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Current Awareness Bulletin – Neurology
June and July 2015

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Cochrane Systematic Reviews

New Reviews – June 2015
Lacosamide add-on therapy for partial epilepsy

Updated Reviews – June 2015
Corticosteroids including ACTH for childhood epilepsy other than epileptic spasms

New Reviews – April 2015
Dimethyl fumarate for multiple sclerosis

Withdrawn Reviews – June 2015
Anticholinergics for urinary symptoms in multiple sclerosis

New from Up To Date

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Neurology related topics
Corticobasal Degeneration Table of Contents:

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Corticobasal Degeneration Journal Articles:

1. Corticobasal degeneration. A tauopathy which is far more than a movement disorder
   **Citation:** Pratique Neurologique - FMC, February 2015, vol./is. 6/1(5-11), 1878-7762 (01 Feb 2015)
   **Author(s):** Sellal F., Lannes B., Mohr M.
   **Language:** French
   **Abstract:** Cortico-basal degeneration (CBD) is classified among focal atrophies. Pathologically, it is precisely defined by the presence of neuronal and glial cortico-striatal lesions, immunostained by antibodies specific for tau protein. While the disease was initially described in patients presenting with a predominantly motor syndrome (asymmetric rigidity or dystonia, focal myoclonus) and most often parietal cortical symptoms (unilateral apraxia, sensory disorders, alien hand syndrome), it appears to be very proteiform. There are many sources of anatomo-clinical discrepancies. Thus, it is wiser to coin the name 'corticobasal syndrome' to design the initially described clinical syndrome, and to reserve the term CBD for neuropathologically confirmed cases. The new diagnostic criteria for probable or possible CBD are presented.
   **Publication type:** Journal: Article
   **Source:** EMBASE

2. Criteria for the diagnosis of corticobasal degeneration
   **Citation:** Brain and Nerve, April 2015, vol./is. 67/4(513-523), 1881-6096 (01 Apr 2015)
   **Author(s):** Shimohata T., Alba I., Nishizawa M.
Abstract: Corticobasal degeneration (CBD) is a distinct neurodegenerative disorder characterized by widespread neuronal and glial accumulation of abnormally phosphorylated tau protein. Patients with CBD often present with corticobasal syndrome (CBS) showing impairment of the motor system, cognition, or both. Several studies demonstrate that they may also present with progressive supranuclear palsy syndrome (PSPS), aphasia, Alzheimer disease-like dementia, or behavioral changes, suggesting that CBS is merely one of the presenting phenotypes of CBD. Accurate diagnosis is important for future clinical trials using drugs aimed at modifying the underlying tau pathology. Although previous CBD diagnostic criteria reflected only CBS, Armstrong et al. proposed new diagnostic criteria for CBD in 2013 (Armstrong's criteria). The new criteria include 4 CBD phenotypes, including CBS, frontal behavioral-spatial syndrome (FBS), nonfluent/agrammatic variant of primary progressive aphasia (naPPA), and PSPS. These phenotypes were combined to create 2 sets of criteria: specific clinical research criteria for probable CBD (cr-CBD) and broader criteria for possible CBD that are more inclusive but have a higher probability of detecting other tau-based pathologies (p-CBD). However, two recent studies revealed that the sensitivity and specificity of these criteria were insufficient. Further refinement of the criteria is needed via biomarker research with prospective study designs.

Language: English
Citation: Neurology Asia, 2015, vol./is. 20/1(23-27), 1823-6138 (2015)
Publication type: Journal: Review
Source: EMBASE

3. Parkinsonism in corticobasal syndrome may not be primarily due to presynaptic dopaminergic deficiency
Citation: Neurology Asia, 2015, vol./is. 20/1(23-27), 1823-6138 (2015)
Author(s): Yun J.Y., Barron D.S., Tantiwongkosi B., Fox P.
Language: English
Abstract: The clinical features of corticobasal degeneration (CBD) are quite asymmetric. The severity of clinical symptoms and dopamine transporter (DAT) bindings were less correlated compared to other parkinsonisms, suggesting that presynaptic nigrostriatal dopaminergic dysfunction may not explain extrapyramidal manifestations in CBD. Therefore we wanted to reexamine asymmetry and severity between DAT imaging and clinical findings. We studied patients meeting the diagnostic criteria for CBD based on clinical features. We collected their clinical information and imaging retrospectively. Seven patients were enrolled and all had asymmetric rigidity, bradykinesia and unilateral limb dystonia. These symptoms did not improve with levodopa. All patients showed symptoms bilaterally in the last visit, but asymmetry of clinical symptoms was remarkable at the time of DAT imaging. The DAT bindings were decreased in six subjects. However, one patient showed normal DAT binding. Four patients had a more evident DAT reduction on the side contralateral to the more clinically affected side, however, two patients had a more prominent reduction on the ipsilateral side. The symptoms that we regard as parkinsonian features in CBD are not only explained by presynaptic dopaminergic dysfunction. Our findings suggest that postsynaptic dopaminergic or nondopaminergic systems may play a major role in parkinsonian symptoms in corticobasal syndrome.

Publication type: Journal: Article
Source: EMBASE

4. Patterns of gray matter atrophy in atypical parkinsonism syndromes: A VBM meta-analysis
Citation: Brain and Behavior, June 2015, vol./is. 5/6(1-10), 2162-3279 (01 Jun 2015)
Author(s): Yu F., Barron D.S., Tantiwongkosi B., Fox P.
Language: English
Abstract: Background and Purpose: Accurate diagnosis of Atypical Parkinsonian Syndromes (APS) is important due to differences in prognosis and management, but remains a challenge in the clinical setting. The purpose of our meta-analysis was to identify characteristic patterns of gray matter atrophy in Corticobasal Degeneration (CBD), Progressive Supranuclear Palsy (PSP), Multisystem-Atrophy Parkinsonian type (MSA-P), and Idiopathic Parkinson's Disease (IPD). Materials and Methods: Whole-brain meta-analysis was performed on 39 published voxel-based morphometry (VBM) articles (consisting of 404 IPD, 87 MSA-P, 165 CBD, and 176 PSP subjects) using the modified Anatomic Likelihood Estimation method. Based on these results, contrast analyses were then utilized to determine areas of atrophy shared by as well as unique to each disorder. Results: CBD was characterized by asymmetric gray matter atrophy in multiple cortical regions, while the thalamus-midbrain and insula were predominantly involved in PSP. The striatum and superior cerebellum were affected in MSA-P, while IPD demonstrated an anterior cerebral pattern. Although there was a mild overlap among PSP, CBD, and MSA-P,
significant regions of atrophy unique to each disorder were identified, including (1) the superior parietal lobule in CBD (2) putamen in MSA-P (3) insula and medial dorsal nucleus in PSP. Conclusion: Our results suggest that there are characteristic patterns of atrophy in APS. Guided by these findings, future studies on the individual subject level may lead to the development of robust imaging biomarkers.

**Publication type:** Journal: Article  
**Source:** EMBASE

5. The feasibility of white matter volume reduction analysis using SPM8 plus DARTEL for the diagnosis of patients with clinically diagnosed corticobasal syndrome and Richardson's syndrome  
**Citation:** NeuroImage: Clinical, 2015, vol./is. 7/(605-610), 2213-1582 (2015)  
**Author(s):** Sakurai K., Imabayashi E., Tokumaru A.M., Hasebe S., Murayama S., Morimoto S., Kanemaru K., Takao M., Shibamoto Y., Matsukawa N.  
**Language:** English  
**Abstract:** Purpose Diagnosing corticobasal degeneration (CBD) and progressive supranuclear palsy (PSP) is often difficult due to the wide variety of symptoms and overlaps in the similar clinical courses and neurological findings. The purpose of this study was to evaluate the utility of white matter (WM) atrophy for the diagnosis of patients with clinically diagnosed CBD (corticobasal syndrome, CBS) and PSP (Richardson's syndrome, RS). Methods We randomly divided the 3D T1-weighted MR images of 18 CBS patients, 33 RS patients, and 32 age-matched controls into two groups. We obtained segmented WM images in the first group using Voxel-based specific regional analysis system for Alzheimer's disease (VSRAD) based on statistical parametric mapping (SPM) 8 plus diffeomorphic anatomical registration through exponentiated Lie algebra. A target volume of interest (VOI) for disease-specific atrophy was subsequently determined in this group using SPM8 group analyses of WM atrophy between patients groups and controls. We then evaluated the utility of these VOIs for diagnosing CBS and RS patients in the second group. Z score values in these VOIs were used as the determinant in receiver operating characteristic (ROC) analyses. Results Specific target VOIs were determined in the bilateral frontal subcortical WM for CBS and in the midbrain tegmentum for RS. In ROC analyses, the target VOIs of CBS and RS compared to those of controls exhibited an area under curve (AUC) of 0.99 and 0.84, respectively, which indicated an adequate diagnostic power. The VOI of CBS revealed a higher AUC than that of RS for differentiating between CBS and RS (AUC, 0.75 vs 0.53). Conclusions Bilateral frontal WM volume reduction demonstrated a higher power for differentiating CBS from RS. This VOI analysis is useful for clinically diagnosing CBS and RS.

**Publication type:** Journal: Article  
**Source:** EMBASE

**Epilepsy Table of Contents:**

1. A bibliometric study of scientific literature on the dietary therapies for epilepsy in Scopus  
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8. The comorbid relationship between migraine and epilepsy: A systematic review and meta-analysis
Epilepsy Journal Articles:

1. A bibliometric study of scientific literature on the dietary therapies for epilepsy in Scopus
Citation: Nutritional Neuroscience, July 2015, vol./is. 18/5(201-209), 1028-415X;1476-8305 (01 Jul 2015)
Author(s): Morandi G., Guido D., Tagliabue A.
Language: English
Abstract: Objectives: The aim of this study was to provide a descriptive overview of the impact and production of literature on dietary therapies for epilepsy and perform a citation analysis of the related research articles. Methods: We searched for 'ketogenic OR low-glycemic OR medium chain OR modified Atkins in TITLE AND epilepsy' in Title/Abstract/Keyword in Scopus database. Results: A total of 661 references were retrieved, 80% had been published after 2000s, 87% were published in English, and 39% of the publications were published in nine journals. The majority (76.3%) of research articles describe the clinical application of the dietary therapies regarding the classical ketogenic diet (80%), followed by the modified Atkins diet (11.5%), medium chain triglyceride diet (6.4%), and low glycemic index treatment (2.0%); the remaining are basic science studies on the mechanisms of action. The citation analysis revealed that the latter have the highest percentage variation in citation per publication across the years. Concerning the article cohorts, the greatest number of citations per publication was in 1998. Discussion: The overview of the literature on the dietary therapy of epilepsy evidences a growing interest in the field with a striking prevalence of clinical over basic science studies. The most cited clinical studies have validated the efficacy of the dietary therapies; the few studies on the mechanisms of action received a great number of citations. Bibliometric analysis measuring the trends and the impact of the scientific literature would help researchers to a best knowledge of this specific topic.
Publication type: Journal: Review
Source: EMBASE

2. Depression and anxiety during pregnancy and the postpartum period in women with epilepsy: A review of frequency, risks and recommendations for treatment
Citation: Seizure, May 2015, vol./is. 28/(33-39), 1059-1311;1532-2688 (01 May 2015)
Author(s): H. Bjork M., Veiby G., A. Engelsen B., Gilhus N.E.
Language: English
Abstract: Purpose To review available data and provide treatment recommendations concerning peripartum depression, anxiety and fear of birth in women with epilepsy (WWE). Method The PubMed, the LactMed, the DART and the Cochrane database were searched for original articles concerning psychiatric disease in the peripartum period in WWE. Results Point prevalence of depression from 2nd trimester to 6 months postpartum ranged from 16 to 35% in women with epilepsy compared to 9-12% in controls. The highest estimates were found early in pregnancy and in the perinatal period. Anxiety symptoms 6 months postpartum were reported by 10 and 5%, respectively. Fear of birth symptoms were increased in primiparous WWE compared to controls. Previous psychiatric disease, sexual/physical abuse, antiepileptic drug (AED) polytherapy, and high seizure frequency emerged as strong risk factors. Depressed WWE rarely used antidepressive medication during pregnancy. No evidence was available concerning treatment effects or impact on the developing child. Conclusion Peripartum depression is frequent in WWE and seldom medically treated. Health personnel should screen WWE for psychiatric disease and risk factors during pre-pregnancy planning, pregnancy and postpartum follow up. Treatment decisions should rely on efficacy and safety data in peripartum patients without epilepsy and non-pregnant people with epilepsy. Consequences of in utero exposure to AED therapy in combination with antidepressants are not known, and non-pharmacological treatment should be tried first.
Publication type: Journal: Review
Source: EMBASE

3. Future of seizure prediction and intervention: Closing the loop
Citation: Journal of Clinical Neurophysiology, June 2015, vol./is. 32/3(194-206), 0736-0258;1537-1603 (03 Jun 2015)
Language: English
Abstract: The ultimate goal of epilepsy therapies is to provide seizure control for all patients while eliminating side effects. Improved specificity of intervention through on-demand approaches may overcome many of the limitations of
current intervention strategies. This article reviews the progress in seizure prediction and detection, potential new therapies to provide improved specificity, and devices to achieve these ends. Specifically, we discuss (1) potential signal modalities and algorithms for seizure detection and prediction, (2) closed-loop intervention approaches, and (3) hardware for implementing these algorithms and interventions. Seizure prediction and therapies maximize efficacy, whereas minimizing side effects through improved specificity may represent the future of epilepsy treatments.

