

International Encyclopedia of Rehabilitation

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Visual Hallucinations in Parkinson's Disease

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Introduction

One of the behavioural problems many patients with Parkinson's Disease (PD) experience in the course of their disease, is the occurrence of hallucinations. These can be missed easily because PD patients do not volunteer about their hallucinatory experiences. A prevalence between 9.7 % and 44% has been reported. Prevalence rates of hallucinations vary depending on the selection of patients, as well as the duration of treatment. In population-based surveys a prevalence of 16-17% is reported (Williams-Gray et al. 2006), whereas 30-40% of PD patients in hospital based series do report hallucinations. The most common subtype of hallucinations are visual hallucinations (VH) in patients with well-established forms of PD. In PD patients receiving long-term anti-Parkinsonian treatment prevalence rates also vary from 6 to 40% (Cummings 1991; Holroyd et al. 2001; Barnes et al. 2003; Thanvi et al. 2005; Benbir et al. 2006). Hallucinations reduce quality of life and cause increased trauma for caregivers. VH are also a risk factor for nursing home placement and increased mortality (Goetz et al. 1993, 1995). In total 25.5% of the PD patients with hallucinations experience minor illusions, which only last a few seconds and consist of a sensation of a presence or a sideways passage. Formed visual hallucinations occur in 22.2%, they last a few minutes and can be divided into three categories: people (73%), animals (33%) and objects (19%). About 10 to 19% report auditory and tactile hallucinations, and a minority experience paranoid hallucinations with anxiety and freight (Goetz et al. 2006a; Williams-Grey et al. 2006). Latter hallucinations are often mixed in nature, including a tactile component, and do occur mainly in patients with clouded consciousness. Hallucinations and illusions may be worsened by dopaminergic medication in PD patients and may lead to an impairment of the bottom-up visual processing in case of underlying pathology.

Clinical characteristics of VH in PD

Data on characteristics come from self and caregiver reports and from objective tests. Because agreement between self and caregiver reports is low, data of these methods of assessment cannot be considered interchangeable (McKinlay et al. 2008). About 45% of PD patients report VH regarding faces, 49 to 71% report figures, while strong emotional interactions were found in 41-59%. In patients with Parkinson's disease dementia (PDD) night-time hallucinations can assume the form of confusion states (oneiroid or oniric confusion) that may precede the appearance of motor symptoms and is considered a precipitating factor for the occurrence of VH. The majority of patients preserve knowledge of the unreal nature of their VH at the onset of these symptoms, also called benign hallucinations (Ffytche 2007). However, recent findings show that VH are only temporarily benign

in PD, because 80% of the patients with VH develop severe cognitive deficits without insight within a couple of years. Hence, the terminology benign VH is considered unsound (Goetz et al. 2006a). VH are often recurrent and triggered in dim surroundings and evening hours (Goetz et al. 2006b). VH are distressing in nearly 35% of PD patients and interfere with daily life in about 25% (Gupta et al. 2004).

Risk factors of visual hallucinations

Risk factors of VH can be divided in endogenous and exogenous factors (Wolters 2006). Endogenous factors are age, duration and severity of PD, depression, sleep disturbance and cognitive impairment. Compared to non-hallucinating PD patients, hallucinating patients have an older age, a longer mean duration of PD symptoms, more severe motor symptoms, and a higher mean L-Dopa equivalent dose (Middleton & Strick 2000; Barnes et al. 2003; Gupta et al. 2004; Davidsdottir et al. 2005). However, hallucinations may occur independently of dopaminergic medication, based on reports of VH in the pre-Dopa era, which suggests that dopaminergic medication is not the direct cause of VH, but seems to serve as a precipitating factor. Exogenous factors are dehydration, fever, infections, alcohol and drug withdrawal, social isolation or social overexposure and several drugs, like anti-cholinergic agents, selegiline, amantadine and dopaminergics. PD patients with right-side hemisphere dysfunction, i.e. left-side disease onset experience relatively more common VH than those with right-side onset (Stavitsky et al. 2008). The question is how all these risk-factors contribute to the phenomenon of VH. Recent studies have shown a strong correlation between visual perceptual disorders and VH in PD patients. These data may lead us to a better understanding of the pathophysiology of VH (see next paragraph).

