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Magnesium in Parkinson's disease: an update in clinical and basic aspects

Kiyomitsu Oyanagi and Tomoyo Hashimoto.

Author Information and Affiliations

Abstract

Magnesium (Mg) is essential for cell functions such as transport of calcium and potassium ions, and modulates signal transduction, energy metabolism, and cell proliferation. Several studies elucidated a reduced concentration of Mg in patients with Parkinson's disease (PD), and experimentally, severe loss of dopaminergic neurons exclusively in the substantia nigra in 1-year-old rats that had been subjected to continuously low Mg intake (one-fifth of the normal level) over generations. A study conducted by the authors revealed a significant and striking effect of Mg to prevent neurite and neuron pathology, and also to ameliorate neurite pathology in a rat Parkinson disease (PD) model involving culture of ventral mesencephalic-striatal cells with 1-methyl-4-phenylpyridinium (MPP+). Mg is expected to prevent and ameliorate Parkinson's disease in cases where it would be able to cross into the brain in a suitable way.

Introduction

Parkinson's disease (PD) is a neurodegenerative disease occurring in middle-aged and aged humans characterized by clinical symptoms including tremor and rigidity (Parkinson, 1817). It has been reported that almost 90% of the patients are sporadic and 10% are familial. Sporadic PD shows neuropathological features involving the appearance of Lewy bodies (Lewy, 1912; Tretiakoff, 1919) and loss of neurons in the substantia nigra (Figures 1 and 2) and substantia innominata. After establishment of the disease as an entity, it was revealed that dopaminergic neurons in the ventral tegmental area, noradren- ergic neurons in the locus coeruleus and motor vagal nucleus, serotonergic neurons in the dorsal raphe nucleus, and neurons in the sympathetic ganglia and visceral autonomic nervous system are involved in the disease with neuronal loss and presence of Lewy bodies (Jellinger, 1999). In the present manuscript, the authors review the role of magnesium (Mg) in the pathogenesis and patho- mechanisms in clinical and basic aspects of PD.

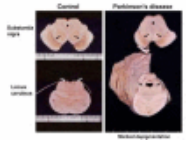

Figure 1.

Midbrain and upper pons. The substantia nigra and locus coeruleus in the patient with Parkinson's disease show marked depigmentation as compared with those of controls.

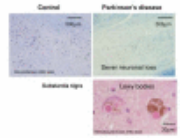

Figure 2.

The substantia nigra of a patient with Parkinson's disease shows severe loss of neurons as compared with a control subject. Some remaining neurons represent Lewy bodies.

Mg in Parkinson's disease and related diseases

Uitti *et al*., (1989) analysed four brain regions (frontal cortex, caudate nucleus, substantia nigra and cerebellum) for concentrations of 24 metals (Ag, Al, As, B, Be, Ca, Cd, Co, Cr, Cu, Fe, K, Pb, Mg, Mn, Mo, Na, Ni, P, Se, Ti, V, W, Zn) by atomic absorption and atomic emission spectroscopy in brains of 9 patients with PD, 15 patients with other chronic neurological diseases and 12 subjects of controls. The results were that brains of PD and parkinsonism secondary to neurofibrillary tangle disease showed lower concentrations of Mg in the caudate nucleus and copper in the substantia nigra than control brains. Barbiloni *et al*., (1999) performed in vivo phosphorus magnetic resonance spectroscopy on the occipital lobes of 13 patients with PD, 15 patients with multiple system atrophy and 16 age-matched healthy subjects. They reported that patients with PD showed significantly increased contents of inorganic phosphate (Pi), decreased cytosolic free [Mg^{2+}], and unchanged phosphocreatine and pH. Bocca *et al*., (2006) examined concentrations of Ca, Cu, Fe, Mg, Si and Zn by inductively coupled plasma atomic emission spectrometry (ICP-AES) in blood, urine and cerebrospinal fluid (CSF) of 91 PD patients and 18 controls. They concluded that Mg concentration in CSF of PD patients decreased with the duration and severity of the disease.

