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**Viral Parkinsonism**

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## Abstract

Parkinson's disease is a debilitating neurological disorder characterized that affects 1-2% of the adult population over 55 years of age. For the vast majority of cases, the etiology of this disorder is unknown, although it is generally accepted that there is a genetic susceptibility to any number of environmental agents. One such agent may be viruses. It has been shown that numerous viruses can enter the nervous system, i.e. they are neurotropic, and induce a number of encephalopathies. One of the secondary consequences of these encephalopathies can be parkinsonism, that is both transient as well as permanent. One of the most highlighted and controversial cases of viral parkinsonism is that which followed the 1918 influenza outbreak and the subsequent induction of von Economo's encephalopathy. In this review, we discuss the neurological sequelae of infection by influenza virus as well as that of other viruses known to induce parkinsonism including Coxsackie, Japanese encephalitis B, St. Louis, West Nile and HIV viruses.

The syndrome, which we know today as Parkinson's disease (PD), was first described in 1817 by Dr. James Parkinson in a paper entitled "An Essay on the Shaking Palsy" [1]. PD is a debilitating neurological disorder that strikes approximately 1-2% of the adult population greater than 50 years of age [2]. Current estimates from the Parkinson's Disease Foundation put the number of people suffering from this disease at 4.1 million people which is predicted to rise to 8.7 million based on a projected increase in lifespan. The costs of treatment of PD can be staggering. At an average per patient cost of \$7859.00 per year (adjusted according to the consumer price index from 1998 figures and includes drugs, physicians and loss of pay to patient and family members), the total cost of the disease may approach \$7,800,000,000.00 per year; of which 85% is borne to private and government (Social Security, Medicare) insurance [3]. In fact, more individuals present with PD than with multiple sclerosis, muscular dystrophy and amyotrophic lateral sclerosis (Lou Gehrig's Disease) combined. Since PD is an incurable disease with an average life expectancy after diagnosis of 15 years, there should be an even larger burden on both the social and financial resources of families, insurance companies and the Federal government in the upcoming decade than is present today.

Parkinson's disease is primarily characterized by a loss of the pigmented cells located in the midbrain substantia nigra pars compacta (SNpc), although cell loss has also been described in the locus coeruleus [4], the dorsal motor nucleus of the vagus nerve [5], and throughout the autonomic nervous system [6, 7]. In addition to the SNpc neuronal loss, there is a reduction in the number of the afferent fibers that project from this structure to the striatum. The motor symptoms of Parkinson's disease that are the most recognizable include the appearance of an expressionless "mask-like" face, rigidity of the extremities also known as "cogwheeling",

bradykinesia or slowness of movement, shuffling, festinating gait and lack of coordination, and a 4 Hz resting tremor called "pill-rolling". These symptoms are thought to first manifest when approximately 60% of the SNpc neurons have already died [8]. . In addition to these motor symptoms, there are a number of non-motor symptoms that precede as well as follow the onset of motor symptoms [9-11]. In addition to neuronal loss, primary PD is also defined by the presence of proteinaceous inclusion bodies called Lewy Bodies. Lewy bodies were first described and linked to PD by Frederic Lewy [12], and subsequently these have been shown to consist of a number of proteins including aggregated alpha-synuclein [13].

The clinical presentation seen in PD can also occur in the absence of Lewy bodies or other pathological hallmarks of primary PD [14] and are referred to here as secondary parkinsonism. Three diseases that fit this description are Multiple System Atrophy [15], Progressive Supranuclear Palsy [16] and Corticobasal Degeneration. Other causes of secondary parkinsonism include infectious agents [17], drugs [18], toxins [19], vascular insults [20], trauma [21], and although rare other physiological problems such as tumor [22, 23].

The underlying cause for the vast majority of PD cases is unknown. Controversy still exists as to how much of the disease results from a strict genetic causation, a purely environmental factor, or the more parsimonious combination of the two risk factors [24-26]. Empirical evidence suggests that only a small percentage (ranging from 2-10%) of diagnosed PD has a strict familial etiology. At this time, there have been 13 identified PD loci, including alpha-synuclein (PARK 1), parkin (PARK2), PINK1 (PARK6), DJ-1 (PARK7) and LRRK2 (PARK8) [27]. Mutations in LRRK2 is thought to account for 1-2% of PD cases in most populations, while the others account for only a few cases in several well documented kindreds [28].