Clinical course of VH in PD

Hallucinations in PD patients occur across a clinical continuum and tend to be progressive over time. They may start with preserved insight. At that stage they are hardly disabling. Contrary to being hardly disabling, they are a severe risk factor because deterioration to florid psychosis with paranoia and delusions has been found to occur in 81% of patients over a period of three years (Goetz et al. 2006a). Some studies have confirmed an association between VH and dementia. In an outpatient cohort of 217 PD patients the overall prevalence of VH rose from nearly 40% to 70% in those with dementia (Fenelon et al. 2000). Compared to non-hallucinating PD patients, the hallucinating have a greater risk of developing dementia. About 45% of non-demented hallucinating PD patients developed dementia during the 1-year period between baseline and follow-up evaluations. Nearly 70% of them showed impairments in multiple cognitive domains. A progressive decline affected mainly visual memory for faces and visuo-perceptive-visuo-spatial functions. Hallucinating PDD patients scored significantly lower on verbal and visual memory measures compared to non-hallucinators (Ramirez-Ruiz et al. 2007). Both image recognition speed and sustained attention decline in PD, in a more progressive way if VH start to occur (Meppelink et al. 2008).

The Santangelo (2007) study showed significant cognitive decline two years after visual hallucinations had occurred. Hallucinating PD patients scored significantly worse than non-hallucinators on phonological and semantic fluency tasks, and on immediate free recall. Reduced phonological fluency at baseline was the only predictor of onset of hallucinations. Various hallucinations and poor phonological fluency independently predicted development of diffuse cognitive impairment.

Are hallucinations related to neurotransmitter deficiencies?

The role attributed to VH in PD has changed immensely over the last decade. As yet, none of the existing hypotheses fits sufficiently the origin of VH in PD. Some examples may illustrate model-deficiencies. (i) Disinhibition due to visual loss does insufficiently explain why some kinds of

hallucinations never seem to occur in PD patients. (ii) Despite that dopaminergic medication corrects visual dysfunction, VH may be induced or worsened by treatment (Poewe 2008).

Hallucinations were commonly considered to be a side effect of the L-dopa treatment. Especially hyperactivity of mesolimbic dopamine pathways has been postulated to induce VH. But how does this fit the deficient retinal dopamine (Rodnitzky 1998)? An alternative hypothesis is that VH are caused by the stimulation of hypersensitive postsynaptic dopamine receptors, due to denervation of the pre-synaptic mesolimbic neurons. However the relationship between VH and L-dopa is not a simple one. VH in PD patients were already present in the pre-Dopa era. Also, they are not simply dose related and only 19% of PD patients with VH had a recent drug dose change. However, antipsychotics, which are anti-dopaminergic agents, are effective, so the dopaminergic system plays a role, but not in a direct causative way (Merims et al. 2004).

Another neurotransmitter involved in causing hallucinations is acetylcholine because there is a strong relationship between the induction of hallucinations and the start of anti-cholinergics. Also diseases with Lewy Body (LB) are associated with decreased choline-acetyl-transferase (ChAT) activity. This is also found in patients with Alzheimer Disease (AD) but in diseases with LB a greater mid-frontal loss of ChAT has been found. Perry (2003) found a reduced ChAT activity in temporal and parietal lobes in patients with LBD. In patients with VH there was less than 20% activity left compared to 50% in patients without VH. In people with AD they found a more archi-cortical loss of ChAT activity, these patient have far fewer VH. The cholinergic system plays an important role in conscious awareness. A decrease in the cortical acetylcholine (Ach) levels impairs the selection of subcortical information streams, causing unselected and chaotic cortical activation, which may give rise to hallucinations.

Also, serotonin may trigger VH as lysergic acid diethyl amide and 3,4-methylenedioxy-methylamphetamine, both serotonin receptor agonists, can induce VH (Kiferle et al. 2007).