**Publication type:** Journal: Review  
**Source:** EMBASE

### 4. Interactions between hormones and epilepsy

**Citation:** Seizure, May 2015, vol./is. 28/(3-11), 1059-1311;1532-2688 (01 May 2015)  
**Author(s):** Tauboll E., Sveberg L., Svalheim S.  
**Language:** English  
**Abstract:** There is a complex, bidirectional interdependence between sex steroid hormones and epilepsy; hormones affect seizures, while seizures affect hormones thereby disturbing reproductive endocrine function. Both female and male sex steroid hormones influence brain excitability. For the female sex steroid hormones, progesterone and its metabolites are anticonvulsant, while estrogens are mainly proconvulsant. The monthly fluctuations in hormone levels of estrogen and progesterone are the basis for catamenial epilepsy described elsewhere in this issue. Androgens are mainly anticonvulsant, but the effects are more varied, probably because of its metabolism to, among others, estradiol. The mechanisms for the effects of sex steroid hormones on brain excitability are related to both classical, intracellularly mediated effects, and non-classical membrane effects due to binding to membrane receptors. The latter are considered the most important in relation to epilepsy. The different sex steroids can also be further metabolized within the brain to different neurosteroids, which are even more potent with regard to their effect on excitability. Estrogens potentiate glutamate responses, primarily by potentiating NMDA receptor activity, but also by affecting GABA-ergic mechanisms and altering brain morphology by increasing dendritic spine density. Progesterone and its main metabolite 5alpha-pregnan-3alpha-ol-20-one (3alpha-5alpha-THP) act mainly to enhance postsynaptic GABA-ergic activity, while androgens enhance GABA-activated currents. Seizures and epileptic discharges also affect sex steroid hormones. There are close anatomical connections between the temporolimbic system and the hypothalamus controlling the endocrine system. Several studies have shown that epileptic activity, especially mediated through the amygdala, alters reproductive function, including reduced ovarian cyclicity in females and altered sex steroid hormone levels in both genders. Furthermore, there is an asymmetric activation of the hypothalamus with unilateral amygdala seizures. This may, again, be the basis for the occurrence of different reproductive endocrine disorders described for patients with left-sided or right-sided temporal lobe epilepsy.

**Publication type:** Journal: Review  
**Source:** EMBASE

### 5. Management of epilepsy during pregnancy: Evidence-based strategies

**Citation:** Future Neurology, March 2015, vol./is. 10/2(161-176), 1479-6708;1748-6971 (01 Mar 2015)  
**Author(s):** Putta S., Pennell P.B.  
**Language:** English  
**Abstract:** Child-bearing years are often the most precarious management period in the life of a woman with epilepsy. This article reviews the results of many different studies with findings that enable the healthcare team to make confident decisions and recommendations during these critical periods. Preconceptional planning, effective contraception and folic acid supplementation are important fundamentals in preparation for pregnancy. There is growing evidence to avoid valproic acid use during the child-bearing years. Emerging data on congenital malformations and neurocognitive outcomes are available for some of the second-generation antiepileptic drugs and appear reassuring for lamotrigine and levetiracetam. Also reviewed are the benefits of postpartum drug tapers and favorable breastfeeding facts. Counseling the mother and her family on medication choices enables the healthcare team to implement informed decisions that are beneficial for the mother and child.

**Publication type:** Journal: Review  
**Source:** EMBASE

### 6. Neurological and neuropsychiatric aspects of tuberous sclerosis complex

**Citation:** The Lancet Neurology, July 2015, vol./is. 14/7(733-745), 1474-4422;1474-4465 (01 Jul 2015)  
**Author(s):** Curatolo P., Moavero R., de Vries P.J.  
**Language:** English
Abstract: Tuberous sclerosis (also known as tuberous sclerosis complex [TSC]) is a multisystem genetic disorder that affects almost every organ in the body. Mutations in the TSC1 or TSC2 genes lead to disruption of the TSC1-TSC2 intracellular protein complex, causing overactivation of the mammalian target of rapamycin (mTOR) protein complex. The surveillance and management guidelines and clinical criteria for tuberous sclerosis were revised in 2012, and mTOR inhibitors are now recommended as treatment options for subependymal giant cell astrocytomas and renal angiomyolipomas-two common features of the disease. However, most morbidity and mortality caused by tuberous sclerosis is associated with neurological and neuropsychiatric manifestations. Treatment of epilepsy associated with tuberous sclerosis remains a major challenge, with more than 60% of patients having ongoing seizures. Tuberous sclerosis-associated neuropsychiatric disorders (TAND) are multilevel and occur in most individuals with the disorder, but are rarely assessed and treated. Clinical trials of mTOR inhibitors to treat seizures and TAND are underway. Management of the neurological and neuropsychiatric manifestations of the disorder should be coordinated with treatment of other organ systems. In view of the age-related expression of manifestations from infancy to adulthood, continuity of clinical care and ongoing monitoring is paramount, and particular attention is needed to plan transition of patient care from childhood to adult services.

Publication type: Journal: Review
Source: EMBASE

7. Role of multiple-scale modeling of epilepsy in seizure forecasting
Citation: Journal of Clinical Neurophysiology, June 2015, vol./is. 32/3(220-226), 0736-0258;1537-1603 (03 Jun 2015)
Author(s): Kuhlmann L., Grayden D.B., Wendling F., Schiff S.J.
Language: English

Abstract: Over the past three decades, a number of seizure prediction, or forecasting, methods have been developed. Although major achievements were accomplished regarding the statistical evaluation of proposed algorithms, it is recognized that further progress is still necessary for clinical application in patients. The lack of physiological motivation can partly explain this limitation. Therefore, a natural question is raised: can computational models of epilepsy be used to improve these methods? Here, we review the literature on the multiple-scale neural modeling of epilepsy and the use of such models to infer physiologic changes underlying epilepsy and epileptic seizures. The authors argue how these methods can be applied to advance the state-of-the-art in seizure forecasting.

Publication type: Journal: Review
Source: EMBASE

8. The comorbid relationship between migraine and epilepsy: A systematic review and meta-analysis
Citation: European Journal of Neurology, July 2015, vol./is. 22/7(1038-1047), 1351-5101;1468-1331 (01 Jul 2015)
Author(s): Keezer M.R., Bauer P.R., Ferrari M.D., Sander J.W.
Language: English

Abstract: A number of studies have suggested a pathophysiologic link between migraine and epilepsy. Our aim was to examine the relative lifetime prevalence of migraine in people with epilepsy (PWE) as well as that of epilepsy in migraineurs. We carried out a systematic review, searching five electronic databases, specified bibliographies and conference abstracts in order to identify population-based studies that measured the lifetime co-prevalence of migraine and epilepsy. Two reviewers independently screened all titles and abstracts, carried out a risk of bias assessment and extracted the data. Meta-analyses were carried out using random effects models. Of the 3640 abstracts and titles screened, we identified 10 eligible studies encompassing a total of 1 548 967 subjects. Few of the studies used validated case ascertainment tools and there were inconsistent attempts to control for confounding. There was an overall 52% increase in the prevalence of migraine among PWE versus those without epilepsy [PR: 1.52 (95% CI: 1.29, 1.79)]. There was an overall 79% increase in the prevalence of epilepsy among migraineurs versus those without migraine [PR: 1.79 (95% CI: 1.43, 2.25)]. Subgroup analyses revealed that the method of ascertaining the epilepsy or migraine status of subjects was an important source of inter-study heterogeneity. Additional high quality primary studies are required, ones that use validated and accurate methods of case ascertainment as well as control for potential confounders.

Publication type: Journal: Review
Source: EMBASE

Author(s): Soltesz, Ivan, Alger, Bradley E, Kano, Masanobu, Lee, Sang-Hun, Lovinger, David M, Ohno-Shosaku, Takako,
Watanabe, Masahiko

Abstract: Endocannabinoids are lipid-derived messengers, and both their synthesis and breakdown are under tight spatiotemporal regulation. As retrograde signalling molecules, endocannabinoids are synthesized postsynaptically but activate presynaptic cannabinoid receptor 1 (CB1) receptors to inhibit neurotransmitter release. In turn, CB1-expressing inhibitory and excitatory synapses act as strategically placed control points for activity-dependent regulation of dynamically changing normal and pathological oscillatory network activity. Here, we highlight emerging principles of cannabinoid circuit control and plasticity, and discuss their relevance for epilepsy and related comorbidities. New insights into cannabinoid signalling may facilitate the translation of the recent interest in cannabis-related substances as antiseizure medications to evidence-based treatment strategies.

Source: Medline

Motor Neurone Disease Table of Contents:

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2. Disease mechanisms and therapeutic approaches in spinal muscular atrophy

3. Evaluation and Management of Amyotrophic Lateral Sclerosis

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6. The critical role of membralin in postnatal motor neuron survival and disease

7. What's in the literature?

Motor Neurone Disease Journal Articles:

1. Autonomic system and amyotrophic lateral sclerosis
   Citation: Muscle and Nerve, May 2015, vol./is. 51/5(676-679), 0148-639X;1097-4598 (01 May 2015)
   Author(s): Piccione E.A., Sletten D.M., Staff N.P., Low P.A.
   Language: English
   Abstract: Introduction: The aim of this study is to characterize autonomic impairment in motor neuron disease. Methods: Neurological evaluations and autonomic testing were analyzed retrospectively in 132 patients: 86 classic amyotrophic lateral sclerosis (ALS), 36 lower motor neuron (LMN), and 10 upper motor neuron (UMN) predominant disease. Results: One-third of patients were symptomatic; urinary urgency and constipation were the most frequent symptoms. Increased Composite Autonomic Severity Score (CASS) was present in 75% with mild impairment (CASS 1-3) in 85% and moderate (CASS 4-7) in 15%. The frequencies of testing abnormalities were: sudomotor 46%, cardiovagal 50%, and adrenergic 14%. The UMN group had significantly higher median CASS scores than the classic ALS (P=0.021) and LMN group (P=0.018). Conclusions: We found predominantly mild autonomic impairment in ALS patients, with mostly cardiovagal and sudomotor involvement. Moderate autonomic failure occurred in 1 of 7 patients, especially those with an UMN presentation. Patients with selective corticospinal tract involvement may have more impairment of autonomic pathways.
   Publication Type: Journal: Article
   Source: EMBASE

2. Disease mechanisms and therapeutic approaches in spinal muscular atrophy
   Citation: Journal of Neuroscience, 2015, vol./is. 35/23(8691-8700), 0270-6474;1529-2401 (2015)
   Author(s): Tisdale S., Pellizzoni L.
Abstract: Motor neuron diseases are neurological disorders characterized primarily by the degeneration of spinal motor neurons, skeletal muscle atrophy, and debilitating and often fatal motor dysfunction. Spinal muscular atrophy (SMA) is an autosomal-recessive motor neuron disease of high incidence and severity and the most common genetic cause of infant mortality. SMA is caused by homozygous mutations in the survival motor neuron 1 (SMN1) gene and retention of at least one copy of the hypomorphic gene paralog SMN2. Early studies established a loss-of-function disease mechanism involving ubiquitous SMN deficiency and suggested SMN upregulation as a possible therapeutic approach. In recent years, greater knowledge of the central role of SMN in RNA processing combined with deep characterization of animal models of SMA has significantly advanced our understanding of the cellular and molecular basis of the disease. SMA is emerging as an RNA disease not limited to motor neurons, but one that involves dysfunction of motor circuits that comprise multiple neuronal subpopulations and possibly other cell types. Advances in SMA research have also led to the development of several potential therapeutics shown to be effective in animal models of SMA that are now in clinical trials. These agents offer unprecedented promise for the treatment of this still incurable neurodegenerative disease.
features of upper and lower motor neuron dysfunction in at least one body region, progressing over a 6 month follow-up period; or muscle wasting and weakness for at least 6 months. All patients underwent threshold tracking TMS at recruitment (index test), with application of the reference standard, the Awaji criteria, to differentiate patients with ALS from those with non-ALS disorders. The investigators who did the index test were masked to the results of the reference test and all other investigations. The primary outcome measures were the sensitivity and specificity of TMS in differentiating ALS from non-ALS disorders; these measures were derived from receiver operator curve analysis. Findings: Between Jan 1, 2010, and March 1, 2014, we screened 333 patients; 281 met our inclusion criteria. We eventually diagnosed 209 patients with ALS and 68 with non-ALS disorders; the diagnosis of four patients was inconclusive. The threshold tracking TMS technique differentiated ALS from non-ALS disorders with a sensitivity of 73.21% (95% CI 66.66-79.08) and specificity of 80.88% (69.53-89.40) at an early stage in the disease. All patients tolerated the study well, and we did not record any adverse events from performance of the index test. Interpretation: The threshold tracking TMS technique reliably distinguishes ALS from non-ALS disorders and, if these findings are replicated in larger studies, could represent a useful diagnostic investigation when combined with the Awaji criteria to prove upper motor neuron dysfunction at early stages of ALS. Funding: Motor Neuron Disease Research Institute of Australia, National Health and Medical Research Council of Australia, and Pfizer.