It has been proposed that Mg deficiency is involved in the pathogenesis of parkinsonism-dementia complex (PDC) and amyotrophic lateral sclerosis (ALS) in the Chamorro population on Guam, which is a member of the Mariana Islands in the western Pacific Ocean, as well as in the Kii peninsula of Japan and in West New Guinea (Yase 1978, Garruto *et al.,* 1984). PDC is a disease entity that was established by Hirano *et al.,* (1961a; 1961b) that affects the neurons in the substantia nigra, brainstem, and temporal and frontal cortex. The disease is characterized by the presence of neurofibrillary tangles in the remaining neurons, and disease-specific granular hazy inclusions in the astrocytes (Oyanagi *et al.,* 1997; Oyanagi, 2005), tau-positive fine granules in the cerebral white matter (Yamazaki *et al.,* 2005), and widespread TDP-43-immunopositive inclusions (Hasegawa *et al.,* 2007). Patients exhibit parkinsonism and dementia, and usually die within about 5 years from infectious diseases (Hirano *et al.,* 1961a; 1961b; Chen and Chase, 1985). ALS is a motor neuron disease affecting the Betz cells in the cerebral cortex, and facial and hypoglossal nuclei in the brainstem and anterior horn cells in the spinal cord, and usually patients die of respiratory failure within 5 years after the onset.

Possible pathomechanisms in Parkinson's disease

Mitochondrial damage and oxidative stress

Increased expression of 4-hydroxy-2-nonenal (HNE) (Yoritaka *et al.,* 1996), decreased activity of mitochondrial complex I and a decreased amountof alpha-ketoglutarate dehydrogenase complex (KGDHC) in the pigmented neurons of the substantia nigra (Hattori *et al.,* 1991; Mizuno *et al.,* 1994) have been reported in affected patients. In the substantia nigra, decreased activity of catalase and peroxidase (Ambani *et al.,* 1975) and increased amounts of protein carbonyls, 8-hydroxy-2'-deoxyguanosine (8-OHdG)/8-hydroxy- guanine (8-OHG), 4-hydroxynonenal-lysine and malondialdehyde-lysine (MDAL) (Alam *et al.,* 1997a,b; Zhang *et al.,* 1999; Dalfo *et al.,* 2005) have been reported.

1-Methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP) was the first human parkinsonian agent to be characterized. It is converted to 1-methyl-4- phenylpyridinium (MPP^+) by monoamine oxidase B in astrocytes. MPP^+ damages mitochondrial complex I of dopaminergic neurons after transfer by the dopamine transporter, and increased calcium permeability of the mitochondrial

membrane induces free radicals (Smeyne *et al.,* 2005). MPP^+ has been used to induce selective degeneration of dopaminergic neurons in an experimental model of PD (Nakamura *et al.,* 2000). In addition, rotenone, 6-hydroxydopamine (6-OHDA), paraquat and annonacin have been used as noxious agents to create in vivo models of PD (Fornai *et al.,* 2003; Champy *et al.,* 2004; Bove *et al.,* 2005) (Figure 3). Dopamine and dopamine quinones themselves are considered to be causes of oxidative stress. PINK1 (PTEN-induced putative kinase 1) maintains mitochondrial function and the gene is causative in some familial PD (Valente *et al.,* 2004).

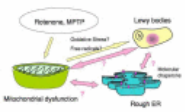

Figure 3.

Possible relationship between mito- chondria, rough ER and Lewy body formation.

Unfolded protein retention and endoplasmic reticulum stress

Alpha-synuclein was found as a main component of the Lewy bodies and the gene was found to be a causative gene of a rare autosomal dominant PD (Polymeropoulos *et al.,* 1997). It has been reported that multiplication of the gene was to be the cause of the disease (Singleton *et al.,* 2003). It has been suggested that aggregates of alpha-synuclein cause potentiation of oxidative stress, possibly with interaction with iron.

Synuclein was considered to be degraded in the proteasome. Knockout of the 26S proteasome in the dopaminergic neurons induced “pale bodies”, which is reported to be a prodrome of the Lewy bodies (Bedford *et al.,* 2008).