Visual perception and visual hallucinations

Visual stimuli are first projected to the primary visual cortex, where these stimuli are further processed and divided into the separate contents of a visual stimulus, like colour, space and movement. This processing can be divided into three streams. There are two main streams, one ventral stream leading to the ventral temporal lobe and one dorsal stream leading to the parietal lobe. A third stream is projecting along the superior temporal sulcus and is connected to both streams. These regions have different functional specialisations. A fMRI study with patients with Charles Bonnet syndrome (CBS) showed that for instance, hallucinations of colour, faces, textures and objects correlate with cerebral activity in ventral extrastriate visual cortex (Ffytche 1998). The content of the hallucinations reflected the functional specialisations of that particular part of the cerebral cortex. A factor analysis of phenomenological variables in 39 patients with CBS syndrome showed three symptom clusters (Santhouse 2000). These clusters could all be ascribed to one specialised cortical area. One cluster consisted of extended landscape scenes, children and figures in costume, wearing hats, which was associated with the ventral temporal lobe. The second cluster consisted of faces, which was associated with the superior temporal sulcus and the third cluster consisted of palinopsia and visual perseveration in the periphery of the visual field, which is related to the dorsal parietal lobe. Patients with PD in particular have well formed visual hallucinations, mostly people and animals, which can be related to dysfunction of the ventral temporal lobe. To our knowledge, Ozer et al. (2007) are the only authors who concluded that visual perceptive functions do not significantly differentiate between VH and non-VH PD-patients.

VH in PD and imaging

Neuropathologically, VH in PD are associated with increased LB deposition in the temporal lobe,

suggesting that VH in PD are at least partially caused by the disease itself.

Imaging studies on VH using fMRI have consistently shown increased activation of the caudate nucleus during visual input in PD patients with VH, compared to PD patients without VH (Stebbins et al. 2004). These striatal activations may possibly reflect the switching from external bottom-up stimuli to internal generated images in PD patients with VH. The cortico-basal ganglia-thalamo-cortical circuits consist of several parallel loops, regulating normal adaptive behaviour by selection of motor and non-motor behavioural responses. Some imaging studies have also shown increased activation of the frontal lobe during VH in PD (Stebbins et al 2004; Holroyd & Wooten 2006). In patients with PD, schizophrenia and CBS also an increased activation of visual association cortices was seen during the occurrence of VH (Silberschweig 1995; Kataoka 2008). These activations may be secondary phenomena following the increased frontal lobe activity. It is thought that a partially analyzed version of the input image is rapidly projected from early visual areas to the prefrontal cortex, where it activates an “initial guess”, that is back-projected to the temporal cortex to be integrated in bottom-up processing (see also Roper Peláez 2000).

Other studies did show a reduction of either activation, perfusion or metabolism in the visual association cortices during rest or visual stimulation (Stebbins et al. 2004; Matsui et al. 2006a,b; Boecker et al. 2007). In CBS, the latter may reflect reduced visual cortical processing following reduced visual input. In PD patients with VH, cortical visual processing itself seems to be impaired, as described below, which fits with the reduced activation of visual cortices.

PD patients with VH also showed, as compared to controls and non-hallucinating PD patients, grey matter volume reductions in the lingual gyrus and superior parietal lobe areas, which are both involved in higher visual processing (Ramirez-Ruiz et al 2007).

Impaired visual processing in PD patients with VH

The majority of patients with visual loss do not experience hallucinations. Hence, Ftyche (2007) argues that visual loss alone cannot explain sufficiently VH in PD patients. Nevertheless, VH in PD tend to occur in dim suboptimal visual circumstances, mostly during the evening, but are not related to wintertime darkness. A wide range of visual perceptual disturbances has been associated with VH in PD, including reduced visual acuity, contrast sensitivity, colour discrimination, visual space perception and visual object perception (Diederich et al. 1998; Holroyd et al. 2001). Relatively impaired visual processing in PD patients with VH could hypothetically lead to compensatory visual processing and internal image generation. This is comparable with VH in CBS, a condition defined by complex VH secondary to profound visual loss in cognitively normal people. Possibly this relative visual impairment leads to a higher reliance on ‘top-down’ mechanisms, whereas especially the frontal lobe seems to play a role in activating the visual cortices, releasing previously seen images, which do not correspond with the external world.

