from Parkinson's disease and other movement disorders. A retrospective series from 1997 by Barclay and Lang reviewed the range of neurological findings of 83 PSP-RS patients they examined [11]. In this study, the authors recognized frequent concomitant features of dystonia together with the parkinsonism and eye movement disorder of PSP. Dystonic manifestations often affected limbs unilaterally. Barclay and Lang drew attention to a distinctive hand posture in PSP described as a "pointing gun" or extended index finger position. An example of this hand posture is illustrated in Fig. 2.

The examination of the PSP patient sometimes presents other diagnostic clues that are attributable to alterations in the functioning of frontal cortex circuitry. One major advance in understanding of the pathophysiology of PSP, particularly its cognitive phenomenology, can be found in another "hidden gem", a 1985 research report by D'Antona and colleagues [12]. These investigators utilized a recently developed technique of regional cerebral metabolism using a ^{18}F-fluoro-2-deoxyglucose positron emission tomography imaging tracer that allowed them to create metabolic maps of the PSP brain. They found marked hypofunction bilaterally in frontal cerebral cortex metabolism, providing important insights into characteristic deficits of cognitive function often detected in PSP patients. This pattern has been described as "subcortical dementia", a term from the 1980 s emphasizing that neuropsychological testing of PSP could be distinguished from typical features of cognitive decline found in Alzheimer's disease. Though the full characterization of subcortical dementia generally requires a thorough neuropsychological evaluation, a unique and useful bedside test devised by Bruno Dubois can highlight one consequence of reduced frontal lobe function [13]. This test, which he termed the *applause sign*, is demonstrated after the examiner's request for a patient to clap hands just three times. In PSP, an abnormal finding commonly encountered is the inability to halt the task at 3 repetitions, reflecting failure of inhibitory motor responses that frontal lobe circuitry normally confers.

Starting with just a single series of cases that appeared in print 6 decades ago [1], the annual published output on PSP continues to expand exponentially. By late 2023, PubMed has already cited 326 articles on this topic. Much of the current race to understand the molecular biology of PSP and its potential cure was spurred on by a "hidden gem" published in 1991 by Flament and colleagues [14]. Their influential discovery was that the characteristic intraneuronal filamentous aggregates of tau protein found in the PSP brain's pathological lesions possessed unique neurochemical properties. These species of proteins could be differentiated from physicochemical features of tau protein aggregates stained in specimens of Alzheimer disease and other neurodegenerative disorders. Eventually, this unique pathological subtype of tau protein in PSP was recognized as an isoform that consists exclusively of four repeated domains (including the E10 region) [7]. The recognition of this molecular signature has fostered a wealth of insights into the pathogenesis of PSP and various ways for targeting the tauopathy for arresting the disease process. Fortunately, today's quest to cure PSP in laboratories and clinics around the world is now aided by resources including extensive and widely shared databases, biospecimen collections, and the increasing ease that the extensive literature of PSP (including its "hidden gems") can be searched. The link between cooperative investigational endeavours, patient advocacy organizations, and an increasingly educated public are helping to bring this once obscure neurological disorder into the forefront of neurological

inquiry.

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