Parkin and UCHL-1 are considered essential for ubiquitination of the unfolded proteins, and the gene mutations were found in some familial PD. It is considered that oxidative stress may lead a combination of Parkin and DJ-1, and the combination suffocates unfolded protein degrad- ation (Kitada *et al.,* 1998; Bonifati *et al.,* 2003). Mg has also been reported to inhibit spontaneous and iron-induced aggregation of alpha-synuclein (Golts *et al.,* 2002) (Figure 4).

Figure 4.

Scheme of possible pathomechanisms of dopaminergic neuron death in Parkinson’s disease.

Low Mg and Parkinson’s disease model

In the course of investigations into the patho- genesis of the PDC, the present authors performed an experiment in which rats were exposed to restricted intake of Ca and/or Mg over two generations. This resulted in severe loss of dopaminergic neurons exclusively in the substantia nigra in 1-year-old rats that had been subjected to continuously low Mg intake (one- fifth of the normal level) over generations (Oyanagi *et al.,* 2006). This finding suggested a deep concern of low Mg intake over several generations to the pathogenesis of degeneration of the substantia nigra in humans.

Therapeutic possibility by Mg for Parkinson’s disease

As a blocker of the glutamatergic NMDA receptor

Mg controls cytochrome c release in mito- chondria (Eskes *et al.,* 1998), and decreases the activity of N-methyl-D-aspartate (NMDA) receptors in excitotoxicity (Mayer *et al.,* 1984). Mg

treatment has also been shown to decrease cerebral infarct volume in rats in vivo (Lyden *et al.,* 2000). The mechanism responsible for the neuroprotective effect of Mg has been considered to be reduced presynaptic release of the neurotrans-mitter glutamate (Lin *et al.,* 2002), and blockade of the glutamatergic NMDA receptor (Nowak *et al.,* 1984)(Figure 5). A relationship between decreased Mg concentration in serum and migraine has been reported in humans, and it has been suggested that migraine might be caused by hypersensitivity of the NMDA receptor to glutamic acid and certain other neuro-excitatory amino acids due to Mg depletion (Cojocaru *et al.,* 2006). A decrease of cytosolic free Mg in the occipital lobe of PD patients has also been demonstrated by phosphorus magnetic response spectroscopy (Barbiroli *et al.,* 1999).

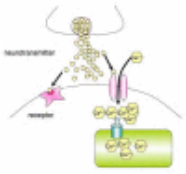

Figure 5.

Metallic elements and neuron conduction.

As an inhibiter of oxidative stress

The present authors conducted a study to clarify the effects of Mg administration in a rat PD model involving culture of ventral mesencephalic- striatal cells with 1-methyl-4-phenylpyridinium (MPP^+), based on recent evidence for significant loss of dopaminergic neurons exclusively in the substantia nigra of 1-year-old rats after exposure to low Mg intake over generations (Oyanagi *et al.,* 2006) (Figure 6). The results indicated that Mg might protect dopaminergic neurons in the substantia nigra from degeneration. The concentration of Mg in the culture medium varied from 0.8 mM, corresponding to the control condition, to 4.0 mM. Effects were estimated by counting the number of surviving dopaminergic neurons immunopositive for tyrosine hydroxylase and measuring the length of dopaminergic neurites. An increase in the concentration of Mg to 1.2 mM significantly inhibited the toxicity of MPP^+, and a concentration of 4.0 mM completely prevented any decrease in the number of dopaminergic neurons. The length of dopam- inergic neurites was significantly preserved in the presence of Mg at 1.2 and 4.0 mM. An increase in the concentration of Mg to 1.2 and 4.0 mM led to a significant amelioration in the length of dopam- inergic neurites after MPP^+ toxicity (Figure 7).

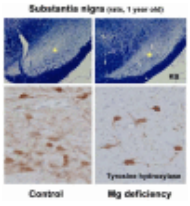

Figure 6.