Previous own data (Meppelink et al. 2008) showed that non-demented PD patients with VH are slower in recognizing images dynamically popping-out of background noise, compared to both PD patients without VH and healthy controls.

By using selective averaging, the dynamics of change in cerebral activation patterns were investigated during the presentation of gradually revealed images. Just before, during and after pop-out, activation of occipital-temporal, inferior parietal and inferior prefrontal areas was seen in healthy controls. This is consistent with other studies investigating visual perception of images that were gradually revealed.

It was shown that PD patients with VH, compared to both PD patients without VH and healthy controls, had reduced activation of the lateral occipital-temporal cortex, several seconds before pop-

out (Meppelink et al. 2009). The lateral and ventral occipital-temporal cortices are important for visual object recognition. The fusiform gyrus, lateral occipital complex and middle temporal gyrus are involved in visual perception of a range of living and non-living objects, while the parahippocampal gyrus is predominantly involved in the perception of scenes. This finding confirmed the hypothesis that bottom-up visual processing is impaired in PD patients with VH. Importantly, this was independent of visual acuity, which was equal in all groups, or contrast sensitivity, which was similar in PD patients with and without VH. Following this early reduced activation of the lateral occipital-temporal cortex, reduced activation before pop-out of parietal and frontal regions was seen. Clinical studies have shown that PD patients have impaired object perception, compared to healthy controls (Mosimann et al. 2004). More interestingly, several studies (Barnes et al. 2003; Ramirez-Ruiz et al. 2006; Meppelink et al. 2008) have shown that non-demented PD patients with VH had more severe impairments on object perception compared to PD patients without VH, indicating a direct relationship between VH and visual processing.

Treatment of VH in PD

More than 60% of PD patients report neuropsychiatric symptoms that may antedate motor symptoms (Aarsland et al. 1999; Shiba et al. 2000). The treatment of VH in PD should include both proper physical and psychosis assessment, adequate treatment of sleeping problems, illumination and sensory stimuli and finally the treatment of the psychotic symptoms. Patient's medication should be thoroughly screened for possible psychotic side-effects (table 1).

Table 1: Medicines with VH side effects

- Anti-acidic drugs
- Antibiotics that contain beta-lactam,
- Anti-cholinergic drugs,
- Antidepressants,
- Anti-epileptics,
- Anti-Parkinson medication,
- Anti-psychotics, may as well diminish hallucinations as trigger them,
- Benzodiazepines,
- Hematopoietic growth factors (> 11% incidence of VH side-effects with erythropoietine in haemodialysis; about 67% of these remain unrecognised),
- Ophthalmic drugs (Brimonidine, Verteporfin)
- Opioids,
- Para-sympatholytic drugs,
- Sympathomimetics (beta-agonists)

Zesiewicz et al. (2006) reported 2 cases who after 3 days topiramate treatment (25 mg. BID) developed VH and other psychotic symptoms that resolved after discontinuation of topiramate. Psychotic symptoms need immediate integrative treatment with psycho-social interventions, antipsychotic medication and adjustment of anti-Parkinson medication, however leaving an adequate L-dopa dose to prevent severe off-states.

In DLB and PDD patients, reduction of choline acetyltransferase and cholinesterases were shown in cholinergic nuclei of the basal fore-brain and in cortical areas receiving afferent neurons from these nuclei. Neuropathological findings do support this hypothesis (Perry et al. 2003) as do long-term benefits of rivastigmine in demented PD patients (Poewe et al. 2006). Only rivastigmine has proven efficacy in PD patients with associated cognitive pathology (Emre et al. 2004).

In the next paragraphs we will focus in more detail on the separate steps to be taken in case of VH in PD.