The idea that viruses or other contaminating agents may be an initiating etiology of primary PD or causative for secondary parkinsonism often relates to the findings of coincident cases of parkinsonism that lie outside of the expected. One of the most famous, and still controversial, examples is the parkinsonism that occurred subsequent to a viral encephalopathy that developed following the 1918 influenza pandemic [29].

Another example that suggests viral agents can act as an initiator of parkinsonism is the appearance of what appears to be “parkinsonian clusters”. These are groups of individuals who share common environments and develop parkinsonism at greater than normal statistical rates without the obvious typical risk factors. In fact, the risk factor for developing Parkinson’s disease is approximately 2X greater in people who share close quarters, including doctors and nurses, teachers and religion-related jobs. Several of these “parkinsonian clusters” have been described, including those living in Israeli kibbutz’s, group of college teachers, garment workers in a manufacturing factory and a group of actors , producers and technical staff working on a television series in Canada [30, 31].

A number of viruses have been associated with both acute and chronic parkinsonism (see Table 1). These viruses include influenza, Coxsackie, Japanese encephalitis B, western equine encephalitis, herpes and those that lead to acquired immunodeficiency disorder (HIV). The literature on these viruses as they relate to parkinsonism will be reviewed.

### **Influenza virus**

Neurological symptoms associated with influenza have been reported as far back as 1385 and intermittent outbreaks with similar symptoms have occurred at other times during influenza outbreaks [32, 33]. Influenza virus has been implicated as both a direct and indirect cause of Parkinson’s disease, based on both clinical descriptions and epidemiological studies.

Influenza viruses are negative sense single-stranded RNA viruses belonging to the family Orthomyxoviridae [34]. Influenza A viruses are highly contagious pathogens which cause mild to severe infections in humans. Most influenza infections, localized to the upper respiratory tract, are self-limited lasting for about one week. Clinical symptoms include acute onset of fever, myalgias, and respiratory symptoms [35, 36]. However, in severe cases, influenza infection may result in primary viral pneumonia, secondary bacterial pneumonia or complications involving the central nervous system [37-40]. Influenza A viruses were the etiological agent of three pandemics in the last century: the 1918 H1N1 pandemic, the 1957 H2N2 pandemic, and the 1968 H3N2 pandemic. The 1918 flu pandemic, the most catastrophic pandemic, affected large parts of the world population and is thought to have killed at least 40 million people in 1918-1919 [41]. The burden of influenza infections during the interpandemic period continues to be an important cause of hospitalizations, and cumulative mortality is greater than those associated with pandemics [42].

There is a large body of evidence that influenza can directly lead to encephalitis [38, 39, 43-51]. However, the link with Parkinson's disease is somewhat controversial. Much of the linkage of parkinsonism with influenza and many other viruses stem from an outbreak of encephalitic lethargica (EL), also known as von Economo's disease, and the postencephalic parkinsonism that occurred subsequent to the 1918 pandemic influenza outbreak caused by a type A H1N1 influenza virus [52]. The symptoms of EL as reported by von Economo in his monograph *Die Encephalitis Lethargica* were varied. He described the acute symptoms of 7 patients ranging in age from 14 to 32 who presented at a psychiatric clinic in Vienna. Common to each of the patients was somnolence, ptosis, and delirium. At the onset of the disease the somnolence was not so severe that the patients could be aroused and follow commands. Later in



the progression of the disease, patients would slip in and out of stupor and coma. Another common feature was a tremor and rigidity in (generally) the upper extremities and most complained of nuchal rigidity. Each of these original patients described by von Economo patients had involvement of at least 1 cranial nerve leading to paresis. Most common was the paresis of the oculomotor nerve with associated amblyopia. He also described paresis of the trigeminal, abducens and facial nerves. All but the 2 patients that died recovered fairly completely. Of the two patients that died, autopsy revealed that there was meningeal involvement with engorgement of the vessels of the brain. The autopsy also noted small red spots that match the description of petechial hemorrhages. These red spots were present in the cerebral cortex, medulla oblongata and cervical spinal cord (including both the dorsal and ventral horns). Microscopic examination showed inflammation of the CNS with evenly disseminated microscopic foci in the grey matter with preference for the midbrain. Von Economo also discussed the etiology of what he saw and ruled out external sources such as bad sausages (wurstvergiftung) and, because of the timing around WWI, poison gas (gasvergiftung). He also ruled out meningitis and polio due to the fact that the patients he saw had no contact with each other and each of these was independent and no evidence of epidemics occurred as was usually seen with these two diseases. He did discuss the possibility of this being related to “grippe” which was another name for influenza. Because his cases, as well as a few others (Cruchet described a similar outbreak of “sleeping sickness” in a number of French soldiers [53] occurred prior to the major outbreak of pandemic influenza), von Economo ultimately concluded that what he saw was a separate disorder from direct influenzal infection. However, he was not able to rule out influenza as a prodromal disease.