Severe atrophy and selective loss of dopaminergic neurons in the substantia nigra in rats with low Mg over generations (Oyanagi K, *et al.,* 2006).

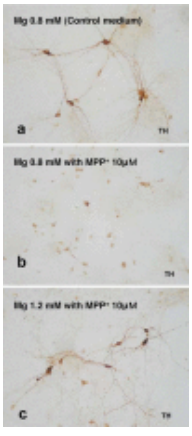

Figure 7.

Prevention of MPP^+ toxicity by Mg in a Parkinson model (Hashimoto *et al.,* 2008). *a:* normal condition of cultured nigral dopaminergic neurons. *b:* severe loss of dopaminergic neurons and the neuritis after MPP^+ administration. *c:* An increase in the concentration (more...)

This was the first report to document a significant and striking effect of Mg for prevention of neurite and neuron pathology, and also amelioration of neurite pathology in a PD model. In addition, an increase in the Mg concentration to 1.2, 2.0, and 4.0 mM did not induce any degenerative features in the cultured dopaminergic cells, suggesting that a Mg concentration of up to 4.0 mM in the extracellular space might not induce any neuron degeneration in humans. Mg oxide per os has often been used as a laxative for patients with PD, but is reportedly not absorbed in the bowels, thus not affecting the serum concentration of Mg (Sakimura *et al.,* 1998). Recent studies by the authors using mice also established that no significant alteration was found in the CSF of B6 mice injected intraperitoneally with Mg, even though the serum Mg concentration was significantly increased (Sun *et al., 2009*). Further research is necessary to find Mg compounds that can easily be absorbed in the bowels and pass through the blood-brain barrier, like Mg-L- threonate (Slutsky *et al.,* 2010) and besides, via transporters that can carry Mg through the bowel mucosa, blood-brain barrier and plasma membrane of neurons.

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References

Alam ZI, Daniel SE, Lees AJ, Marsden CD, Jenner P, Halliwell B. A generalized increase in protein carbonyls in the brain in Parkinson's but incidental Lewy body disease. J Neurochem. 1997a;69:1326–9. [PubMed: 9282961]

Alam ZI, Jenner A, Daniel SE, Lees AJ, Cairns N, Marsden CD, Jenner P, Halliwell B. Oxidative DNA damage in Parkinsonian brain; An apparent selective increase in 8-Hydroxyguanine levels in substantia nigra. J Neurochem. 1997b;69:1196–203. [PubMed: 9282943]

Ambani LM, Van Woert MH, Murphy S. Brain peroxidase and catalase in Parkinson disease. Arch Neurol. 1975;32:114–8. [PubMed: 1122174]

Barbiroli B, Martinelli P, Patuelli A, Lodi R, Iotti S, Cortelli P, Montagna P. Phosphorus magnetic resonance spectroscopy in multiple system atrophy and Parkinson's disease. Mov Disord. 1999;14:430–5. [PubMed: 10348465]

Bedford L, Hay D, Devoy A, Paine S, Powe DG, Seth R, Gray T, Topham I, Fone K, Rezvani N, Mee M, Soane T, Layfield R, Sheppard PW, Ebendal T, Usoskin D, Lowe J, Mayer RJ. Depletion of 265S proteasomes in mouse brain neurons caused neurodegeneration and Lewy-like inclusions resembling human pale bodies. J Neurosci. 2008;28:8189–98. [PMC free article: PMC6670564] [PubMed: 18701681]

Bocca B, Alimonti A, Senofonte O, Pino A, Violante N, Petrucci F, Sancesario G, Forte G. Metal changes in CSF and peripheral compartments of parkinsonian patients. J Neurol Sci. 2006;248:23–30. [PubMed: 16765382]

Bonifati V, Rizzu P, van Baren MJ, Schaap O, Breedveld GJ, Krieger E, Dekker MC, Squitieri F, Ibanez P, Joosse M, van Dongen JW, Vanacore N, van Swieten JC, Brice A, Meco G, van Duijn CM, Oostra BA, Heutink P. Mutations in the DJ-1 gene associated with autosomal recessive early-onset parkinsonism. Science. 2003;299:256–9. [PubMed: 12446870]

