REVIEW

What do patients with scans without evidence of dopaminergic deficit (SWEDD) have? New evidence and continuing controversies

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ABSTRACT

The term SWEDD (scans without evidence for dopaminergic deficit) refers to the absence, rather than the presence, of an imaging abnormality in patients clinically presumed to have Parkinson's disease (PD). However, such a term has since been widely used in the medical literature, even as a diagnostic label. While many authors have suggested that different disorders of PD lookalikes may account for a proportion of SWEDD cases, others have claimed that some of them may have a benign subtype of PD. Thus, there has been ensuing controversy and confusion and the use of this term continues without clarity of what it represents. We have systematically reviewed all the studies involving patients with SWEDD with the aim of shedding light on what these patients actually have. It becomes clear from this systematic review that while most 'SWEDD' cases are due to a clinical misdiagnosis of PD, there exists a small proportion of patients with SWEDD who may have PD on the basis of a positive levodopa response, clinical progression, imaging and/or genetic evidence. The latter challenge the seemingly incontrovertible relationship between dopaminergic tracer binding and the diagnosis of nigrostriatal parkinsonism, particularly PD. Patients with SWEDD are unlikely to reflect a single clinical entity and we suggest that the term SWEDD should be abandoned.

INTRODUCTION

Among patients enrolled in some of the largest drug trials of neuroprotection or imaging studies for Parkinson's disease (PD), and undergoing presynaptic dopaminergic tracer imaging, up to 20% have been found to have normal scans (table 1).[1–6] These patients' scans were therefore given the acronym SWEDD (scans without evidence of dopaminergic deficit),[7] but what these patients represent remains controversial. Although the acronym SWEDD does not provide any aetiological information, it has been widely used in the medical literature and clinical practice both as a descriptive term and even as a diagnostic label.[8 9] It has been shown that most patients with SWEDD represent a clinical misdiagnosis of PD.[10–12] However, there are some indications that a few patients with SWEDD could truly have PD (or a PD-subtype), implying that, at least in the early stage of PD, a presynaptic positron emission tomography (PET) or single photon emission CT SPECT scan may be normal.[12] To complicate matters further, it has also been suggested that the imaging findings in these patients were incorrect.[12] The continuing relevance of this debate is reflected by the fact that one arm of the largest ongoing observational study on *de novo* patients with PD, the Parkinson's Progression Markers Initiative (PPMI - http://www.ppmi-info.org/), has also been found to include patients with SWEDD.[13]

Recent evidence and follow-up studies of patients with SWEDD might give insight into this debate.[14–16] We have reviewed all published studies providing evidence supporting an alternative diagnosis to PD, and on the other hand also studies supporting a diagnosis of PD in patients with SWEDD in order to address the following two questions: (1) How often have patients with SWEDD been mislabelled as PD and which conditions are commonly mistaken for PD? and (2) Do some patients with SWEDD actually have early PD despite their scan being normal?

SEARCH STRATEGY

We searched the MEDLINE database (via PubMed, a service of the National Library of Medicine's National Center for Biotechnology Information; http://www.ncbi.nlm.nih.gov) for anytime publications using the search terms: "scans without evidence of dopaminergic deficit", "SWEDD", "SWEDDs", "normal dopamin* imaging" AND "Parkinson*" (accessed 28 April 2015). Only English articles were included. All the titles and abstracts of publications identified by the search were evaluated for their eligibility. The reference lists of the retrieved articles were then checked to include relevant reports not indexed in the electronic database.

Evidence supporting an alternative diagnosis to PD in patients with SWEDD

There is good evidence that many patients with SWEDD have a variety of clinical conditions masquerading as PD. Many of them have had overt clinical signs of dystonia.[10 11 17] We first reported on a cohort of 10 patients with unilateral or asymmetrical arm tremor, including a rest component and reduced arm swing on the affected side, sometimes accompanied by masked face and jaw tremor, in whom a diagnosis of PD had been considered but later discarded on the basis of a normal dopamine transporter (DaT) scan.[10] All had signs of dystonia and none had true bradykinesia with

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Table 1 Frequency of scans without evidence for dopaminergic deficit (SWEDD) cases in some of the drug trials or imaging studies for Parkinson's disease (PD)