Publication Type: Journal: Article
Source: EMBASE

6. The critical role of membralin in postnatal motor neuron survival and disease
Citation: eLife, May 2015, vol./is. 4/MAY, 2050-084X (15 May 2015)
Language: English
Abstract: Hitherto, membralin has been a protein of unknown function. Here, we show that membralin mutant mice manifest a severe and early-onset motor neuron disease in an autosomal recessive manner, dying by postnatal day 5-6. Selective death of lower motor neurons, including those innervating the limbs, intercostal muscles, and diaphragm, are predominantly responsible for this fatal phenotype. Neural expression of a membralin transgene completely rescues membralin mutant mice. Mechanistically, we show that membralin interacts with Erll2, an endoplasmic reticulum (ER) membrane protein that is located in lipid rafts and known to be important in ER-associated protein degradation (ERAD). Accordingly, the degradation rate of ERAD substrates is attenuated in cells lacking membralin. Membralin mutations or deficiency in mouse models induce ER stress, rendering neurons more vulnerable to cell death. Our study reveals a critical role of membralin in motor neuron survival and suggests a novel mechanism for early-onset motor neuron disease.
Publication Type: Journal: Article
Source: EMBASE
Full Text: Available from Highwire Press in eLife

7. What's in the literature?
Citation: Journal of Clinical Neuromuscular Disease, June 2015, vol./is. 16/4(229-238), 1522-0443;1537-1611 (06 Jun 2015)
Author(s): Bromberg M.B., Lacomis D., Silvestri N.J., Wolfe G.I.
Language: English
Abstract: In this issue, we review new information related to amyotrophic lateral sclerosis, diagnostic testing practices, differences in clinical management between patients seen in multidisciplinary and regular clinics, and managing end-of-life care issues. There is new information on genes and genetic risk factors and environmental risk factors. There are 2 other forms of motor neuron disease, progressive muscular atrophy, and spinal muscular atrophy that are also considered. Inflammatory neuropathies are important to identify as they can be treated. Ultrasound is being applied to the diagnosis of chronic inflammatory demyelinating polyradiculoneuropathy, but its utility is more likely supportive than as a stand-alone test. There is some evidence that follow-up nerve conduction studies can reveal patients with chronic inflammatory demyelinating polyradiculoneuropathy who might relapse if intravenous immunoglobulin is stopped. The spectrum of inflammatory neuropathies is broad and some may have focal pathology at the node of Ranvier, and the term "nodopathies" has been proposed to highlight this important region of the nerve. The diagnosis of hereditary neuropathies relies on gene testing, and
data on the frequency of particular mutations show the utility of initial testing for 4 genes. Chemotherapeutic drugs can be toxic to nerves, and the incidence of neuropathies from bortezomib is discussed. The risk of development of diabetes mellitus in patients with myasthenia gravis (MG) is reviewed as is the risk of development of MG after thymectomy in patients who are asymptomatic preoperatively. A vaccine to "cure" MG has been tested in animal models. Recent work in Oxford has demonstrated direct evidence that antibodies from patients with Lambert-Eaton myasthenic syndrome acts directly on P/Q-type voltage-gated calcium channels to inhibit exocytosis of synaptic vesicles. The clinical and pathological features of myopathy associated with mutations in MATR-3 are reviewed. The natural history of myotonic dystrophy type 1 (DM1) is discussed as are potential therapies to treat myotonia in a number of disorders.

**Publication Type:** Journal: Review

**Source:** EMBASE

**Multiple Sclerosis Table of Contents:**

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2. Disease-modifying therapy for multiple sclerosis
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4. Exercise in the management of persons with multiple sclerosis
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6. Novel and imminently emerging treatments in relapsing-remitting multiple sclerosis
7. Reducing falls and improving mobility in multiple sclerosis
8. Spinal cord MRI in multiple sclerosis-diagnostic, prognostic and clinical value
9. Targeted clinical audits immediately following the establishment of clinical practice guidelines for multiple sclerosis in 17 neurology departments: A pragmatic and collaborative study

**Multiple Sclerosis Journal Articles:**

1. **Classification, diagnosis, and differential diagnosis of multiple sclerosis**
   **Citation:** Current Opinion in Neurology, June 2015, vol./is. 28/3(193-205), 1350-7540;1473-6551 (06 Jun 2015)
   **Author(s):** Sand I.K.
   **Language:** English
   **Abstract:** The increasing availability of effective therapies for multiple sclerosis as well as research demonstrating the benefits of early treatment highlights the importance of expedient and accurate multiple sclerosis diagnosis. This review will discuss the classification, diagnosis, and differential diagnosis of multiple sclerosis. Recent findings An international panel of multiple sclerosis experts, the MS Phenotype Group, recently revised the multiple sclerosis phenotypic classifications and published their recommendations in 2014. Recent research developments have helped improve the accuracy of multiple sclerosis diagnosis, especially with regard to differentiating multiple sclerosis from neuromyelitis optica spectrum disorders. Summary Current multiple sclerosis phenotypic classifications include relapsing-remitting multiple sclerosis, clinically isolated syndrome, radiologically isolated syndrome, primary-progressive multiple sclerosis, and secondary-progressive multiple sclerosis. The McDonald 2010 diagnostic criteria provide formal guidelines for the diagnosis of relapsing-remitting multiple sclerosis and primary-progressive multiple sclerosis. These require demonstration of dissemination in space and time, with consideration given to both clinical findings and imaging data. The criteria also require that there exist no better
explanation for the patient's presentation. The clinical history, examination, and MRI should be most consistent with multiple sclerosis, including the presence of features typical for the disease as well as the absence of features that suggest an alternative cause, for a diagnosis of multiple sclerosis to be proposed.

Publication Type: Journal: Review
Source: EMBASE
Full Text: Available from Ovid in Current Opinion in Neurology

2. Disease-modifying therapy for multiple sclerosis

Citation: Future Neurology, May 2015, vol./is. 10/3(253-279), 1479-6708;1748-6971 (01 May 2015)
Author(s): Klineova S., Mitiku N., Miller A.E.
Language: English
Abstract: Remarkable expansion of new diagnostic criteria and disease-modifying treatments for multiple sclerosis has occurred in the last two decades. Revision of diagnostic criteria and characterization of disease course has allowed earlier diagnosis and better characterization of individual patients. With the current treatment armamentarium in the USA offering 11 agents, patients can now benefit from increasingly individualized therapy. The therapeutic decision-making process has become more complex, with the availability of multiple medications. Relative efficacy, potentially severe adverse events, tolerability issues and patient's preferences must now all be considered so that increasingly disease management more frequently involves physicians with multiple sclerosis subspecialty expertise. This article aims to provide a clinically oriented and concise review of currently available, as well as emerging, disease-modifying treatment therapies in multiple sclerosis.

Publication Type: Journal: Review
Source: EMBASE
Full Text: Available from ProQuest in Future Neurology

3. Established disease-modifying treatments in relapsing-remitting multiple sclerosis

Citation: Current Opinion in Neurology, June 2015, vol./is. 28/3(220-229), 1350-7540;1473-6551 (06 Jun 2015)
Author(s): Oh J., O'Connor P.W.
Language: English
Abstract: The purpose of this review is to summarize mechanisms of action, efficacy and safety of established disease-modifying treatments (DMTs) that have been widely approved for use in relapsing-remitting multiple sclerosis (RRMS). Recent findings Established and widely used DMTs for the treatment of RRMS include the interferon-beta agents, glatiramer acetate, natalizumab, fingolimod, teriflunomide and dimethyl fumarate. These DMTs have quite different mechanisms of action, efficacy and safety and tolerability profiles, which are summarized concisely in the article below. Summary The treatment algorithm for RRMS is becoming increasingly complex with the ever-expanding armamentarium of DMTs. The choice of DMT will become an increasingly individual decision, based on a number of factors, including disease activity and severity, safety/tolerability profile and patient preference. Neurologists treating patients with multiple sclerosis (MS) will need a thorough knowledge of efficacy, safety and tolerability of the spectrum of DMTs available for treatment of RRMS to provide comprehensive clinical care.

Publication Type: Journal: Review
Source: EMBASE
Full Text: Available from Ovid in Current Opinion in Neurology

4. Exercise in the management of persons with multiple sclerosis

Citation: Therapeutic Advances in Neurological Disorders, May 2015, vol./is. 8/3(123-130), 1756-2856;1756-2864 (05 May 2015)
Author(s): Giesser B.S.
Language: English
Abstract: For decades, persons with multiple sclerosis (MS) were counseled to avoid excessive physical activity and exercise because of concerns about worsening disease activity. Recent studies indicate that, not only can those with MS tolerate physical exercise, but that it is helpful in managing symptoms, preventing complications and comorbidities, and may possibly have neuroprotective actions. This article reviews previous studies on the
effects of different exercise protocols in people with MS, and provides summaries of suggested exercise regimens that may be appropriate and beneficial for this patient population.

**Publication Type:** Journal: Review  
**Source:** EMBASE  
**Full Text:** Available from *National Library of Medicine* in *Therapeutic Advances in Neurological Disorders*

5. **Hormonal and gender-related immune changes in multiple sclerosis**

**Citation:** Acta Neurologica Scandinavica, July 2015, vol./is. 132/S199(62-70), 0001-6314;1600-0404 (01 Jul 2015)  
**Author(s):** Airas L.

**Language:** English  
**Abstract:** Similarly to many other autoimmune diseases, multiple sclerosis (MS) is more common among women than men, and its incidence among women is rising. There are also qualitative differences in the disease course between men and women, with male patients experiencing increased disease progression, brain atrophy, and cognitive impairment. During pregnancy, women with MS typically have a greatly reduced relapse rate, whereas very soon after the delivery, the disease activity returns, often even at a higher level than seen in the pre-pregnancy year. The reasons for the increased postpartum activity are not entirely clear, but factors such as the abrupt decrease in estrogen levels immediately after the delivery and the loss of the immunosuppressive state of pregnancy are of importance. There is compelling evidence that estrogen, progesterone, and testosterone control MS pathology by influencing immune responses and by contributing to repair mechanisms in the nervous system. Hormones may thus offer important insights into MS disease prevention and treatment. In this review, the possible reasons for the sex bias in autoimmune diseases will be discussed. The pregnancy-related alterations in MS, including the effect of pregnancy on disease activity, long-term disability accumulation, and prevalence will be reviewed, as well as the hormonal and immunological mechanisms potentially underlying these changes. Finally, the present thinking on the effect of hormones on the changing incidence of MS will be elucidated.

**Publication Type:** Journal: Review  
**Source:** EMBASE  
**Full Text:**

6. **Novel and imminently emerging treatments in relapsing-remitting multiple sclerosis**

**Citation:** Current Opinion in Neurology, June 2015, vol./is. 28/3(230-236), 1350-7540;1473-6551 (06 Jun 2015)  
**Author(s):** Oh J., O'Connor P.W.

**Language:** English  
**Abstract:** To summarize mechanisms of action, efficacy, and safety of novel and imminently emerging disease-modifying treatments (DMTs) intended to be used in relapsing-remitting multiple sclerosis (RRMS). Recent findings Novel and imminently emerging DMTs for the treatment of RRMS include alemtuzumab, daclizumab, ocrelizumab, pegylated interferon-beta-1a, and three times weekly glatiramer acetate. These DMTs have substantially different mechanisms of action, efficacy, and safety and tolerability profiles, which are summarized concisely in this article. Summary The treatment landscape of RRMS is evolving rapidly as the available treatment options have doubled in recent years, and a number of novel DMTs will likely become available in the near future. Choosing the optimal DMT for patients is becoming an increasingly complex process, and the care of patients with MS will likely require regular input from neurologists subspecializing in the care of patients with MS. As the use of novel DMTs with unknown long-term safety profiles increases, postmarketing surveillance and vigilance with regards to safety monitoring will be essential to confirm the safety and clinical efficacy of these DMTs for patients with RRMS.