Bove J, Prou D, Perier C, Przedborski S. Toxin- induced models of Parkinson's disease. Neurotherapeutics. 2005;2:484–94. [PMC free article: PMC1144492] [PubMed: 16389312]

Champy P, Hoglinger GU, Feger J, Gleye C, Hocquemiller R, Laurents A, Guerineau V, Laprevote O, Medija F, Lombes A, Michel P P, Lannuzel A, Hirsch EC, Ruberg M. Annonacin, a lipophilic inhibitior of mitochondrial complex I, induces nigral and striatal neurodegeneration in rats. J Neurochem. 2004;88:63–9. [PubMed: 14675150]

Chen K-M, Chase TN (1985) Parkinsonism-dementia. In: *Handbook of Clinical Neurology Vol. 49* (Vinken PJ, Bruyn GW, Klawans HL, eds), Amsterdam, Elsevier, pp. 167-83.

Cojocaru M, Cojocaru IM, Muuroi C, Botezat M, Lazar L, Duruta A (2006) Serum magnesium concentrations in migraine with aura. In: *Advances in Magnesium Research: New Data* (Nechifor M, Porr PJ, eds), Cluj Napoca, Casa Cartii de Stiinta Press, pp 31-5.

Dalfo E, Protero-Otin M, Ayala V, Martinez A, Pamplona R, Ferrer I. Evidence of oxidative stress in the neocortex in incidental Lewy body disease. J Neuropathol Exp Neurol. 2005;64:816–30. [PubMed: 16141792]

Eskes R, Antonsson B, Osen-Sand A, Montessuit S, Richter C, Sadoul R, Mazzei G, Nichols A, Martinou JC. Bax-induced cytochrome C release from mitochondria is independent of the permeability transition pore but highly dependent on Mg^{2+} ions. J Cell Biol. 1998;143:217–24. [PMC free article: PMC2132823] [PubMed: 9763433]

Fornai F, Lenzi P, Gesi M, Ferrucci M, Lazzeri G, Busceti CL, Ruffoli R, Soldani P, Ruggieri S, Alessandri MG, Paparelli A. Fine structure and biochemical mechanisms underlying nigrostriatal inclusions and cell death after proteasome inhibition. J Neurosci. 2003;23:8955–66. [PMC free article: PMC6740387] [PubMed: 14523098]

Garruto RM, Yanagihara R, Gajdusek DC. Arion DM (1984) Concentration on heavy metals and essential minerals in garden soil and drinking water in the Western Pacific. In: *Amyotrophic Lateral Sclerosis in Asia and Oceania* (Chen KM, Yase Y, eds), Taipei, National Taiwan University, 265-330.

Golts N, Snyder H, Frasier M. Magnesium inhibits spontaneous and iron-induced aggregation of alpha-synuclein. J Biol Chem. 2002;277:16116–23. theisler C, Choi P, Wolozin B. [PubMed: 11850416]

Hasegawa M, Arai T, Akiyama H, Nonaka T. TDP-43 is deposited in the Guam parkinsonism- dementia complex brains. Brain. 2007;130:1386–94. Hiroshi Mori, Hashimoto T, Yamazaki M, Oyanagi K. [PubMed: 17439983]

Hattori N, Tanaka M, Ozawa T, Mizuno Y. Immunohistochemical Studies on complexes I, II, III, and VI of mitochondoria in Parkinson's disease. Ann Neurol. 1991;30:563–71. [PubMed: 1665052]

Hirano A, Kurland LT, Krooth RS, Lessell S. Parkinsonism-dementia complex, an endemic disease on the island of Guam. I. Clinical features. Brain. 1961a;84:642–61. [PubMed: 13907609]

Hirano A, Malamud N, Kurland LT. Parkinsonism-dementia complex, an endemic disease on the Island of Guam. II. Pathological features. Brain. 1961b;84:662–79. [PubMed: 13907610]