Study (reference)	Number of SWEDD cases (%)
Elldopa[1]	21/142 (14.7)
InSPECT[2]	15/112 (13.3)
PRECEPT[3]	90/799 (11.3)
REAL-PET[4]	21/186 (11.2)
CALM-PD[5]	3/82 (3.6)
European FP-CIT study[6]	10/51 (19.6)

fatiguing, even after a mean follow-up period of almost 6 years.[10] We therefore suggested that adult-onset dystonia could account for some patients with SWEDD.[10] However, there were a number of potential criticisms of this proposition, given that there is no definitive diagnostic test for dystonia and/or dystonic tremor and also because those patients were not assessed by a clinician blinded to the results of the DaT Scan. Schwingenschuh *et al*[11] therefore attempted to blindly compare, on clinical and electrophysiological grounds, patients with SWEDD with tremulous patients with PD with abnormal DaT scans. Although patients with PD and those with SWEDD shared several clinical features, it was found that lack of true decrement on finger tapping, presence of dystonia and position-specificity and task-specificity of tremor favoured a diagnosis of SWEDD, whereas re-emergent tremor, a good response to dopaminergic drugs, as well as the presence of non-motor symptoms, made the diagnosis of PD more likely.[11] Moreover, patients with SWEDD had electrophysiological features similar to those observed in patients with segmental dystonia, strengthening the hypothesis that adult-onset dystonia is the underlying diagnosis in a subset of patients with SWEDD.[11] Other studies have further shown that patients with SWEDD typically have intact olfactory function[18] and a different non-motor symptom profile,[19 20] normal size, or even macrographic handwriting,[21] normal gait[22] and normal transcranial sonography.[23] Additionally, a *TOR1A* (DYT1) carrier with late-onset asymmetric rest tremor[24] and a patient with a novel heterozygous frameshift mutation in the *SGCE* (DYT11) gene[25] have been reported with SWEDD, further supporting the hypothesis that dystonia may underlie a 'PD look-alike' clinical phenotype, even in the presence of clinical clues pointing towards the clinical diagnosis of PD such as re-emergent tremor.[26 27] In line with this, De Rosa *et al*[28] recently investigated the hypothesis that tremulous patients with SWEDD could be affected with dopa-responsive dystonia due to *GCH1* mutations. Although they did not find any *GCH1* mutation carrier, most of their patients (8/11) showed dystonic features and were eventually diagnosed with dystonic tremor.[28]

Table 2 Alternative conditions to Parkinson's disease (PD) accounting for some of the scans without evidence for dopaminergic deficit (SWEDD) cases

Condition(s)	References
Essential Tremor	14
Dystonia (including monogenic forms)	8 9 15 21 23–27 46
Fragile X premutation	28 29
Iatrogenic/Tardive	30–32
Symptomatic (vascular/brain neoplasm, toxic)	33–37
Psychogenic	38 39
Supranigral parkinsonism	40
Soft extrapyramidal signs of the elderly	14

Besides dystonia, however, other conditions presenting with or without rest tremor and additional parkinsonian features have been suggested to account for some of the patients with SWEDD.[14 29–42] This has been the case for essential tremor (ET), fragile X premutation, vascular, iatrogenic, supranigral or psychogenic parkinsonism, depression with psychomotor slowness and soft extrapyramidal signs of the elderly (table 2). In all these cases, the unexpected imaging results drove the authors to reconsider the diagnosis through detailed clinical reappraisal and diagnostic workup.

Another study has shown that patients with SWEDD do not develop the metabolic fingerprint (hypermetabolism in the basal ganglia, with hypometabolism in the premotor and posterior parietal cortex) characteristic of PD,[43] suggesting an alternative diagnosis. Despite the above, the diagnosis in a residual number of patients with SWEDD has remained unclear.[15] Follow-up clinical and imaging studies on the patients with SWEDD initially enrolled in drug trials for PD showed a lack of clinical progression and preserved dopaminergic imaging in the vast majority of them, as nicely demonstrated in the ELLDOPA-CIT and CALM-CIT follow-up studies (published only in abstract form[15 44]) as well as in a 22-month follow-up of the PRECEPT study.[14] In the last of these, in 66 out of 72 (91.6%) patients with SWEDD undergoing a repeat DaT scan, the result was normal. These results led the authors to strongly suggest that patients with SWEDD, regardless of what their actual condition is, are unlikely to have idiopathic PD.[14]