Further studies on this disease have described 28 specific subtypes of von Economo's encephalitis. Of these subtypes, only three will be relevant should another influenza pandemic occur. These three subtypes are the somnolent-ophthalmoplegic type, the parkinsonian type and the juvenile pseudopsychopathia type [54]. The second type is most related to this review, so only it will be described. The features of postencephalic parkinsonism both share and have distinct symptomatology as idiopathic Parkinson's disease. Similarities include many of the classic motor symptoms including bradykinesia, and tremor and some parkinsonian "mask-like" features such as ptosis, while differences can include facial twitching, myoclonus, catatonia, mutism, the lack of Lewy bodies and the presence of neurofibrillary tangles that are common to Alzheimer's disease [54].

As discussed, the cause of EL and the link to subsequent postencephalic parkinsonism is controversial. There is an epidemiological tie, mostly based on increased incidence of PD, to the 1918 H1N1 influenza A pandemic [55-57]. For example, it has been shown that people born during the time of the pandemic influenza outbreak of 1918 have a 2-3 fold-increased risk of Parkinson's disease than those born prior to 1888 or after 1924 [58, 59]. Pozkanzer and Schwab [56] also showed an increase in PD onset based on an external event occurring around 1920.

It has also been shown that several type A influenza viruses are neurotropic, i.e. they can travel into the nervous system following systemic infection [60-62]. Related to the finding of H1N1 neurovirulence, immunofluorescent staining against antigens from two type A influenza strains have been found in the brain of a number of EL patients, suggesting that at some time, a neurovirulent form of influenza was present in the brain [63].

Other evidence has been put forward suggesting that the tie to H1N1 influenza A is specious. This includes the lack of viral RNA recovered from brains of EL and PEP patients

[64], the absence of any known mutations that would make the H1N1 virus neurotropic [52], and questions regarding the timeline of pandemic flu and EL [65]. In addition, some recent cases of EL-like illnesses have shown the presence of electrophoretic oligoclonal banding in the CSF, suggesting the presence of an immune reaction within the CNS. There has even been some evidence that some of the cases may have a streptococcal origin [66-68]. Recently, Kobasa et al intranasally administered the 1918 H1N1 influenza virus that was generated by plasmid-based reverse genetics [69] and found no evidence of this virus in any tissue other than lung, heart and spleen [70]. However, they also noted that despite the physical absence of the virus (based on lack of immunohistochemical detection), that there was a robust induction of cytokines in tissues not directly infected by the virus, including those shown to be active in long-termed microglial responses and induction of cell death [71, 72], .

As suggested by Vilensky writing in a report for the Sophie Cameron Trust (<http://www.thesophiecamerontrust.org.uk/research-epedemic.htm>), proving a negative in this case is difficult. The lack of recovery of viral RNA from EL or PEP patients is not surprising. First, and especially in the case of PEP patients, the time from infection to symptoms was many years and the viral infection would have been transient. In addition, it has been shown in many cases of encephalitis as well as toxin induced parkinsonism the offending agent may cause a long lasting immune response in the brain that persists many years after the insult has resolved, leading to a “hit and run” mechanism where the original insult is no longer present but the secondary sequelae persists [73]. Thus, if one accepts that influenza can activate the innate CNS immune system [74, 75], one has to identify potential second hits that could lead to development of parkinsonian symptoms.