**Publication Type:** Journal: Review  
**Source:** EMBASE  
**Full Text:**

7. **Reducing falls and improving mobility in multiple sclerosis**

**Citation:** Expert Review of Neurotherapeutics, June 2015, vol./is. 15/6(655-666), 1473-7175;1744-8360 (01 Jun 2015)  
**Author(s):** Sosnoff J.J., Sung J.

**Language:** English
Abstract: Falls are common in persons with multiple sclerosis (MS), and are related to physical injury and reduce the quality of life. Mobility impairments are a significant risk factor for falls in persons with MS. Although there is evidence that mobility in persons with MS can be improved with rehabilitation, much less is known about fall prevention. This review focuses on fall prevention in persons with MS. Ten fall prevention interventions consisting of 524 participants with a wide range of disability were systematically identified. Nine of the 10 investigations report a reduction in falls and/or proportion of fallers following treatment. The vast majority observed an improvement in balance that co-occurred with the reduction in falls. Methodological limitations preclude any firm conclusions. Numerous gaps in the understanding of fall prevention in persons with MS are discussed. Well-designed randomized control trials targeting mobility and falls are warranted.

Publication Type: Journal: Review

Source: EMBASE

8. Spinal cord MRI in multiple sclerosis-diagnostic, prognostic and clinical value

Citation: Nature Reviews Neurology, June 2015, vol./is. 11/6(327-338), 1759-4758;1759-4766 (09 Jun 2015)

Author(s): Kearney H., Miller D.H., Ciccarelli O.

Language: English

Abstract: Multiple sclerosis (MS) is an inflammatory disorder of the CNS that affects both the brain and the spinal cord. MRI studies in MS focus more often on the brain than on the spinal cord, owing to the technical challenges in imaging this smaller, mobile structure. However, spinal cord abnormalities at disease onset have important implications for diagnosis and prognosis. Furthermore, later in the disease course, in progressive MS, myelopathy becomes the primary characteristic of the clinical presentation, and extensive spinal cord pathology-including atrophy, diffuse abnormalities and numerous focal lesions—is common. Recent spinal cord imaging studies have employed increasingly sophisticated techniques to improve detection and quantification of spinal cord lesions, and to elucidate their relationship with physical disability. Quantitative MRI measures of cord size and tissue integrity could be more sensitive to the axonal loss and other pathological processes in the spinal cord than is conventional MRI, putting quantitative MRI in a key role to elucidate the association between disability and spinal cord abnormalities seen in people with MS. In this Review, we summarize the most recent MS spinal cord imaging studies and discuss the new insights they have provided into the mechanisms of neurological impairment. Finally, we suggest directions for further and future research.

Publication Type: Journal: Review

Source: EMBASE

Full Text:

9. Targeted clinical audits immediately following the establishment of clinical practice guidelines for multiple sclerosis in 17 neurology departments: A pragmatic and collaborative study

Citation: Revue Neurologique, May 2015, vol./is. 171/5(407-414), 0035-3787 (01 May 2015)

Author(s): Lairy G., Zephir H., Ouallet J.-C., Le Page E., Laplaud D., Bensa C., De Seze J.

Language: English

Abstract: Following the publication practice guidelines for multiple sclerosis by a group of neurologists (multiple sclerosis study group [GRESEP]), the primary objective of this study was to compare the reality of practice to the guidelines according to the targeted clinical audit (TCA) method. The study was conducted at 17 neurology sites and was administered during two periods of MS care (diagnostic - TCA-DIAG, and disease course - TCA-EVOL). Two complementary surveys were done on the record keeping and the root causes of the deviations. The percentages of compliance ranged from 8 to 98% for the TCA-DIAG, and from 15 to 99% for the TCA-EVOL, with wide disparity between sites. The audits were able to identify causes of the flaws in traceability or accessibility. At the end of the study, despite its limitations, we think that the sharing of the results from different sites provided interesting approaches for the use of the assessment criteria defined by GRESEP in a complete audit cycle. This study is to our knowledge the first report of an experiment in which guidelines were created, and subsequently followed by the development of assessment criteria and then the performance of targeted clinical audits using them, all by the same participants. Context. - Clinical practice guidelines (CPGs) are intended to help practitioners and patients make informed treatment choices, but their integration into actual practice remains problematic. This study was done immediately following the publication of CPGs for multiple sclerosis (MS) by the multiple sclerosis study group [GRESEP]. The primary objective was to generate quality criteria, to test them within the same group, and to analyze the observed deviations. Materials and methods. - The study was conducted in the 17 voluntary departments that had participated in the development of the CPGs. The targeted clinical audit method was
administered during two periods of MS care (diagnostic - TCA-DIAG, and disease course - TCA-EVOL). All the files were evaluated by a clinical research technician using digital format, which ensured thoroughness of the collection. Two complementary surveys were done on the record keeping and the potential causes of the deviations. Results. - The percentages of compliance to the criteria ranged from 8 to 98% (out of 240 files) for the TCA-DIAG, and from 15 to 99% (221 files) for the TCA-EVOL, with wide disparity between sites (interquartile distance ranges: TCA-DIAG between 0% and 55%; TCA-EVOL between 0% and 70%). The mean percentage of compliance with all the criteria as measured by the TCA-DIAG was 83.9% for the sites with digital files vs. 76.4% for those with only paper files (P < 0.01). For the TCA-EVOL, the difference was not significant. Explanations for the observed deviations were suggested (1 to 9 according to the participants). Discussion and conclusion. - The quantified results could not be compared to other studies given the unique nature of the experiment. The importance of the traceability of practices in the patient files was discussed and assessed with regard to continuity and safety of care, as well as the medical-legal perspectives. Causes of lack of compliance were suggested (particularly the absence of reminders, the lack of means and/or time). Despite the limitations of the study, we think it is advisable that when a group becomes involved in the development of CPGs that they follow with the development of assessment criteria in order to evaluate the validity as well as their character as intermediate indicators of the quality of practices.

Publication Type: Journal: Review
Source: EMBASE

Multiple System Atrophy Table of Contents:

1. Clinical utility of skin biopsy in differentiating between Parkinson's disease and multiple system atrophy
2. Decreased vesicular storage and aldehyde dehydrogenase activity in multiple system atrophy
3. Differentiating multiple-system atrophy from Parkinson's disease
4. Fluid biomarkers in multiple system atrophy: A review of the MSA Biomarker Initiative
5. Pain in multiple system atrophy and progressive supranuclear palsy compared to Parkinson's disease
6. Quantitative analyses of REM sleep without atonia discriminates between major synucleinopathy phenotypes of Parkinson disease and multiple system atrophy
7. Transcriptome analysis of grey and white matter cortical tissue in multiple system atrophy
8. Treating Multiple System Atrophy: Be sure the treatment is not worse than the disease

Multiple System Atrophy Journal Articles:

**1. Clinical utility of skin biopsy in differentiating between Parkinson's disease and multiple system atrophy**

Citation: Parkinson's Disease, 2015, vol./is. 2015/, 2042-0080 (2015)
Author(s): Haga R., Sugimoto K., Nishijima H., Miki Y., Suzuki C., Wakabayashi K., Baba M., Yagihashi S., Tomiyama M.
Language: English
Abstract: Background. It is often difficult to differentiate Parkinson's disease (PD) from multiple system atrophy (MSA), especially in their early stages. Objectives. To examine the clinical utility of histopathological analysis of biopsied skin from the chest wall and/or leg in differentiating between the two diseases. Methods. Skin biopsies from the lower leg and/or anterior chest wall were obtained from 38 patients with idiopathic PD (26 treated with levodopa and 12 levodopa-naive) and 13 age-matched patients with MSA. We sought aggregates of
phosphorylated alpha-synuclein on cutaneous nerve fibers using double fluorescence immunohistochemistry and confocal microscopy and measured intraepidermal nerve fiber density (IENFD). Results. Phosphorylated alpha-synuclein aggregates were identified on cutaneous nerves in two patients with PD (5.3%) but in none of the patients with MSA, and IENFD was significantly lower in patients with PD when compared to those with MSA. There was no difference in IENFD between levodopa-treated and levodopa-naive patients with PD. Conclusions. Our findings suggest that an assessment of IENFD in biopsied skin could be a useful means of differentiating between PD and MSA but that detection of alpha-synuclein aggregates on cutaneous nerves in the distal sites of the body is insufficiently sensitive.

Publication type: Journal: Article
Source: EMBASE
Full text: Available National Library of Medicine at No link? Ask Salisbury Healthcare Library - please click here to request article.

Full text: Available National Library of Medicine at Parkinson's Disease

2. Decreased vesicular storage and aldehyde dehydrogenase activity in multiple system atrophy
Citation: Parkinsonism and Related Disorders, June 2015, vol./is. 21/6(567-572), 1353-8020;1873-5126 (01 Jun 2015)
Author(s): Goldstein D.S., Sullivan P., Holmes C., Kopin I.J., Sharabi Y., Mash D.C.
Language: English
Abstract: Background: Parkinson disease (PD) and multiple system atrophy (MSA) share some neuropathologic features (nigrostriatal dopaminergic lesion, alpha-synuclein deposition) but not others (Lewy bodies in PD, glial cytoplasmic inclusions in MSA). In PD evidence has accrued for a vesicular storage defect and decreased aldehyde dehydrogenase (ALDH) activity in residual dopaminergic terminals, resulting in accumulation of the toxic dopamine (DA) metabolite 3,4-dihydroxyphenylacetaldehyde (DOPAL). In this study we asked whether MSA entails a similar abnormal neurochemical pattern. Methods: DA and its main neuronal metabolite 3,4-dihydroxyphenylacetic acid (DOPAC), norepinephrine (NE) and its main neuronal metabolite 3,4-dihydroxyphenylglycol (DHPG), the catecholamine precursor DOPA, and DOPAL were measured in striatal and frontal cortical tissue from patients with pathologically proven end-stage MSA (N = 15), sporadic PD (N = 17), and control subjects (N = 18). Results: Compared to the control group, the MSA and PD groups had similarly decreased putamen DA (by 96% and 93%, p < 0.0001), DOPAC (97% and 95%, p < 0.0001), NE (91% and 74%, p < 0.0001), and DHPG (81% and 74%, p < 0.0001). In the MSA and PD groups, ratios of DOPAL:DA were 2.3 and 3.5 times control and DHPG:NE 3.1 and 2.6 times control, while DOPAC:DOPAL ratios were decreased by 61% and 74%. In both diseases cortical NE and DHPG were decreased, while DA and DOPAC were not. Conclusions: MSA and PD entail a catecholamine metabolic profile indicating impaired vesicular storage, decreased ALDH activity, and DOPAL buildup, which might be part of a common pathway in catecholamine neuronal death. Targeting this pathway by interfering with catecholaldehyde production or effects constitutes a novel treatment approach.

Publication type: Journal: Article
Source: EMBASE

3. Differentiating multiple-system atrophy from Parkinson’s disease
Citation: Clinical radiology, May 2015, vol./is. 70/5(555-564), 1365-229X (01 May 2015)
Author(s): Ramli N., Nair S.R., Ramli N.M., Lim S.Y.
Language: English
Abstract: The purpose of this review is to illustrate the differentiating features of multiple-system atrophy from Parkinson’s disease at MRI. The various MRI sequences helpful in the differentiation will be discussed, including newer methods, such as diffusion tensor imaging, MR spectroscopy, and nuclear imaging.

Publication type: Journal: Review
Source: EMBASE

4. Fluid biomarkers in multiple system atrophy: A review of the MSA Biomarker Initiative
Citation: Neuropsychology of Disease, August 2015, vol./is. 80/(29-41), 0969-9961;1095-953X (August 01, 2015)
Language: English
Abstract: Despite growing research efforts, no reliable biomarker currently exists for the diagnosis and prognosis
of multiple system atrophy (MSA). Such biomarkers are urgently needed to improve diagnostic accuracy, prognostic guidance and also to serve as efficacy measures or surrogates of target engagement for future clinical trials. We here review candidate fluid biomarkers for MSA and provide considerations for further developments and harmonization of standard operating procedures. A PubMed search was performed until April 24, 2015 to review the literature with regard to candidate blood and cerebrospinal fluid (CSF) biomarkers for MSA. Abstracts of 1760 studies were retrieved and screened for eligibility. The final list included 60 studies assessing fluid biomarkers in patients with MSA. Most studies have focused on alpha-synuclein, markers of axonal degeneration or catecholamines. Their results suggest that combining several CSF fluid biomarkers may be more successful than using single markers, at least for the diagnosis. Currently, the clinically most useful markers may comprise a combination of the light chain of neurofilament (which is consistently elevated in MSA compared to controls and Parkinson's disease), metabolites of the catecholamine pathway and proteins such as alpha-synuclein, DJ-1 and total-tau. Beyond future efforts in biomarker discovery, the harmonization of standard operating procedures will be crucial for future success.