Exclusion of a delirium

Hallucinations in PD patients are significantly (HR 3.42, 95% CI 1.59 – 7.38, $p=0.0002$: CALM-PD study) correlated with co-morbid illnesses in at least 5 systems. Proper assessment of inter-current physical illness, medication, electrolyte imbalance, systemic infection, hypoxaemia, and alcohol and benzodiazepine withdrawal, as well as reduction of non-essential medication are warranted especially for excluding delirium with its high death risk (Moser et al. 2003). Patients with hallucinations that are part of a superimposed medical illness are usually confused and agitated. Hallucinations in chronic patients with advanced PD mostly develop gradually, are mainly visual in content and are generally without agitation and confusion.

How to score VH in PD?

The Task Force on Rating Scales in PD of the Movement Disorder Society recommends to apply a combination of tests (Thanvi et al. 2005):

- (i) The Neuro-Psychiatric Inventory is suitable for the cognitively impaired PD population and when caregivers are involved.
- (ii) The Positive And Negative Syndrome Scale and the Brief Psychiatric Rating Scale can be used when patient is the sole informant and has intact cognitive functions.
- (iii) The Clinical Impression Scale is recommended as an additional scale to measure change and response to treatment.

In addition to these general psychopathology inventories, specific hallucination inventories can be applied.

- (a) The Queen Square Visual Hallucination Inventory is a structural interview that identified VH in 75% of PD patients and 47% of those with unclassifiable PD. Specificity for VH is 91%, sensitivity 62%; positive predictive value = 95% and negative predictive value = 48% (Williams et al. 2008).
- (b) Auditory hallucinations can be easily assessed with the Auditory Vocal Hallucination Rating Scale (AVHRS: Jenner & van de Willige 2002). AVHRS is a structured interview used to assess the number, content, frequency, duration, context, organisation and location, degree of control, emotional experience, meaning and explanation, and perceived impact of the auditory vocal hallucination. The reliability coefficient for the AVHRS, based on 92 ratings was 0.84 (weighted kappa), for life-time assessment = 0.71. Internal consistency was 0.84 (Cronbach's alpha). The AVHRS sum score was substantially associated with the PANSS total score ($r=0.60$, $p<0.01$). According to patients face validity was very good (Bartels-Velthuis et al. submitted).
- (c) Almost 60% of psychiatric patients with auditory verbal hallucinations hear as well positive voices and over 40% hear voices they experiences as useful (Jenner et al. 2008). With the Positive and Useful Voices scale (PUVI), a self-report inventory, these auditory verbal hallucinations can be assessed.
- (d) The self-report Groningen Coping with Voices Inventory (Jenner & Geelhoed-Jenner 1998) helps both to assess which coping strategies a patient uses and may also help to select alternative more effective strategies

Adjusting anti Parkinson medication

Adjustment of anti-Parkinson medication is the next step, starting with agents with the lowest anti-Parkinson efficacy. Anticholinergics, selegiline and amantadine can more likely cause confusion and psychosis with frightening hallucinations than dopamine-agonists and COMT-inhibitors (Wolters 2006).

Dopamine-agonists are often associated with non-threatening hallucinations (Wolters 2006). At present, medication withdrawal seems possible in patients in an initial stage of PD and with hallucinations that are early side effects of dopamine agonist treatment. After withdrawal, VH may disappear in some patients even for as long as years. However, VH tend to recur with progression of PD. Withdrawal of L-dopa however is contraindicated in all PD patients. Most patients experience severe worsening of their motor status and require additional anti-psychotic treatment.

Psychosocial interventions for psychotic manifestations of PD

Effectiveness of some psycho-social therapies for psychotic symptoms, Cognitive Behaviour Therapy (CBT) and Hallucination focused Integrative Treatment (HIT) have been demonstrated in randomised controlled trials (RCT) in the past decade. These interventions may increase mastery and control, as well as reduce symptoms and secondary negative emotions. Seeding doubt of unreal beliefs by use of Socratic reasoning is pivotal in both CBT and HIT. The Socratic interviewing style seeks to give as little direct advice to the patient as possible and does not focus on proving that the therapist is right and the hallucinating person is wrong. Rather it seeks to elicit suggestions for change and solutions from the hallucinating subject. The therapist helps or seduces the patient to draw his own doubt with an indirect style of disputing and testing the patient's inferences about the power of his inferences and experiences (Chadwick et al. 1996). Sentences such as: 'could it be possible that...', and have you ever considered ..., what do you think of...' have proved their effectiveness. Socratic reasoning remains the preferred style of communication with psychotic persons and is probably the most effective approach for inserting doubt about beliefs and misinterpretations.