One possible class of agents that could act as a “second hit” includes agricultural products that were prevalent around the time of the 1918 influenza virus and the subsequent outbreak of postencephalic parkinsonism. The first, originally called nicouline by its discoverer Emmanuel Geoffroy [76], and now known as rotenone, was isolated from the roots and stems of several plants. This chemical has been used in one form or another as a crop insecticide since 1848 and has been recognized as a registered pesticide in the United States under the Federal Insecticide Fungicide Rodenticide Act (FIFRA) since 1947. Rotenone has also been found to also have properties of a piscicide where it is generally used to rid environments of non-native predatory fish species, such as has recently occurred on populations of the Northern Snakehead [77]. A second pesticide that has been linked to parkinsonism is paraquat. The herbicidal properties of the bipyridinium compounds, including that of paraquat, were recognized in 1954 at the Imperial Chemical Industries PLC (ICI). The first compound to be discovered and used was diquat dibromide but shortly afterwards in 1955, paraquat salts were discovered to be active as herbicides [78] and were introduced to world markets around 1962 [79]. Prior to its use as an herbicide, and as early as 1882, paraquat (also known as methyl viologen) was synthesized by the reaction of 4,4'-bipyridium with methyl iodide where it had been used as an oxidation-reduction indicator [80]. Each of these chemicals induce oxidative stress and the generation of free radicals, either through blockade of Complex I (rotenone) [81, 82] or direct redox formation independent of complex I inhibition (paraquat) [83, 84]. Whatever the cause of increased oxidative stress, it is clear that prior activation of microglia increases sensitivity to these agents [85, 86]. As noted earlier, it is well established that influenza can induce microglial activation in the CNS [74].

Despite the controversy regarding the linkage of EL and the 1918 influenza virus- and as stated above- it has been shown that certain strains of influenza are neurotropic in mammals. Takahashi et al have shown that one influenza A virus (A/WSN/33 (H1N1)) preferentially targets the substantia nigra and ventral tegmental area prior to its spread throughout the CNS [87]. In a similar fashion, the highly pathogenic H5N1 influenza virus, which currently has pandemic potential, has been shown to be neurotropic [60, 88, 89]. According to the WHO, this strain of influenza A, H5N1 subtype has spread through the Eurasian avian population and has infected at least 350 humans, of which more than 50% have died. Following infection with H5N1, animal populations infected with H5N1 demonstrate clear motor effects that include abnormal postures, difficulties in maintaining an upright posture, inability to initiate movement. The onset of post-influenzal encephalopathies are not limited to animals as there is one case report of humans exposed to H5N1- a 4 year old and his 9 year old sister- both of whom presented with rapid encephalopathy followed by coma and death [45]; its rapid course and lack of resources did not allow MRI studies to be performed. In addition to this one published case report, there are other reports of post H5N1 influenza infection encephalitis including a 67-year-old woman from Indonesia's West Java province who in addition to her severe respiratory symptoms developed encephalitis [90].

### **Other viruses associated with postencephalic parkinsonism**

Although rare, there have been many case reports of non-traditional secondary parkinsonism subsequent to viral infection. An excellent compendium of historical cases has been reviewed by Casals et al [65] (also see Table 1). In the following section, we will review literature on some of the more common viruses associated with secondary parkinsonism

including coxsackie virus, Japanese encephalitis B, St. Louis and West Nile, and HIV. While each of these viruses have been shown to induce some of the cardinal motor symptoms of PD, and some are treatable by L-DOPA therapy [91, 92], none have been reported to induce Lewy body formation and as such only phenocopy the disease symptoms.

### **Coxsackie virus**

Coxsackie virus was first isolated from human feces in the town of Coxsackie, New York, in 1948 by Gilbert Dalldorf and Grace Sickles [93, 94]. Coxsackie virus is a member of the *Picornaviridae* family of viruses in the genus termed Enterovirus. According to the Center for Disease Prevention and Control, there are 66 serotypes of enterovirus' and these include 3 polioviruses. Coxsackie viruses are RNA viruses that primarily affect children and young adults [95]. Infection with Coxsackie virus can easily be passed from person to person and been associated with a number of diseases, including meningitis [96], myocarditis [97], and pericarditis [98].

Acute parkinsonism has been noted after infection with Coxsackie virus [99, 100] although its association with traditional aged-onset idiopathic Parkinson's disease has never been established. As with influenza virus, it is possible that early infection with Coxsackie virus can induce a long lived activation with glial cells that would predispose to oxidative insult much later in life [101].

### **Japanese encephalitis B, St. Louis and West Nile viruses**

Japanese encephalitis B (JEV), St. Louis and West Nile viruses are single-stranded RNA viruses that are transmitted by the bite of culicine mosquitoes [102-104]. Although infection

with these three viruses are often resolved prior to any CNS involvement, on rare occasion, these viruses can lead to encephalitis [105]. In fact, JEBV is the most common cause of encephalitis in Asia [106]. If infection does involve the CNS, the regions of the brain noted to become involved include the thalamus, basal ganglia, brain stem, cerebellum, hippocampus, and cerebral cortex [107-109].