**Publication type:** Journal: Review  
**Source:** EMBASE

5. **Pain in multiple system atrophy and progressive supranuclear palsy compared to Parkinson’s disease**  
**Citation:** Brain and Behavior, May 2015, vol./is. 5/5, 2162-3279 (01 May 2015)  
**Author(s):** Kass-Iliyya L., Kobylecki C., Mcdonald K.R., Gerhard A., Silverdale M.A.  
**Language:** English  
**Abstract:** Background: Pain is a common nonmotor symptom in Parkinson’s disease (PD). The pathophysiology of pain in PD is not well understood. Pain characteristics have rarely been studied in atypical parkinsonian disorders such as Multiple System Atrophy (MSA) and Progressive Supranuclear Palsy (PSP). Aim of the study: We aimed to evaluate pain intensity, location, and associated symptoms in atypical parkinsonian disorders compared to PD. Methods: Twenty-one patients with MSA, 16 patients with PSP, and 65 patients with PD were screened for pain using question 1.9 of the MDS-UPDRS. Pain intensity was quantified using the short form McGill Pain Questionnaire (SFMPQ). Pain locations were documented. Motor disability was measured using UPDRS-III. Affective symptoms were assessed using the Hospital Anxiety and Depression Scale (HADS). Results: Pain was significantly more common and more severe in PD and MSA compared to PSP (P < 0.01). Pain locations were similar with limb pain being the most common followed by neck and back pain. Pain intensity correlated with HADS scores but not motor severity. Conclusions: Pain is more common and more intense in PD and MSA than PSP. Differences in distribution of neurodegenerative pathologies may underlie these differential pain profiles.  
**Publication type:** Journal: Article  
**Source:** EMBASE

6. **Quantitative analyses of REM sleep without atonia discriminates between major synucleinopathy phenotypes of Parkinson disease and multiple system atrophy**  
**Citation:** Sleep, 2015, vol./is. 38/(A254), 0161-8105 (2015)  
**Language:** English  
**Abstract:** Introduction: REM sleep behavior disorder (RBD) is a core feature of synucleinopathies, especially Parkinson Disease (PD) and multiple system atrophy (MSA). The neurophysiologic substrate of RBD is REM sleep without atonia (RSWA), comprised of excessive phasic and tonic muscle activity during REM. RSWA differences between PD and MSA are currently unknown. We aimed to determine whether Polysomnographic RSWA profiles could discriminate between PD and MSA patients. Methods: RSWA was manually scored in the submentalis (SM) and anterior tibialis (AT) muscles according to established methods in 25 clinically diagnosed MSA patients and 20 PD and 25 OSA control patients. Group comparisons of phasic, tonic, and "any" muscle activity percentages, phasic burst duration, and automated REM atonia index (RAI) were completed utilizing non-parametric statistical tests. Results: Automated RAI was significantly different across groups, with lowest RAI (and greatest atonia loss) in MSA patients (MSA: 0.34, PD: 0.59, OSA: 0.94, p < 0.02). Manual RSWA analyses demonstrated higher SM/AT combined "any" activity within synucleinopathy groups (MSA: 64%, PD: 70%, OSA: 17%, p < 0.0001). Manual RSWA profiles also varied across groups, with higher tonic muscle activity in MSA patients (MSA: 50%, PD: 23%, OSA: 0%, p < 0.03), but higher overall (combined SM/AT) phasic muscle activity in PD patients (PD: 67%), MSA:
36%, OSA: 17%, p < 0.0005). SM phasic burst duration was similar between PD and MSA patients (1.15 s vs. 1.02 s, p = 0.3917). Both REM atonia index and SM/AT combined activity were able to detect MSA among synucleinopathy patients with excellent sensitivity and specificity (RAI: 80%, 70%, AUC = 0.708; SM/AT: 80%, 80%, AUC = 0.81). Conclusion: MSA and PD RSWA was greater than in OSA controls, with automated RAI discriminating most clearly between the three groups. Different quantitative RSWA profiles were found between the synucleinopathy groups, with comparatively higher tonic muscle activity in MSA, and higher phasic muscle activity in PD patients, suggesting that quantitative RSWA profiles could help discriminate synucleinopathy phenotypes.

**Publications**

7. Transcriptome analysis of grey and white matter cortical tissue in multiple system atrophy

**Citation:** Neurogenetics, 2015, vol./is. 16/2(107-122), 1364-6745;1364-6753 (2015)

**Author(s):** Mills J.D., Kim W.S., Halliday G.M., Janitz M.

**Language:** English

**Abstract:** Multiple system atrophy (MSA) is a distinct member of a group of neurodegenerative diseases known as alpha-synucleinopathies, which are characterized by the presence of aggregated alpha-synuclein in the brain. MSA is unique in that the principal site for alpha-synuclein deposition is in the oligodendrocytes rather than neurons. The cause of MSA is unknown, and the pathogenesis of MSA is still largely speculative. Brain transcriptome perturbations during the onset and progression of MSA are mostly unknown. Using RNA sequencing, we performed a comparative transcriptome profiling analysis of the grey matter (GM) and white matter (WM) of the frontal cortex of MSA and control brains. The transcriptome sequencing revealed increased expression of the alpha and beta haemoglobin genes in MSA WM, decreased expression of the transthyretin (TTR) gene in MSA GM and numerous region-specific long intervening non-coding RNAs (lincRNAs). In contrast, we observed only moderate changes in the expression patterns of the alpha-synuclein (SNCA) gene, which confirmed previous observations by other research groups. Our study suggests that at the transcriptional level, MSA pathology may be related to increased iron levels in WM and perturbations of the non-coding fraction of the transcriptome.

**Publication type:** Journal: Article

**Source:** EMBASE

8. Treating Multiple System Atrophy: Be sure the treatment is not worse than the disease

**Citation:** American Journal of Kidney Diseases, April 2015, vol./is. 65/4(A23), 0272-6386 (April 2015)

**Author(s):** Bernstein E.L., Meyer J., Bernstein P.L.

**Language:** English

**Abstract:** Multiple System Atrophy (MSA) is a progressive CNS disease resulting in neuronal loss in the suprachiasmatic nucleus, striatonigral and autonomic systems. Decreased number of vasopressin-producing cells result in polyuria and blunted response to hemodynamic input. Orthostatic changes are treated with Fludrocortisone (FC) to maintain ECV. We present a patient with repeated falls and syncope receiving very high dose FC (0.3 mg bid) without supplemental K+ or potassium-sparing diuretics, admitted with life-threatening hypokalemia (1.6meq/l), metabolic alkalosis (venous pH 7.55) hypocalcemia (ionized calcium, 3.5meq/l) and hypernatremia (148 meq/l). The patient is a 63-year-old normotensive gentleman diagnosed with MSA the previous year because of repeated falls, neurologic exam and MRI findings. Electrolytes were documented as normal. Nocturia progressed to 5-6/night with uniformly "water-clear" urine, regardless of the time of day all fluids were stopped. Escalating doses of FC and salt tabs, (3 g/day), were prescribed for orthostasis with little success. Falls increased until he became bedbound. Creatinine remained normal. Cessation of the FC, treatment of the hypokalemia (580 meq over 3 days) and resolution of the alkalosis and hypercalcemia was complicated by a 12L urine output in the first 24 hours. Orthostasis resolved little. Hypokalemic metabolic alkalosis is a known complication of FC treatment for orthostatic symptoms, but this is the lowest potassium recorded in the literature as a consequence of its use. The DI-like picture may have been progressive loss of vasopressin production or release, or a loss of concentrating ability from the hypokalemia. The extreme muscle weakness may have been disease progression, the hypokalemia or hypocalcemia, resulting from a pseudo-Bartert's picture. The efficacy of long-term FC treatment is questionable with little additional benefit in doses greater then 0.3mg/day. Higher doses risk life-threatening consequences that should be anticipated.

**Publication type:** Journal: Conference Abstract
**Parkinson’s Disease Table of Contents:**

1. A systematic review and meta-analysis of cognitive behavioral and psychodynamic therapy for depression in Parkinson’s disease patients

2. Biomarkers of cognitive decline in Parkinson's disease

3. Effective delivery of apomorphine in the management of parkinson disease: Practical considerations for clinicians and parkinson nurses

4. Parkinson’s disease and intensive exercise therapy - A systematic review and meta-analysis of randomized controlled trials

5. Parkinson's disease: A review of non-motor symptoms


7. The rationale for exercise in the management of pain in Parkinson's disease

8. The role of functional dopamine-transporter SPECT imaging in parkinsonian syndromes, part 1.


10. To operate or not?: A literature review of surgical outcomes in 95 patients with Parkinson's disease undergoing spine surgery

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**Parkinson’s Disease Journal Articles:**

1. A systematic review and meta-analysis of cognitive behavioral and psychodynamic therapy for depression in Parkinson’s disease patients

   **Citation:** Neurological Sciences, June 2015, vol./is. 36/6(833-843), 1590-1874;1590-3478 (05 Jun 2015)

   **Author(s):** Xie C.-L., Wang X.-D., Chen J., Lin H.-Z., Chen Y.-H., Pan J.-L., Wang W.-W.

   **Language:** English

   **Abstract:** Numerous practice guidelines have recommended cognitive behavioral therapy (CBT) and psychodynamic therapy as a treatment of choice for depression in Parkinson's disease (PD). However, no recent meta-analysis has examined the effects of brief psychotherapy (which includes both CBT and psychodynamic therapy) for adult depression in PD. We decided to conduct such a systematic review and meta-analysis. We included randomized controlled trials (RCTs) examining the effects of brief psychotherapy compared with control groups, other support nursing, or pharmacotherapy. The quality of included studies was strictly evaluated. Twelve studies including 766 patients met all inclusion criteria. The result showed that brief psychotherapy could evidently improve the HAMD (p < 0.00001) and Moca scale (p = 0.006). There was no statistical significance in PDQ-39 scale (p = 0.31). In the subgroup analysis by types of brief psychotherapy, the efficacy of psychodynamic psychotherapy was better than CBT (SMD = -2.02 vs SMD = -0.90) for the outcome measure according to HAMD scale. Meanwhile, we found brief psychotherapy in China was more effective than in US (SMD = -1.54 vs SMD = -1.23), and in low quality studies was more efficacious than in high quality studies (SMD = -1.50 vs SMD = -1.33). Time of brief psychotherapy treatment above 6 weeks was superior to studies with less than 6 weeks treatment. We found brief psychotherapy is probable effective in the management of depression in PD patients. But one
reason to undermine the validity of findings is high clinical heterogeneity and low methodological quality of the included trials.

**Publication Type:** Journal: Review  
**Source:** EMBASE

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### 2. Biomarkers of cognitive decline in Parkinson's disease

**Citation:** Parkinsonism and Related Disorders, May 2015, vol./is. 21/5(431-443), 1353-8020;1873-5126 (01 May 2015)  
**Author(s):** Lin C.-H., Wu R.-M.  
**Language:** English  
**Abstract:** Cognitive impairment is a frequent and devastating non-motor symptom of Parkinson's disease (PD). Impaired cognition has a major impact on either quality of life or mortality in patients with PD. Notably, the rate of cognitive decline and pattern of early cognitive deficits in PD are highly variable between individuals. Given that the underlying mechanisms of cognitive decline or dementia associated with PD remain unclear, there is currently no mechanism-based treatment available. Identification of biological markers, including neuroimaging, biofluids and common genetic variants, that account for the heterogeneity of PD related cognitive decline could provide important insights into the pathological processes that underlie cognitive impairment in PD. These combined biomarker approaches will enable early diagnosis and provide indicators of cognitive progression in PD patients. This review summarizes recent advances in the development of biomarkers for cognitive impairments in PD.

**Publication Type:** Journal: Review  
**Source:** EMBASE  
**Full Text:**

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### 3. Effective delivery of apomorphine in the management of parkinson disease: Practical considerations for clinicians and parkinson nurses

**Citation:** Clinical Neuropharmacology, May 2015, vol./is. 38/3(89-103), 0362-5664;1537-162X (30 May 2015)  
**Author(s):** Bhidayasiri R., Chaudhuri K.R., LeWitt P., Martin A., Boonpang K., Van Laar T.  
**Language:** English  
**Abstract:** The clinical utility of long-term oral levodopa therapy in Parkinson disease (PD) is often limited by the emergence of motor complications. Over time, many patients with PD experience regular and/or unpredictable "off" periods, despite taking optimized oral medication regimens, with a major negative impact on their ability to undertake routine activities of daily living and consequently on their overall quality of life. One established approach for treating patients experiencing off periods and controlling motor fluctuations refractory to conventional oral drug therapy is the subcutaneous administration of the dopaminergic agonist apomorphine. This article outlines how the pharmacokinetic properties of apomorphine underpin its efficacy for the treatment of PD and provides practical guidance for the 3 main approaches in which it is used: subcutaneous intermittent apomorphine injection as a "rescue" therapy for off states, subcutaneous continuous apomorphine infusion for PD patients with intractable motor fluctuations as an alternative to other dopaminergic treatment, and in the apomorphine response (or challenge) test for assessment of dopamine-induced motor response in patients thought to have PD, or in establishing the optimal tolerated dose of apomorphine in patients already known to have PD. Also discussed is the management of potential adverse events with subcutaneous administration of apomorphine, the majority of which are mild and easily managed in practice. The importance of a multidisciplinary PD team in the optimal management of PD patients is now recognized, in particular the role of the specialist PD nurse.