Jellinger KA. The role of iron in neurodegeneration : prospects for pharmacotherapy of Parkinson's disease. Drugs Aging. 1999;14:115–40. [PubMed: 10084365]

Kitada T, Asakawa S, Hattori N, Matsumine H, Yamamura Y, Minoshima S, Yokochi M, Mizuno Y, Shimizu N. Mutations in the parkin gene cause autosomal recessive juvenile parkinsonism. Nature. 1998;392:605–8. [PubMed: 9560156]

Lewy FH (1912) Paralysis agitans. In: *Pathologische Anatomi* (Lewandowsky M, ed). Handbuch der Neurologie, vol. 3. Berlin, Springer, 920-33.

Lin JY, Chung SY, Lin MC, Cheng FC. Effects of magnesium sulfate on energy metabolites and glutamate in the cortex during focal cerebral ischemia and reperfusion in the gerbil monitored by a dural- probe microdialysis technique. Life Sci. 2002;71:803–11. [PubMed: 12074939]

Lyden P, Wahlgren NG. Mechanisms of action of neuroprotectants in stroke. J Stroke Cerebrovasc Dis. 2000;9:9–14. [PubMed: 17895214]

Mayer ML, Westbrook GL, Guthrie PB. Voltage- dependent block by Mg^{2+} of NMDA responses in spinal cord neurones. Nature. 1984;309:261–3. [PubMed: 6325946]

Mizuno Y, Matuda S, Yoshino H, Mori H, Hattori N, Ikebe S. An immunohistochemical study on alpha-ketoglutarate dehydrogenase complex in Parkinson's disease. Ann Neurol. 1994;35:204–10. [PubMed: 8109900]

Nakamura K, Bindokas VP, Marks JD, Wright DA, Frim DM, Miller RJ, Kang UJ. The selective toxicity of 1-methyl-4-phenylpyridinium to dopaminergic neurons: the role of mitochondrial complex I and reactive oxygen species revisited. Mol Pharmacol. 2000;58:271–8. [PubMed: 10908294]

Nowak L, Bregestovski P, Ascher P, Herber A, Prochiantz A. Magnesium gates glutamate-activated channels in mouse central neurons. Nature. 1984;307:462–5. [PubMed: 6320006]

Oyanagi K. The nature of the parkinsonism- dementia complex and amyotrophic lateral sclerosis of Guam and magnesium deficiency. Parkinson Rel Dis. 2005;11:S17–S23. [PubMed: 15885623]

Oyanagi K, Kawakami E, Kikuchi-Horie K, Ohara K, Ogata K, Takahama S, Wada M, Kihira T, Yasui M. Magnesium deficiency over generations in rats with special references to the pathogenesis of the parkinsonism-dementia complex and amyotrophic lateral sclerosis of Guam. Neuropathology. 2006;26:115–28. [PubMed: 16708544]

Oyanagi K, Makifuchi T, Ohtoh T, Chen K-M, Gajdusek DC, Chase TN. Distinct pathological features of the Gallyas- and tau-positive glia in the parkinsonism- dementia complex and amyotrophic lateral sclerosis of Guam. J Neuropathol Exp Neurol. 1997;56:308–16. [PubMed: 9056545]

Parkinson J (1817) *An Essay on the Shaking Palsy*. (Neely and Jones, ed) Whittingham and Rowland for Sherwood, London.

Polymeropoulos MH, Lavedan C, Leroy E, Ide SE, Dehejia A, Dutra A, Pike B, Root H, Rubinstein J, Boyer R, Stenroos ES, Chandrasekharappa S, Asanassiadou A, Papapetropoulos T, Johnston WG, Lazzarini AM, Duvoisin RC, Di Iorio G, Golbe LI, Nussbaum RL. Mutation in the alpha-synuclein gene identified in families with Parkinson's disease. Science. 1997;276:2045–7. [PubMed: 9197268]

Sakimura K, Machino H, Miyoshi K, Nakata K, Ueda K, Ide M, Minegishi A, Harada Y. Clinical evaluation of YO-106 (magnesium oxide tablets) in the treatment of Habitual constipation-A cross over study with Magnesium oxide powders (JP)- Jpn Pharmacol Ther. 1998;26:1027–53.