Main aim of CBT is changing a patient's interpretation of his beliefs as powerful and malevolent (Chadwick & Birchwood 1994). Focuses of CBT are (a) attribution of external causes to internally generated ones and labelling them as just annoying symptoms, (b) contesting the power of beliefs and voices by examining their predictive power, and disobedience to command hallucinations, and (c) removing the supposed meaning of beliefs and reducing voices to annoying noise. Delusions, depression and anxiety improved significantly more on CBT than on treatment as usual (TAU). Effect size of CBT on delusions is reasonable (ES varies between 0.37 and 0.64). Unfortunately effectiveness of CBT on hallucinations appeared not significantly better than TAU.

HIT integrates several interventions with proven evidence such as selective application of both congruent and hyper-congruent motivational strategies, medication, CBT, coping training, psycho-education and rehabilitation. Coping training of patient as well as relatives is pivotal in HIT. Anxiety management, distraction and focussing are the main coping categories. The format is problem-solving family treatment applied in a directive style. Compared with TAU, HIT reduced significantly more PANSS-measured auditory hallucinations (ES = 0.71, NNT = 2) as well as depression/anxiety (NNT = 4), disorganisation (NNT = 5) and general psychopathology (NNT = 4). Additional significant improvements could be assessed in subjective burden (Jenner et al. 2004). Also, quality of life and social disabilities improved (NNT = 7). While 51% of HIT-treated patients showed more than 20% improvement from their initial status at baseline no improvements in social functions were found among control subjects, (Wiersma et al. 2004). Improvements in all domains remained upon 18 month follow-up (Jenner et al. 2006; Wiersma et al. 2004). In addition to high patient satisfaction with the program and low drop-out rates (< 10%) in all HIT studies (Jenner & van de Willige 2001; Wiersma et al. 2001,2004; Jenner 2002; Jenner et al. 2004,2006a,b), findings

also suggest that the interventions were helpful in motivating formerly medication-refusing (non-compliant) patients to accept drugs in later instances.

Treatment with antipsychotic medication

If the above mentioned disease management interventions fail proper anti-psychotic medication should be considered. (Ravina et al.: NINDS, NIMH work group 2007; Fernandez et al. 2005). First, general (typical) anti-psychotics should be avoided because of their severe motor side effects. Anti-psychotic medication is more effective in auditory hallucinations than in visual ones. Effectiveness in auditory hallucinations is in about 70% of schizophrenia patients if they are medication compliant, i.e. AVH persist in about 30% of AP-compliant patients (Johnstone et al. 1991). However, non-compliance rises from 30% in the first year to over 70% from the 2nd year onwards (Young et al. 1987). Such high non-compliance rates are common among patient with various chronic illnesses. Goetz et al. (2008) studied in a prospective natural design the potential stabilizing effects of anti-psychotic medication on the progressive deterioration in hallucinations in PD. It appeared that early treatment of VH at the point when they occur positively influenced long-term progression and delayed deterioration towards loss of insight or florid psychosis. However, data of several other studies indicate that some anti-psychotics such as thioridazine, aripiprazole, olanzapine, quetiapine and risperidone may worsen motor symptoms in PD patients to such extent that they should therefore be avoided. Also, olanzapine and risperidone may cause severe sedation, and an increased risk on strokes in the elderly. Olanzapine can worsen cognition and hyperglycaemia too. So, the only really effective AP is clozapine. Recurrent and rebound psychosis may occur when medication is stopped in patients in remission (Fernandez et al. 2000). Continuous awareness of akinetic crisis and a malignant neuroleptic syndrome is warranted. Anti-psychotics should be started at low dose. Screening on (prolongation of) QT-interval with baseline ECG and periodic ECG monitoring are needed as is regular screening on diabetes type II.