**Publication Type:** Journal: Review  
**Source:** EMBASE  
**Full Text:**

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### 4. Parkinson's disease and intensive exercise therapy - A systematic review and meta-analysis of randomized controlled trials

**Citation:** Journal of the Neurological Sciences, June 2015, vol./is. 353/1-2(9-19), 0022-510X;1878-5883 (15 Jun 2015)  
**Author(s):** Uhrbrand A., Stenager E., Pedersen M.S., Dalgas U.  
**Language:** English
Abstract: Objective To evaluate and compare the effect of 3 intensive exercise therapy modalities - Resistance Training (RT), Endurance Training (ET) and Other Intensive Training Modalities (OITM) - in Parkinson's Disease (PD). Design A systematic review and meta-analysis of randomized controlled trials. Methods A systematic literature search was conducted (Embase, Pubmed, Cinahl, SPORTDiscus, Cochrane, PEDro), which identified 15 studies that were categorized as RT, ET or OITM. The different exercise modalities were reviewed and a meta-analysis evaluating the effect of RT on muscle strength was made. Results In PD intensive exercise therapy (RT, ET and OITM) is feasible and safe. There is strong evidence that RT can improve muscle strength in PD, which is underlined by the meta-analysis ($g' = 0.54 [95\% CI 0.22;0.86]$). There is moderate evidence that ET can improve cardio-respiratory fitness in PD. RT, ET and OITM may have beneficial effects on balance, walking performance, Unified Parkinson's Disease Rating Scale-III (UPDRS-III) score and quality of life in PD, but findings are inconsistent. No studies find deterioration in any outcomes following exercise therapy. Conclusion RT, ET and OITM all represent feasible, safe and beneficial adjunct rehabilitation therapies in PD.

Publication Type: Journal: Review
Source: EMBASE
Full Text:

5. Parkinson's disease: A review of non-motor symptoms
Citation: Expert Review of Neurotherapeutics, May 2015, vol./is. 15/5(549-562), 1473-7175;1744-8360 (01 May 2015)
Author(s): Rana A.Q., Ahmed U.S., Chaudry Z.M., Vasan S.
Language: English
Abstract: Parkinson's disease (PD) is a neurodegenerative disorder resulting from degeneration of the substantia nigra and the dopaminergic nigrostriatal pathway. Most treatments are geared toward the management and relief of motor symptoms in Parkinson's patients; however, as the disease progresses, various complications can be observed. Non-motor symptoms (NMS) may arise simply from the disease itself and are highly destructive to quality of life. These symptoms include mood disorders, cognitive dysfunction, pain, sensory dysfunction, and dysautonomia. Though it is undisputed that many NMS may appear years or even decades prior to the clinical diagnosis of PD, the focus of this review will be the overt motor phase of the condition. As such, the focus of this paper is to review the major NMS found in PD patients status post-diagnosis, their etiology, as well as treatment options available for the individual NMS.

Publication Type: Journal: Review
Source: EMBASE

Citation: Parkinsonism and Related Disorders, July 2015, vol./is. 21/7(683-691), 1353-8020;1873-5126 (01 Jul 2015)
Author(s): Lenka A., Jhunjhunwala K.R., Saini J., Pal P.K.
Language: English
Abstract: Patients with Parkinson's disease (PD) may develop various non-motor symptoms (NMS) during the course of the illness and psychosis is one of the common NMS of PD. Visual hallucinations (VH) are the most common manifestation of psychosis in PD. The exact pathogenesis of VH in patients with PD is not clearly understood. Presence of VH has been described to be associated with rapid cognitive decline and increased nursing home placements in PD patients. A large number of structural and functional neuroimaging studies have been conducted to understand the cerebral basis of VH in PD. Structural imaging studies (Voxel Based Morphometry) have reported grey matter atrophy in multiple regions of the brain such as primary visual cortex, visual association cortex, limbic regions, cholinergic structures such as pedunculopontine nucleus and substantia innominata, which conclude possible alterations of brain regions associated with functions such as visuospacial-perception, attention control and memory. Most functional neuroimaging studies (functional MRI, positron emission tomography and single photon emission computerized tomography) have reported altered activation, blood flow, or reduced metabolism in both dorsal and ventral visual pathways, which probably indicates an alteration in the normal bottom-top visual processing and the presence of an aberrant top-down visual processing. This review critically analyzes the published studies on the structural and functional neuroimaging in PD patients with VH.

Publication Type: Journal: Review
7. The rationale for exercise in the management of pain in Parkinson's disease
Citation: Journal of Parkinson's Disease, June 2015, vol./iss. 5/2(229-239), 1877-7171;1877-718X (01 Jun 2015)
Author(s): Allen N.E., Moloney N., Van Vliet V., Canning C.G.
Language: English
Abstract: Pain is a distressing non-motor symptom experienced by up to 85% of people with Parkinson's disease (PD), yet it is often untreated. This pain is likely to be influenced by many factors, including the disease process, PD impairments as well as co-existing musculoskeletal and/or neuropathic pain conditions. Expert opinion recommends that exercise is included as one component of pain management programs; however, the effect of exercise on pain in this population is unclear. This review presents evidence describing the potential influence of exercise on the pain-related pathophysiological processes present in PD. Emerging evidence from both animal and human studies suggests that exercise might contribute to neuroplasticity and neurorestoration by increasing brain neurotrophic factors, synaptic strength and angiogenesis, as well as stimulating neurogenesis and improving metabolism and the immune response. These changes may be beneficial in improving the central processing of pain. There is also evidence that exercise can activate both the dopaminergic and non-dopaminergic pain inhibitory pathways, suggesting that exercise may help to modulate the experience of pain in PD. Whilst clinical data on the effects of exercise for pain relief in people with PD are scarce, and are urgently needed, preliminary guidelines are presented for exercise prescription for the management of central neuropathic, peripheral neuropathic and musculoskeletal pain in PD.
Publication Type: Journal: Review
Source: EMBASE

8. The role of functional dopamine-transporter SPECT imaging in parkinsonian syndromes, part 1.
Citation: AJNR. American journal of neuroradiology, Feb 2015, vol. 36, no. 2, p. 229-235 (February 2015)
Author(s): Booth, T C, Nathan, M, Waldman, A D, Quigley, A-M, Schapira, A H, Buscombe, J
Abstract: As we defeat infectious diseases and cancer, one of the greatest medical challenges facing us in the mid-21st century will be the increasing prevalence of degenerative disease. Those diseases, which affect movement and cognition, can be the most debilitating. Dysfunction of the extrapyramidal system results in increasing motor disability often manifest as tremor, bradykinesia, and rigidity. The common pathologic pathway of these diseases, collectively described as parkinsonian syndromes, such as Parkinson disease, multiple system atrophy, progressive supranuclear palsy, corticobasal degeneration, and dementia with Lewy bodies, is degeneration of the presynaptic dopaminergic pathways in the basal ganglia. Conventional MR imaging is insensitive, especially in early disease, so functional imaging has become the primary method used to differentiate a true parkinsonian syndrome from vascular parkinsonism, drug-induced changes, or essential tremor. Unusually for a modern functional imaging technique, the method most widely used in European clinics depends on SPECT and not PET. This SPECT technique (described in the first of 2 parts) commonly reports dopamine-transporter function, with decreasing striatal uptake demonstrating increasingly severe disease. © 2015 by American Journal of Neuroradiology.
Source: EMBASE

Citation: AJNR. American journal of neuroradiology, Feb 2015, vol. 36, no. 2, p. 236-244 (February 2015)
Author(s): Booth, T C, Nathan, M, Waldman, A D, Quigley, A-M, Schapira, A H, Buscombe, J
Abstract: The functional imaging technique most widely used in European clinics to differentiate a true parkinsonian syndrome from vascular parkinsonism, drug-induced changes, or essential tremor is dopamine-transporter SPECT. This technique commonly reports dopamine-transporter function, with decreasing striatal uptake demonstrating increasingly severe disease. The strength of dopamine-transporter SPECT is that nigrostriatal degeneration is observed in both clinically inconclusive parkinsonism and early, even premotor, disease. In this clinical review (Part 2), we present the dopamine-transporter SPECT findings in a variety of neurodegenerative diseases, including multiple system atrophy, progressive supranuclear palsy, corticobasal degeneration, and dementia with Lewy bodies. The findings in vascular parkinsonism, drug-induced parkinsonism, and essential tremor are also described. It is hoped that this technique will be the forerunner of a range of routinely used, process-specific ligands that can identify early degenerative disease and subsequently guide disease-modifying interventions. © 2015 by American Journal of Neuroradiology.
10. To operate or not?: A literature review of surgical outcomes in 95 patients with Parkinson's disease undergoing spine surgery

Citation: Clinical Neurology and Neurosurgery, May 2015, vol./is. 134/(122-125), 0303-8467;1872-6968 (17 May 2015)

Author(s): Sarkiss C.A., Fogg G.A., Skovrlj B., Cho S.K., Caridi J.M.

Language: English

Abstract: Introduction: Degenerative spondylosis and kyphoscoliosis are increasingly recognized entities in patients with Parkinson's disease. Surgical treatment with spinal fusion can be complicated due to poor bone quality and muscular dysfunction in this patient population. The goal of this paper is to investigate surgical outcomes in Parkinson's patients undergoing spine surgery. Methods: We performed a literature review using the PubMed and Google Scholar search engines investigating "Parkinson's disease and spinal fusion surgery" from the period of 2000 to 2013. The inclusion criteria included only English articles with Parkinson's patients that underwent spinal surgery. We identified and reviewed all six articles that included ninety-five patients with Parkinson's disease who underwent spinal surgery. Results: A total of 95 patients with Parkinson's disease who underwent spinal fusion surgery were reviewed with average patient age of 69 and a 3:4 male to female ratio. With an average follow up of 40 months, 46 out of 73 patients (63%) were judged to have satisfactory outcomes with poor outcomes noted in the remaining 37%. These included but were not limited to pseudoarthrosis, hardware failure/pullout, development of adjacent level disease, persistent kyphosis or sagittal imbalance, and no improvement or worsening in their postoperative visual analog pain scale. There was a 45% (29/65) revision rate and a 59% (30/51) complication rate following the index procedure. Conclusion: It remains unclear whether Parkinson's patients benefit from spinal fusion surgery. Further prospective research is warranted to investigate surgical outcomes in this subset of patients.