Evidence supporting a PD diagnosis in patients with SWEDD

In contrast to the above, there have also been other SWEDD cases in whom PD remained, or became, the most likely diagnosis. Some of these were based solely on clinical features. Thus, out of 12 patients with SWEDD in the study by Sixel-Döring *et al*[45] where DaT scans were assessed both visually and semiquantitatively, 5 (42%) could not be reclassified to an alternative diagnosis to PD, and showed clinical benefit from levodopa treatment as evidenced by positive standardised levodopa testing. In a prospective 2-year follow-up study using both visual and semiquantitative analyses of dopamine transporter binding, Marshall *et al* found 4 of 150 SWEDD cases (2.6%), in whom clinical progression was noted, leading to a clinical diagnosis of degenerative parkinsonism.[46] Some other cases 'converted' from normal to abnormal scans. Thus, in the aforementioned 22-month follow-up of the PRECEPT study, 6 of 72 patients with SWEDD were subsequently abnormal, 4 in the indeterminate range (ie, 65–80% of age-expected putamen uptake) and 2 clearly abnormal (ie, <65%).[14] Similarly, Menéndez-Gonzáles *et al*[47] reported on 30 tremulous patients with SWEDD over a 36-month follow-up period. While in 18 patients the diagnosis of PD could be clinically revised, diagnostic uncertainty in the remaining 12 patients led the authors to perform a second DaT scan, again using both visual and semiquantitative analyses. In 4 (13.3%) of the total 30 cases, the second DaT scan result was abnormal and they were finally diagnosed with PD.[47] These results support the notion that an initial normal DaT-SPECT cannot always exclude early degenerative parkinsonism.[48–50]

Also complicating this issue are the results of follow-up of our original cohort.[16] Although most showed no clinical or

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imaging progression, in 2 of 16 patients the repeated scan was abnormal (specifically, 14 and 16 years after their clinical onset).[16] It is unlikely that those two patients had PD at the time of the first normal scan, since it was performed more than 8 years following the clinical onset,[16] so we therefore suggested that they could have some sort of adult-onset dystonia (accounting for their SWEDD status), with the further development of superimposed PD later in life.[16] However, the possibility that those two patients were false-negative imaging cases, although unlikely, cannot be entirely ruled out. Such a possibility has indeed been suggested in a recent ^{123}I-metaiodobenzylguanidine (MIBG) imaging study, which reported on some patients with SWEDD with abnormal MIBG findings, in keeping with the diagnosis of PD.[51] It is also interesting to note that one of the original patients with SWEDD (with a clinical phenotype of levodopa-responsive parkinsonism with dyskinesias), who was enrolled in the REAL-PET study, was subsequently discovered to have the G2019S mutation in the *LRRK2* gene.[52]

Taken together, this evidence supports the notion that a small minority of patients with SWEDD may truly have degenerative presynaptic nigrostriatal parkinsonism, despite normal dopaminergic imaging when performed in the early stage of the disease.

Dissecting the SWEDD phenomenon

The term SWEDD was first coined by Marek *et al*[7] to refer to normal presynaptic dopaminergic scans in patients supposed, on a clinical basis, to have PD. The rates of SWEDD cases in several studies in PD ranged from 3.6% (CALM-PD[5]) to 19.6% (European FP-CIT study[6]), with higher rates in studies recruiting patients with shorter disease duration (table 1). This confirmed the idea that PD is over-diagnosed, as also suggested both by a specialist review of community diagnosis[53 54] and in post-mortem studies.[55 56] The evidence reviewed here indicates that patients with SWEDD represent quite a heterogeneous group of patients. A number of conditions should therefore be considered when faced with a patient suspected to have PD but having normal dopaminergic imaging, and from the clinical standpoint, it can be useful to distinguish between patients with SWEDD of the tremulous and non-tremulous form, since their differential diagnosis is not the same.

Supranigral parkinsonism[41] and some forms of secondary parkinsonism, including normal pressure hydrocephalus and vascular parkinsonism,[14 47] have in fact been suggested to account for some of the non-tremulous patients with SWEDD. This underlines the importance of performing structural along with dopaminergic imaging studies. On the other hand, tremulous patients probably constitute the large majority of patients with SWEDD. In this regard, a number of studies have shown that rest tremor and/or subtle motor deficits may occur on finger tapping in a subset of ET cases or in patients with 'indeterminate tremor',[57–60] most likely accounting for the relatively high frequency of diagnostic error. Furthermore, some authors have reported that patients with adult-onset dystonia can also present with asymmetric rest tremor, reduced arm swing and facial hypomimia,[10 11 17 24–28 61] rendering the differential diagnosis with PD challenging.