Clozapine and if not tolerated also quetiapine are the only suitable anti-psychotics in PD. Klein et al. (2003) monitored the long-term effect of clozapine administered to PD patients with psychosis. No correlation was found between age, gender, duration and severity of disease (Yahr score), presence of dementia, and the response to clozapine. The Movement Disorders Task Force (2007) concluded that clozapine is efficacious in the short term, but has insufficient data on long-term. Efficacy and safety of quetiapine was considered insufficient. Olanzapine was considered to have insufficient evidence for its efficacy and unacceptable risk of motor deterioration, aripiprazol can cause severe worsening of motor function too. The Task Force recommended specialized monitoring at clozapine doses of less than 50mg/day and close monitoring of agranulocytosis (Rudolf 1997).

Treatment with cholinesterase inhibitors

Acetylcholinesterase inhibitors, donepezil and rivastigmine may improve cognitive functions as well as behavioural and psychotic symptoms (Bergman 2002; Bullock 2002). "Rivastigmine was found beneficial for patients with PD-associated dementia regardless of the presence or absence of VH, but the treatment effect was most marked in patients who had VH" (Burn et al. 2006). In a review article Poewe et al. (2008) conclude that compared to placebo rivastigmine has significant better results on cognition, ADL, and behaviour (Emre et al. 2004), effects of donepezil are equivocal on cognition (Aarsland et al. 2002: positive, Ravina et al. 2005: not positive), and no significantly better results on behaviour (Aarsland et al. 2002; Ravina et al. 2005). Effects of rivastigmine have been extensively studied in a 24-week double-blind placebo-controlled study that stratified PD-patients according to the presence of hallucinations at baseline (Burn et al. 2006). Another study with same duration (Emre et al. 2004) compared placebo with 3 to 12 mg. of rivastigmine daily. Both studies measured primary effects with Alzheimer's Disease Assessment Scale cognitive subscale (ADAS-cog) and Alzheimer's Disease Cooperative Study-Clinician's Global Impression of Change (ADCS-CGIC). Studies applied different instruments for measuring

secondary effects. These varied from behavioural symptoms and daily living to verbal fluency, Mini Mental State, Ten Point-Clock Drawing test. These studies allow for the conclusions that rivastigmine (1) is associated with moderate improvements in dementia associated with Parkinson's disease, in both visual and non-visual hallucinators; (2) effects on ADAS-cog and -CGIC are comparable, but rivastigmine-placebo effect tends to be larger in visual hallucinators; (3) provides benefits on all secondary measures; (4) is associated with higher rates of nausea, vomiting, and tremor, but adverse events were less marked in visual hallucinators who seem to have greater therapeutic benefit from rivastigmine than non-hallucinators.

Conclusions

The role attributed to VH in PD has changed immensely over the last decade. From a mere medication side-effect, VH have been claimed a diagnostic hallmark of synucleinopathies.

PD patients with VH show an impaired occipital, parietal and inferior frontal cortex activation, when trying to recognise images popping out of at random noise, as compared with HC and PD patients without VH. This is confirmed by several imaging studies, showing the same deficit in visual bottom-up processing. Other data also showed an activation of the inferior frontal cortex, during the existence of VH. This means that the inferior frontal cortex seems to play a major role in the generation of 'internally existing' images, not related to the external world.

So, overall VH seem to arise from an impaired bottom-up processing. This processing can be negatively influenced by a dopaminergic overstimulation or a cholinergic understimulation. Especially the cholinergic underactivation is related to an attentional deficit, which is related to a higher risk on visual hallucinations.

This concept leads primarily to measures trying to improve the visual perception, for instance. by improving adequate visual acuity, and arranging adequate light in the direct environment in combination with psychosocial interventions (e.g. CBT and HIT), and thereafter to therapies improving the cholinergic activation, finally supported by measures trying to reduce dopaminergic overactivation, for instance. partial reduction of the dopaminomimetics and the prescription of atypical antipsychotics.

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