Publication Type: Journal: Review

Source: EMBASE
10. Pathophysiology, genetics, clinical features, diagnosis and therapeutic trials in progressive supranuclear palsy

11. Patterns of gray matter atrophy in atypical parkinsonism syndromes: A VBM meta-analysis

12. Progressive supra-nuclear palsy: Frequency of cardinal extrapyramidal features at first presentation

13. Progressive supranuclear palsy: What do we know about it?

14. Prolonged sleep latency and sleep onset REM in a neurodegenerative tauopathy disease

15. Square-wave jerks and macrosaccadic oscillations

**Progressive Supranuclear Palsy Journal Articles:**

1. **A neuroimaging rating scale to enhance the inter-rater reliability and diagnostic validity of hummingbird sign**
   **Citation:** Neurodegenerative Diseases, March 2015, vol./is. 15/(1640), 1660-2854 (March 2015)
   **Author(s):** Kim Y.E., Kang S., Ma H., Kim Y.
   **Language:** English
   **Abstract:** Although Hummingbird sign (HBS) is a distinctive feature of Progressive supranuclear palsy (PSP) vs. idiopathic Parkinson's disease (IPD) and other parkinsonian disorders, there are no consensus criteria. To enhance inter-rater reliability (IRR) and diagnostic validity, we developed a new radiologic rating scale for HBS (HBS-RS). Two raters blinded to the clinical diagnosis reviewed T1 midsagittal magnetic resonance images of 133 patients with IPD (n=93) or with PSP (n=40). The existence of HBS was assessed in two steps, separated by two weeks, first based on their own experience, and then according to the HBS-RS. The HBS-RS is comprised of 4 items (contour of third ventricle floor, shape of beak, shape of Hummingbird head, and midbrain atrophy), with weighted scores from 0 to 2. IRRs of individual items in HBS-RS, and of composite scores, showed moderate to good agreement (kappa, 0.479 - 0.766) and were observed to be highest in item #1. IRRs for HBS-RS total scores were better than HBSs (Cohen's kappa, 0.666 VS. 0.596). Sensitivities and specificities varied depending upon the cut-off for each item or for composite scores. Sensitivities in each item were high (85.0 - 92.5) at low cut-off (0 VS. 1 or 2). Specificities reached higher than 80% by using composite scores of HBS-RS. Receiver operating characteristic curves for HBS-RS total score showed fair diagnostic accuracy for PSP (AUC, 0.76 and 0.73). HBS-RS is a simple and measurable visual assessment tool to determine HBS with higher inter-rater agreement and adjustable diagnostic validity for PSP.
   **Publication type:** Journal: Conference Abstract
   **Source:** EMBASE

2. **Cognitive aspects of progressive supranuclear palsy**
   **Citation:** Neurodegenerative Diseases, March 2015, vol./is. 15/(209), 1660-2854 (March 2015)
   **Author(s):** Litvan I., Gerstenecker A.
   **Language:** English
   **Abstract:** Cognitive difficulties are a prevalent clinical feature in progressive supranuclear palsy (PSP). We evaluated a cross-sectional sample of 350 patients who met the NINDS-SPSP Criteria for PSP with a variety of commonly used neuropsychological tests. We found that approximately 1 in 4 patients had a Dementia Rating Scale Total score at or below the 1st percentile and had at least two tests at or below the 5th percentile. More than half of the sample had a primary executive dysfunction (e.g., 63% impaired on the Frontal Assessment Battery), with milder difficulties in memory, construction, and naming. These results have important clinical implications for clinicians following patients with PSP.
   **Publication type:** Journal: Conference Abstract
   **Source:** EMBASE
3. Cortical synaptic plasticity responses in Progressive Supranuclear Palsy may reflect disease progression

Citation: Brain Stimulation, March 2015, vol./is. 8/2(358), 1935-861X (March-April 2015)

Author(s): Bertram K.L., Williams D.R.

Language: English

Abstract: Diagnosis and measurement of disease progression in Progressive Supranuclear Palsy (PSP) remains a challenge as there are no diagnostic tests and clinical measures of disease progression are highly variable between patients. In addition to neuronal hyperphosphorylated tau deposits, cortical interneurons are lost in primary motor cortex and the motor thalamus. This pathology may influence cortical plasticity. Direct measurement of interneuronal dysfunction in PSP may provide a biomarker for disease progression. Objective: Long term potentiation-like plasticity has been shown to be abnormal in PSP with some correlation with disease progression over a 12 month period. Transcranial Magnetic Stimulation (TMS) studies can produce highly variable results between groups and patient cohorts. The aim of this study was to determine if these reported findings could be replicated in an independent cohort of patients with clinically diagnosed PSP. Methods: Thirteen patients with clinical PSP (10M 3F) were studied on two occasions 12 months apart, and measures of cortical excitability including the response to intermittent Theta burst induced long-term potentiation compared between visits and to clinical markers of disease progression. TMS was performed using a MagPro X100 (Magventure, Denmark) stimulating the Left M1 with recording electrodes over the right first dorsal interosseous. Intermittent Theta Burst stimulation was delivered in the protocol reported by Huang et al. Response to this was recorded at 5, 15 and 30 minutes following the theta burst stimulation. Results: Thirteen patients with an average disease duration of 3.4 years and PSPRS of 37 at baseline were studied. A correlation of R=0.57 (p=0.056) was seen between the changes in the degree of post-iTBS MEP facilitation between the baseline and 12 month assessment and the changes in PSPRS at these time points. Conclusions: Changes in plasticity responses in PSP parallel clinical disease progression and may be of value in objective measurement of disease progression.

Publication type: Journal: Conference Abstract

Source: EMBASE

4. Disease-specific structural and functional changes in thalamus and dentatorubrothalamic tract in PSP

Citation: Neurodegenerative Diseases, March 2015, vol./is. 15/(1860), 1660-2854 (March 2015)


Language: English

Abstract: Objectives To identify disease-specific changes of the thalamus, the basal ganglia, pons and midbrain in progressive supranuclear palsy (PSP) using diffusion tensor imaging, resting state fMRI (rs-fMRI) and volumetric analysis. Material and methods Two cohorts were used. In cohort A, MRI diffusion and volumetric data were acquired in controls (n=21), PSP (n=27), Parkinson’s disease (PD) and multiple-system atrophy (MSA-P) (n=11). In cohort B, comprising 30 controls and 8 patients with PSP, rs-fMRI data and clinical measures of motor performance and balance were available in addition to MRI diffusion and volumetric data. ROI-based analysis and tractography of diffusion data and seed-based analysis of rs-fMRI data were performed. Results In cohort A, we observed changes in mean diffusivity (MD) in the thalamus, red nucleus, superior cerebellar peduncle and midbrain in patients with PSP; most of these, including thalamic abnormalities, were not found in patients with PD or MSA-P. These changes were validated in cohort B. Further, MD of the dentatorubrothalamic tract was increased in PSP patients from both cohorts. Increased MD in the thalamus and along the dentatorubrothalamic tract correlated with impaired motor function or balance in patients with PSP. Volumetric analysis showed reduced thalamic volumes in PSP. The connectivity between the thalamus and anterior cingulate gyrus, caudate nucleus as well as frontal regions was reduced in PSP compared to controls. Conclusions Patients with PSP, but not PD or MSA-P, exhibit signs of structural and functional abnormalities in thalamus and in the dentatorubrothalamic tract. These changes might be associated with impaired balance.

Publication type: Journal: Conference Abstract

Source: EMBASE

5. Midbrain catecholaminergic neurons co-express alpha-synuclein and tau in progressive supranuclear palsy
Objective: To analyze the frequency and distribution of α-synuclein deposits in progressive supranuclear palsy (PSP).

Methods: The brains of 25 cases of pathologically confirmed PSP were evaluated with immunohistochemistry for α-synuclein and tau. Multiple immunofluorescent stains were applied to analyze the expression of tau and α-synuclein aggregates in catecholaminergic neurons. Patients’ clinical symptoms were retrospectively recorded. Results: Deposits α-synuclein in the form of typical Lewy bodies (LBs) were only found in two PSP cases (8%) that fulfilled the clinical subtype of PSP known as Richardson's syndrome (RS). LBs were present in the locus ceruleus (LC), substantia nigra pars compacta (SNc), basal forebrain, amygdala and cingulated cortex in a distribution mimicking that of Parkinson's disease (PD). Triple-immunolabeling revealed co-expression of α-synuclein and tau proteins in some tyrosine hydroxilase (TH)-positive neurons of the LC and SNc. Conclusions: There is no apparent clinical correlation between the presence of LBs in PSP. Tau protein co-aggregate with α-synuclein in catecholaminergic neurons of PSP brains suggesting a synergistic interaction between the two proteins. This is in keeping with the current view of neurodegenerative disorders as "misfolded protein diseases".

Publication type: Journal: Article
Source: EMBASE
Full text: Available Frontiers in Neuroanatomy at Frontiers in Neuroanatomy

6. Neurofilament light chain level in cerebrospinal fluid can differentiate Parkinson's disease from atypical parkinsonism: Evidence from a meta-analysis

Citation: Journal of the Neurological Sciences, May 2015, vol./is. 352/1-2(84-87), 0022-510X;1878-5883 (15 May 2015)

Author(s): Sako W., Murakami N., Izumi Y., Kaji R.

Language: English

Abstract: A reliable test that facilitates the accurate diagnosis of Parkinson's and disorders will help with both, clinical management and therapeutic research. In this context, neurofilament light chain (NFL) is candidate for a biomarker in cerebrospinal fluid (CSF). A comprehensive literature search yielded 4 eligible studies. We expressed between-group difference of NFL concentration in CSF as the standardized mean difference. Four studies involved 166 Parkinson's disease (PD), 116 multiple system atrophy (MSA) and 73 progressive supranuclear palsy (PSP) patients. Patients with MSA showed higher concentration of NFL concentration in CSF than those with PD (standardized mean difference = 1.60, P < 0.0001). These studies were homogeneous (P = 0.17). NFL in CSF in PSP was significantly elevated relative to PD with homogeneous studies (standardized mean difference = 2.04, P < 0.0001; P = 0.99). The present meta-analysis suggested that NFL concentration in CSF in MSA and PSP was significantly increased relative to PD, and that this could help us to separate PD from atypical parkinsonian syndromes.

Publication type: Journal: Article
Source: EMBASE

7. Neuropathologic features of suicide victims who presented with acute poststroke depression: significance of association with neurodegenerative disorders

Citation: Journal of neuropathology and experimental neurology, May 2015, vol./is. 74/5(401-410), 1554-6578 (01 May 2015)

Author(s): Nishida N., Hata Y., Yoshida K., Kinoshita K.

Language: English

Abstract: To investigate the neuropathologic characteristics of poststroke depression (PSD) leading to suicide, we retrospectively selected deceased subjects who had been diagnosed as having early PSD. Cases were divided into subjects who had committed suicide and those who had not. Neuropathologic examinations, including immunohistochemistry, were conducted. Twenty-four subjects fulfilled criteria for early PSD; 11 of these had committed suicide, and the other 13 had not. Lesion type, size of stroke, and location of stroke were variable but did not differ significantly between the groups. Alzheimer disease-related pathology stages also did not differ between the groups. Argyrophilic grain disease was found in both the suicide group (6 of 11) and the nonsuicide group (2 of 13); there were 2 highly possible cases of early progressive supranuclear palsy in the suicide group. Together, argyrophilic grain disease and progressive supranuclear palsy were found significantly more frequently
in suicide cases than in nonsuicide cases (p = 0.01). These data suggest that overlapping 4-repeat tauopathies, which include argyrophilic grain disease and progressive supranuclear palsy, might be an important aggravating factor of PSD that could lead to suicide. The presence of other neurodegenerative diseases does not preclude PSD because the prevalence of these diseases in older persons suggests that they might often occur concomitantly.

**Publication type:** Journal: Article

**Source:** EMBASE

**Full text:** Available *Journal of neuropathology and experimental neurology* at [Journal of Neuropathology and Experimental Neurology](https://www.journals.elsevier.com/journal-of-neuropathology-and-experimental-neurology)

8. Olfactory function combined with morphology distinguishes Parkinson's disease

**Citation:** Parkinsonism and Related Disorders, July 2015, vol./is. 21/7(771-777), 1353-8020;1873-5126 (01 Jul 2015)

**Author(s):** Sengoku R., Matsushima S., Bono K., Sakuta K., Yamazaki M., Komatsu T., Mitsumura H., Kono Y., Kamiyama T., Ito K., Mochio S., Iguchi Y.

**Language:** English

**Abstract:** Objective: This study aimed to examine whether the volume of the olfactory bulbs and tracts (OB & T) on magnetic resonance imaging (MRI) is useful for differentiating Parkinson's disease (PD) from PD-related disorders. Methods: The study group comprised 13 patients with PD, 11 with multiple system atrophy (MSA), five with progressive supranuclear palsy, and five with corticobasal degeneration (PSP/CBD). All patients were evaluated using the odor stick identification test for Japanese (OSIT-J), I-meta-iodobenzylguanidine (MIBG) scintigraphy, and brain MRI. OB & T areas on 1-mm-thick coronal images were measured and summed for volumes. We examined relationships between olfactory function and volume, and cardiovascular dysautonomia. We defined the cut-off values for OSIT-J score or MIBG uptake and OB & T volume to discriminate PD from PD-related disorders and calculated the proportional rate of PD in four categorized groups. Results: OB & T volume was smaller in PD than in MSA or PSP/CBD (<p=0.05 each). The cut-off for detecting PD patients was OSIT-J score <8, heart/mediastinum ratio <1.6, and OB & T volume <270 mm<sup>3</sup>. In the group with OSIT-J score <8 and OB & T volume <270 mm<sup>3</sup>, the proportion of PD patients among all patients with PD-related disorders was 91%. The rate of probable PD gradually increased as OSIT-J score and OB & T volume decreased (<p=0.001). Conclusions: Although preliminary, these data obtained from a combined morphological and functional evaluation of OB or cardiovascular dysautonomia could be useful for further differential of PD and other PD-related disorders.