Saris NE, Mervaala E, Karppanen H, Khawaja JA, Lewenstam A. Magnesium. An update on physiological, clinical and analytical aspects. Clin Chim Acta. 2000;294:1–26. [PubMed: 10727669]

Singleton AB, Farrer M, Johnson J, Singleton A, Hague S, Kachergus J, Hulihan M, Peuralinna T, Dutra A, Nussbaum R, Lincoln S, Crawley A, Hanson M, Maraganore D, Adler C, Cookson MR, Muenter M, Baptista M, Miller D, Blancato J, Hardy J, Gwinn-Hardy K. Alpha-synclein locus triplication causes Parkinson’s disease. Science. 2003;302:841. [PubMed: 14593171]

Slutsky I, Abumaria N, Wu LJ, Huang C, Zhang L, Li B, Zhao X, Govindarajan A, Zhao MG, Zhuo M, Tonegawa S, Liu G. Enhancement of learning and memory by elevating brain magnesium. Neuron. 2010;65:165–77. [PubMed: 20152124]

Smeyne RJ, Jackson-Lewis V. The MPTP model of Parkinson’s disease. Brain Res. Mol Brain Res. 2005;134:57–66. [PubMed: 15790530]

Sun L, Kosugi Y, Kawakami E, Piao Y-S, Hashimoto T, Oyanagi K. Magnesium concentration in the cerebrospinal fluid of mice and its response to changes in serum magnesium concentration. Magnes Res. 2009;22:266–72. [PubMed: 20228005]

Tretiakoff C (1919) Contribution a l’etude del l’Anatomie pathologique du Locus Niger de Soemmering avec quelques deduction relatives a la pathogenie des troubles du tonus musculaire et de la maladie de Parkinson. *Theses de Paris*.

Uitti Rj, Rajput AH, Rozdilsky B, Bickis M, Wollin T, Yuen WK. Regional metal concentrations in Parkinson’s disease, other chronic neurological diseases, and control brains. Can J Neurol Sci. 1989;16:310–4. [PubMed: 2766123]

Valente EM, Abou-Sleiman PM, Caputo V, Muqit MMK, Harvey K, Gispert S, Ali Z, Del Turco D, Bentivoglio AR, Healy DG, Albanese A, Nussbaum R. Hereditary Early-Onset Parkinson's Disease Caused by Mutations in *PINK1*. Science. 2004;304:1158–60. González- Maldonado R, Deller T, Salvi S, Cortelli P, Gilks WP, Latchman DS, Harvey RJ, Dallapiccola B, Auburger G, Wood NW. [PubMed: 15087508]

Yamazaki M, Hasegawa M, Mori O, Murayama S, Tsuchiya K, Ikeda K, Chen K-M, Katayama Y, Oyanagi K. Tau-positive fine granules in the cerebral white matter: a novel finding among tauopathies exclusive to parkinsonism-dementia complex of Guam. J Neuropathol Exp Neurol. 2005;64:1–8. [PubMed: 16215455]

Yase Y (1978) ALS in the Kii peninsula: one possible etiological hypothesis. In: *Amyotrophic lateral sclerosis* (Tsubaki T, Toyokura Y, eds), Tokyo, University of Tokyo Press, pp. 307-18.

Yoritaka A, Hattori N, Uchida K, Tanaka M, Stadtman ER, Mizuno K. Immunohistochemical detection of 4-hydroxynonenal protein adducts in Parkinson's disease. Proc Natl Acad Sci USA. 1996;93:2696–701. [PMC free article: PMC39693] [PubMed: 8610103]

Zhang J, Perry G, Smith MA, Robertson D, Olson SJ, Graham DG, Montine TJ. Parkinson's disease is associated with oxidative damage to cytoplasmic DNA and RNA in substantia nigra neurons. Am J Pathol. 1999;154:1423–9. [PMC free article: PMC1866598] [PubMed: 10329595]

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