Historical Insight

Freezing of gait before the introduction of levodopa

Freezing of gait (FOG) occurs in over half of patients with advanced Parkinson's disease. It is characterised by sudden, brief episodes of inability to produce effective forward stepping that typically occur upon gait initiation or during turning while walking. FOG can be subdivided into three clinically distinguishable phenotypes. The two most common forms, which can be seen both when patients are 'on' or 'off' their dopaminergic medication, are shuffling forward with very small steps and trembling in place without effective forward motion. The third and most severe, but also least common, form of FOG is complete akinesia. FOG is associated with increased disease severity and with prolonged levodopa treatment (although the latter could also be explained by greater disease severity). FOG is generally responsive to dopaminergic medication, and episodes are therefore more frequent and of longer duration when dopaminergic medication has worn off. Paradoxically, our general impression is that FOG is nowadays more common than before the introduction of levodopa. In a brief report published in 2011, Pedro J Garcia-Ruiz also reached this conclusion, but he did not perform a systematic assessment of all resources.

To explore the prevalance of FOG before the introduction of levodopa, we reviewed films and medical textbooks from before 1972 (see methodological details in the appendix). In the films, we found 51 patients with symptoms consistent with parkinsonism. 39 patients had Parkinson's disease (76%), nine had post-encephalitic parkinsonism (18%), and three patients had an undetermined form of parkinsonism (6%). 24 patients (20 with Parkinson's disease, two with post-encephalitic parkinsonism, and two with parkinsonism) could be seen walking. None of them exhibited any FOG episodes. In 23 textbooks, out of the 24 reviewed, FOG was not described. We found a description of gait abnormalities resembling FOG in one textbook. This description of FOG was found in a chapter written by George Selby, in a textbook by Vinken and Bruyn (1968), which describes the subtype of complete akinesia: '*The gait thus becomes arrested by even the minutest obstacle, and the patient stands motionless, as if he were 'frozen' or 'glued' to the ground.*'

Our search for films resulted in an additional source, a letter by the Australian medical historian Paul Foley, who wrote that '*freezing was noted during the 1920s as an early feature of post-encephalitic parkinsonism*'. He referred to the work of Josef Gerstmann and Paul Schilder in the early twenties in Vienna, who applied the term 'movement gaps' ('Bewegungslücke'). These movement gaps were also observed during chewing or speaking, and were considered as akinetic attacks ('interruption of innervation'). Finally, we found a possible case in a paper by Thomas Buzzard (1888), that was also found by Garcia-Ruiz. Buzzard stated: '*And when attempting to walk, William W—an engine-driver—remains for a time unable to start, his feet beating the ground rapidly as he marks time before setting off at a fair pace—the patient likening his condition to 'the wheels of a locomotive failing to bite the rails when they are slippery with frost and making, in consequence, ineffective revolutions.*'

These data endorse our general impression that FOG was not as common before the introduction of levodopa as it is nowadays. We found some sources describing FOG before 1972, but their scarcity underscores our impression that FOG occurred more often after the introduction of levodopa than before. This notion is consistent with the initial observations on the effect of levodopa. In 1969, André Barbeau described the positive effects of high-dose levodopa treatment in patients with Parkinson's disease, and 2 years later reported an increase in FOG. With only one exception, the scarce descriptions in the pre-levodopa era were invariably of the akinetic type. These akinetic cases might represent genuine freezing or merely reflect an extreme slowness in initiating movements.

Our observations are in line with those from the historical case series of five of the original index patients with MPTP-induced parkinsonism. Upon hospital admission (while still drug-naive), and also after the initial treatment with levodopa and carbidopa, we only observed FOG (complete akinesia with marked start hesitation upon walking) in one patient. Interestingly, the trembling FOG phenotype did appear in one patient, but only 6 years after chronic levodopa treatment.

We conclude that FOG episodes have increased after the introduction and long-term use of levodopa. One plausible explanation might be that in the pre-levodopa-era patients with advanced Parkinson's disease or atypical parkinsonism were too disabled to walk and demonstrate FOG. Also, life-expectancy was significantly shorter, and disease duration might have been too short to develop FOG. Another possibility is that clinicians were much less aware of the typical circumstances that can provoke FOG, such as making rapid full turns on the spot. However, clinicians practising in the early years of levodopa introduction clearly felt they were witnessing a novel phenomenon that had not existed in the pre-levodopa era. It is therefore possible that chronic levodopa use could somehow increase the frequency of FOG events, but future studies must evaluate whether levodopa-induced maladaptive mechanisms underlie these events.

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For more on **FOG and its management** see **Personal View** *Lancet Neurol* 2015; **14:** 768–78

For more on **FOG subtypes** see *Eur J Neurol* 2003; **10:** 391–98

For more on **FOG and disease severity** see *J Neural Transm* 2001; **108:** 53–61

For the **previous historical report** see *J Neurol Sci* 2011; **307:** 15–17

For **Paul Foley's letter** see *J Neurol Sci* 2012; **323:** 266

For **André Barbeau's review** see *Can Med Assoc J* 1969; **101:** 59–68

For **Barbeau's report on FOG** see **Correspondence** *Lancet* 1971; **1:** 395

For more on the **MPTP-induced historical cases** see **Correspondence** *Lancet Neurol* 2018; **17:** 300–01

For more on **life expectancy in Parkinson's disease** see *Neurology* 2018; **91:** 22

See **Online** for appendix