**Publication type:** Journal: Article

**Source:** EMBASE

9. Pain in multiple system atrophy and progressive supranuclear palsy compared to Parkinson's disease

**Citation:** Brain and Behavior, May 2015, vol./is. 5/5, 2162-3279 (01 May 2015)

**Author(s):** Kass-Iliyya L., Kobylecki C., Mcdonald K.R., Gerhard A., Silverdale M.A.

**Language:** English

**Abstract:** Background: Pain is a common nonmotor symptom in Parkinson's disease (PD). The pathophysiology of pain in PD is not well understood. Pain characteristics have rarely been studied in atypical parkinsonian disorders such as Multiple System Atrophy (MSA) and Progressive Supranuclear Palsy (PSP). Aim of the study: We aimed to evaluate pain intensity, location, and associated symptoms in atypical parkinsonian disorders compared to PD. Methods: Twenty-one patients with MSA, 16 patients with PSP, and 65 patients with PD were screened for pain using question 1.9 of the MDS-UPDRS. Pain intensity was quantified using the short form McGill Pain Questionnaire (SFMPQ). Pain locations were documented. Motor disability was measured using UPDRS-III. Affective symptoms were assessed using the Hospital Anxiety and Depression Scale (HADS). Results: Pain was significantly more common and more severe in PD and MSA compared to PSP (<p < 0.01). Pain locations were similar with limb pain being the most common followed by neck and back pain. Pain intensity correlated with HADS scores but not motor severity. Conclusions: Pain is more common and more intense in PD and MSA than PSP. Differences in distribution of neurodegenerative pathologies may underlie these differential pain profiles.

**Publication type:** Journal: Article

**Source:** EMBASE
10. Pathophysiology, genetics, clinical features, diagnosis and therapeutic trials in progressive supranuclear palsy
Citation: Expert Opinion on Orphan Drugs, March 2015, vol./is. 3/3(253-265), 2167-8707 (01 Mar 2015)
Author(s): Bluett B., Litvan I.
Language: English
Abstract: Introduction: Progressive supranuclear palsy (PSP) is an atypical parkinsonian syndrome formally recognized in 1964. Historically considered sporadic, recent research has shown genes strongly associated with PSP. Pathologically, it is characterized by aggregated tau protein forming neurofibrillary tangles in predominantly subcortical neurons, tufted astrocytes and oligodendroglial inclusions. Patients typically present with progressive parkinsonism, ocular motility disturbances and early falls. Although rare in the general population, it is the most common atypical parkinsonian disorder - approximately 6% of all parkinsonian patients evaluated at a specialty clinic are diagnosed with PSP.

Areas covered: A relentlessly progressive neurodegenerative disorder, PSP is still commonly misdiagnosed. Genetic studies continue to provide insight into the pathophysiology of PSP, guiding future therapeutic trials. This paper summarizes the history, clinical features and subtypes, diagnostic criteria, neuroimaging, pathophysiology, genetic studies, current and future therapeutic trials in PSP.

Expert opinion: As PSP becomes more widely recognized and imaging modalities continue to advance, clinical diagnostic accuracy should improve. Currently, no proven disease-modifying agents are available for parkinsonian disorders such as PSP. Biochemical analysis of genes associated with PSP may elucidate how mutations impact brain cells, in hopes of directing future trials of disease-modifying agents and symptomatic therapeutic intervention.

Publication type: Journal: Article
Source: EMBASE

11. Patterns of gray matter atrophy in atypical parkinsonism syndromes: A VBM meta-analysis
Citation: Brain and Behavior, June 2015, vol./is. 5/6(1-10), 2162-3279 (01 Jun 2015)
Author(s): Yu F., Barron D.S., Tantiwongkosi B., Fox P.
Language: English
Abstract: Background and Purpose: Accurate diagnosis of Atypical Parkinsonian Syndromes (APS) is important due to differences in prognosis and management, but remains a challenge in the clinical setting. The purpose of our meta-analysis was to identify characteristic patterns of gray matter atrophy in Corticobasal Degeneration (CBD), Progressive Supranuclear Palsy (PSP), Multisystem Atrophy Parkinsonian type (MSA-P), and Idiopathic Parkinson's Disease (IPD). Materials and Methods: Whole-brain meta-analysis was performed on 39 published voxel-based morphometry (VBM) articles (consisting of 404 IPD, 87 MSA-P, 165 CBD, and 176 PSP subjects) using the modified Anatomic Likelihood Estimation method. Based on these results, contrast analyses were then utilized to determine areas of atrophy shared by as well as unique to each disorder. Results: CBD was characterized by asymmetric gray matter atrophy in multiple cortical regions, while the thalamus-midbrain and insula were predominantly involved in PSP. The striatum and superior cerebellum were affected in MSA-P, while IPD demonstrated an anterior cerebral pattern. Although there was a mild overlap among PSP, CBD, and MSA-P, significant regions of atrophy unique to each disorder were identified, including (1) the superior parietal lobule in CBD (2) putamen in MSA-P (3) insula and medial dorsal nucleus in PSP. Conclusion: Our results suggest that there are characteristic patterns of atrophy in APS. Guided by these findings, future studies on the individual subject level may lead to the development of robust imaging biomarkers.

Publication type: Journal: Article
Source: EMBASE

12. Progressive supra-nuclear palsy: Frequency of cardinal extrapyramidal features at first presentation
Citation: Postgraduate Medical Journal, 2015, vol./is. 91/1075(274-277), 0032-5473;1469-0756 (2015)
Author(s): Pradhan S., Tandon R.
Language: English
Abstract: Objectives Cardinal extrapyramidal features of progressive supranuclear palsy (PSP) help in clinically differentiating this condition from Parkinson's disease and other Parkinsonian syndromes. However, not all extrapyramidal features may be initially present, thus posing a difficulty in early diagnosis. We studied their frequency at the time of first presentation. Methods Patients diagnosed clinically with PSP using the National Institute for Neurological Disorders and Society for PSP (NINDS/SPSP) criteria and seen between August 2010 and April 2013 were examined for the presence, 'presence with deviation' or absence of six extrapyramidal features:
axial rigidity, symmetry, extended posture, backward falls, absence of tremors and lack of levodopa response. Results Twenty-eight patients (mean (SD) age 64.86 (9.72) years; 16 (57%) men) met the inclusion criteria. Of these, 14% had all six extrapyramidal features associated with PSP, 39% had five, 29% had four, 14% had three and 4% had two. The most frequent extrapyramidal sign was axial rigidity (68%). Axial plus peripheral rigidity was found in 18% of patients and peripheral rigidity alone in 14%. Extrapyramidal features were symmetrical in 29% and asymmetrical beyond 1 year in 29%. Body posture was extended in 46% and flexed in 21%. Backward falls were found in 50% and forward falls in 11%. Pill-rolling tremors were observed in 29%. Response to levodopa therapy was poor in 21% and good beyond 6 months in 39%. Conclusions Only 14% of PSP patients present with all six cardinal extrapyramidal features. Also, deviations from standard descriptions are common in the initial stages of disease.

Publication type: Journal: Article
Source: EMBASE
Full text: Available Postgraduate medical journal at Postgraduate medical journal

13. Progressive supranuclear palsy: What do we know about it?
Citation: Current Medicinal Chemistry, 2015, vol./is. 22/10(1182-1193), 0929-8673;1875-533X (2015)
Language: English
Abstract: Progressive supranuclear palsy (PSP) is a progressive tauopathy characterized by supranuclear ophthalomoplegia, pseudobulbar palsy, dysarthria, axial rigidity, frontal lobe dysfunction, and dementia. The typical pathology includes neuronal loss, gliosis and microtubule-associated protein tau (MAPT)-positive inclusions in neurons and glial cells, primarily in basal ganglia, brainstem and cerebellum. The pathogenesis of PSP is not yet completely understood; however, there are several hypotheses. This article reviews the present knowledge about PSP, and the concepts underlying mitochondrial dysfunction, lipoperoxidation, and gene mutations. The clinical features of PSP are also discussed; these include vertical gaze palsy, pseudobulbar palsy, aphasia, dysarthria, axial rigidity, and neuropsychiatric symptoms, such as amnesia, irritability, loss of interest, and dementia. In terms of diagnosis, there is considerable interest in neuroimaging for detecting PSP; therefore, neuroimaging techniques such as magnetic resonance imaging (MRI) and [18F]- fluorodeoxyglucose positron-emission tomography (FDG-PET) are reviewed. A definitive diagnosis of PSP depends on pathology, and the introduction of new clinical subtypes challenges presents the widely adopted diagnosis criteria. PSP treatments such as serotonin antagonists, alpha2 receptor antagonists, and coenzyme Q10 are also discussed. There is no curative therapy for PSP; all of the available treatments are palliative.
Publication type: Journal: Review
Source: EMBASE

14. Prolonged sleep latency and sleep onset REM in a neurodegenerative tauopathy disease
Citation: Sleep, 2015, vol./is. 38/(A281-A282), 0161-8105 (2015)
Author(s): Walsh C.M., Ruoff L., Varbel J., Walker K., Boxer A.L., Kramer J.H., Miller B.L., Neylan T.C.
Language: English
Abstract: Introduction: Though there has been little research in the area to date, tauopathies are typically thought to be associated with sleep disturbance. Of the tauopathies, sleep in individuals with Progressive supranuclear palsy (PSP), a 4 repeat (4r)-tauopathy, may be particularly affected as early neurodegenerative processes start in the brainstem. We hypothesized that individuals with PSP have a higher incidence of sleep disorders, poorer night-time sleep and are sleepier during the day compared to controls. Methods: Individuals with PSP (n = 13; 8 men; mean age: 61.5 +/- 6.4 years) and clinically healthy older adults (n = 9; 5 men; mean age: 72.7 +/- 4.5 years) were studied in the UCSF clinical research center with overnight polysomnography and a multiple sleep latency test (MSLT) the next day. Results: We found an increased incidence of periodic limb movements but not sleep apnea in PSP. Individuals with PSP took longer to fall asleep (p = 0.005), spent less time asleep (p = 0.03), less time in REM sleep (p = 0.02) and overall had poorer sleep efficiency (p = 0.004) and maintenance (p = 0.01). Unexpectedly, on the MSLT, 3/13 PSP never fell asleep. Of those that did fall asleep (10 PSP, 9 controls), individuals with PSP took longer to fall asleep (p = 0.02) and 3/10 individuals entered REM sleep. REM sleep was absent in the daytime sleep periods in controls. Conclusion: As expected, PSP had a higher incidence of some sleep disorders and greater nighttime sleep disturbance. Contrary to our hypotheses, PSP individuals appeared less able to sleep though had increased incidence sleep-onset REM episodes. Sleep-onset REM sleep during an MSLT with prolonged sleep latencies are both unexpected and novel. Based on our current
findings, regulatory mechanisms for sleep/waking, as well as REM sleep are disrupted in PSP Future work includes increasing our sample and adding an additional 4r-tauopathy cohort (Corticobasal Degeneration).

**Publication type:** Journal: Conference Abstract

**Source:** EMBASE

15. Square-wave jerks and macrosaccadic oscillations

**Citation:** Neuro-Ophthalmology Japan, 2015, vol./is. 32/1(23-31), 0289-7024 (2015)

**Author(s):** Komiyama A.

**Language:** Japanese

**Abstract:** It is well known that the primary feature of nystagmus is a drift of the eyes from the desired position of the eyes; saccadic intrusions, however, are characterized by inappropriate saccadic movements that interfere with steady fixation. Several types of saccadic intrusions have their own salient features including the presence or absence or duration of their saccadic intervals. In this article, we aim to update readers on the latest advances in understanding square-wave jerks (SWJs) and macrosaccadic oscillations (MSOs), in which the abnormal eye movements have saccadic intervals, and present video clips and electrooculograms of the typical eye movements for a comparison. SWJs are small, conjugated saccades, ranging from 0.5 to 5 degrees (usually less than 2 degrees) in size, which take the eyes away from the fixation position, subsequently returning to the original position after a period of about 200 ms. SWJs are commonly found in healthy subjects, especially the elderly; they occur frequently in cerebral disease, spinocerebellar degeneration, and progressive supranuclear palsy. SWJs may likely result from abnormally enlarged microsaccades that play a pivotal role in optimizing the perception of an object by shifting the image on the retina in small portions of approximately 0.5 degrees. On the other hand, MSOs are a rare form of large-sized saccadic oscillations around the fixation point that wax and wane, reportedly with a "normal" saccadic interval of 200 ms, and were documented in cerebellar disorders and myasthenia gravis with edrophonium administration. MSOs, however, are considered to be an enhanced variation of saccadic hypermetria with the saccadic gain over 2.0, and therefore, the saccadic interval of MSOs should be the same as that of short-latency corrective saccades after saccadic hypermetria, which is around 125 ms in reported cases.

**Publication type:** Journal: Article

**Source:** EMBASE

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**News**

**Athlete’s foot cream could also treat multiple sclerosis**

Wednesday 22nd April 2015

“Two common drugs – one used for treating athlete's foot and another for alleviating eczema – may be useful therapies for multiple sclerosis,” BBC News reports. The drugs have shown promise in lab and animal studies.

**'Missing link' between brain and immune system discovered**

Monday 8th June 2015

“Newly discovered vessels beneath skull could link brain and immune system,” The Guardian reports. It is has been suggested that the discovery, which has been described as textbook-changing, could lead to new treatments for a range of neurological conditions.

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