In this context, it is worth noting that the clinical syndrome of 'benign tremulous parkinsonism' (BTP) has been proposed to describe those patients with rest tremor as an early sign that consistently overshadows additional non-tremor parkinsonian features, and only mild deterioration (apart from tremor) despite at least 8 years of disease history.[62] In a postmortem study of 21 such patients, 16 had pathologically proven PD (with relatively little nigral cell loss, thus explaining their benign phenotype), whereas 5 did not, despite their diagnosis being PD at the last follow-up.[63] This demonstrates frequent diagnostic uncertainty in some tremulous patients at the borders of the classification of PD,[64 65] with motor fluctuations and levodopa-induced dyskinesias being the only reliable clinical features predicting PD pathology.[63]

A reflection on the significance of DaT scan

Clearly, our understanding of the SWEDD phenomenon relies heavily on the seemingly incontrovertible relationship between dopaminergic tracer binding and nigral cell counts, and raises the question of whether we should consider a positive DaT scan as the gold standard for the diagnosis of degenerative presynaptic parkinsonism. Dopaminergic imaging has been deemed to be more sensitive than clinical examination alone as an indicator of nigrostriatal defects.[66–71] However, there is only limited neuropathological validation for the DaT scan, the accuracy of which has always been calculated on the basis of the clinical diagnosis as the standard of truth, whereas this does not always reflect the underlying condition of patients.[72]

On the one hand, Kraemmer *et al*[73] recently reported pathological findings in nine patients with different conditions who had undergone dopaminergic imaging) and died a mean of 29 (range: 4 to 68) months later. Semiquantitative evaluation of DaT binding correlated highly with morphometric assessment of neuromelanin-positive and tyrosine hydroxylase–positive nigral cell counts,[73] indicating that quantitative imaging can provide valid insights into the integrity of the nigrostriatal dopamine pathway. On this basis, it seems reasonable to consider most patients with SWEDD as having been mislabelled as PD. Following this rationale, the authors of the PRECEPT study concluded that the clinical diagnosis of 'confident PD' (occurring in up to 44% of patients at 22-month follow-up) was incorrect.[14]

On the other hand, the negative predictive value of dopaminergic imaging (ie, the probability of not developing nigrostriatal deficit after a normal scan) is not 100% in early cases.[74] Thus, some of the SWEDD cases reviewed here subsequently had an abnormal repeat scan after a variable period of time and/or a clinical progression in keeping with a diagnosis of PD.[14 45–47] In this regard, the notion that patients with early parkinsonism due to nigrostriatal degeneration can occasionally have normal dopaminergic imaging is supported by reports describing normal DaT scans in pathologically proven patients with either multiple system atrophy[75] or corticobasal degeneration.[76 77] Moreover, the discovery of a proven pathogenic mutation of the *LRRK2* gene in one of the SWEDD cases enrolled in the REAL-PET study[52] also supports the notion that dopaminergic imaging can be normal in the early stage of PD.

The two seemingly opposite lines of evidence indicate that we do not entirely understand the relationship between dopaminergic dysfunction and the clinical manifestations of PD and argue against the role of DaT scan as a universally reliable surrogate biomarker for early diagnosis.[72 78] In fact, the preliminary results from the only available, still ongoing, project assessing the accuracy of DaT scan using the neuropathological diagnosis as the standard of truth (the Walker study[79]) found 85% sensitivity and 86% specificity of DaT scan to predict the presence of degenerative parkinsonism, figures similar to those obtained for clinical diagnosis of PD.[55 56]

A final comment is needed regarding the chance that in a number of SWEDD cases the scans were incorrect. Even though good consistency has been reported between visual and semiquantitative assessment of dopaminergic imaging,[80] there remains the possibility that in the earliest studies, when

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semiquantitative analysis was not available, the scan reports were in fact wrong. Although all the studies reviewed above used both visual and semiquantitative analysis, making this unlikely, it is interesting to note that in the follow-up of the PRECEPT study, 3 (0.5%) of 629 patients with an abnormal baseline DaT scan subsequently had normal follow-up scans.[14] This highlights the fact that there are a number of practical issues with this technique, including the radiologists' expertise, dosage of tracer injected, correct head position, time frame of image acquisition and also in regard to a number of medications and/or substances of abuse that can potentially interfere with DaT scan results.[81–83]

CONCLUSIONS

The evidence reviewed here indicates that those patients with suspected PD who undergo dopamine transporter imaging with normal results represent a very heterogeneous group of patients, and in the large majority there was a misdiagnosis of PD. This argues against the notion that patients with 'SWEDD' represent a (benign) subtype of PD. However, a small proportion of these cases may be false-negative imaging cases with a degenerative condition, arguably PD. The latter proposition is obviously a presumption, since to date there has been no pathological confirmation in these patients, so that the true diagnosis in some of them remains to be determined.

There is no doubt that the term SWEDD does not reflect a single clinical entity and since this term implies only the absence of a dopaminergic imaging abnormality, it can obviously only be applied in patients who have undergone such scans. Equally obviously, clinically similar or identical patients who have not been scanned, by definition, do not have SWEDD. Perhaps it is time for the term SWEDD to be abandoned.

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