Ogata et al experimentally infected Fisher rats with JEBV and noted a marked gliosis in the SNpc, in a pattern typical of the lesion seen in Parkinson's disease [110]. Behaviorally, the rats exhibited bradykinesia that was reversed with administration of L-DOPA and a MAO inhibitor suggesting that the virus had the ability to directly induce one of the cardinal symptoms of Parkinson's disease.

Secondary Parkinson's disease subsequent to St. Louis encephalitis has also been described. Like JEBV, this virus primarily affects children and the aged, although numerous cases of infection and secondary parkinsonism has been reported in all age groups. Pranzatelli et al report a number of cases of secondary parkinsonism in children, one of which appear to be the result of active St. Louis encephalopathy [92]. In this case, the patient had features of moderate parkinsonism (a UPDRS score of 92 and a MHYS of 5) with a predominant symptom of dysphagia and dystonic posture. The parkinsonism symptoms did not progress and resolved after a few months. During the clinical course of the parkinsonism, MRI revealed a slight enhancement of the basal ganglion. In the adult cases, each patient presented with involvement of the substantia nigra as determined by MRI [111]. The first patient was a 21-year-old male who presented with a 1-week history of fever and headache. Neurologic examination was normal, and an admitting diagnosis of aseptic meningitis was made. The symptoms progressed with new symptoms of fever, ataxia, nystagmus, and tremulousness. MRI imaging revealed a T2-weighted

bilateral hyperintensity in the substantia nigra without enhancement. In a second case, a 37-year-old male with a history of paranoid schizophrenia and seizures presented with fever and confusion and was generally unresponsive to commands. Other symptoms included nuchal rigidity diffuse, generalized hypertonicity, and abnormal postures including flexed upper extremities, a bilateral Babinski response and an absent gag reflex. Like the previous patient, MRI imaging showed an asymmetric T2-weighted non-enhanceable hyperintensity in the substantia nigra. Similar lesions have been reported in other cases of St. Louis encephalopathies.

## **HIV**

Human immunodeficiency virus (HIV, originally called HTLV) is a retrovirus that has been shown to be the cause of acquired immunodeficiency syndrome (AIDS) [112]. Infection with HIV results in a failure of the immune system, leading to life-threatening opportunistic infections. The underlying cellular lesion in HIV is a progressive loss of CD4+ T cells whose levels correlate with the viral load. In addition to the loss of the peripheral immune system, one of the most common associated pathologies from HIV infection involves motor disturbances [113, 114]. The involvement of the CNS can occur quickly since HIV has been detected in the brain within two weeks of the initial infection [115]. Once in the brain, HIV has been clearly shown to infect astrocytes and microglia [116-118]. In addition, and although controversial, there is also some evidence that HIV can also directly infect neurons [119-121]. No matter where the infection, the presence of the virus has been shown to induce a cytokine “storm” [122, 123].

Depending on the size of the study cohorts, it has been estimated that from 5-50% of all AIDS patients suffer from some sort of motor dysregulation including those seen in Parkinson’s



disease such as bradykinesia, cogwheel rigidity and tremor [114]. These movement disorders result from both primary HIV infection and secondary opportunistic infections. Primary HIV-associated parkinsonism often appears within several months of the diagnosis of HIV infection [113] and its appearance portends a poor prognosis. Cerebral imaging (CT and MRI) of HIV-induced parkinsonism has shown lesions at various levels of the basal ganglia including calcifications throughout the basal ganglia, hypodense lesions of the striatum [124], putamen hypertrophy [125, 126] as well as intensifying lesions of the basal ganglia [127, 128] and midbrain [129]. Functional imaging using [ $^{18}\text{F}$ ] fluorodeoxyglucose PET have shown that early CNS changes in AIDS involved thalamic and basal ganglia hypermetabolism while cortical and subcortical gray matter hypometabolism was more characteristic of later CNS changes [130].

### **Viral Neurotropism**

If one is to understand the neurological pathogenesis of viruses, understanding how they enter into the nervous system is of critical importance. A number of viruses, including obviously the viruses described in this manuscript have the ability to enter the CNS. Although the phenomenon is well described, the mechanism to which this occurs has not been defined. Most of the work on neurotropism has been done using the influenza virus as an experimental model. In a study examining neurovirulence in mice, Lipatov et al [89] examined 5 H5N1 influenza viruses isolated in Hong Kong in 2001 of which 4 were neurotropic (Ck/HK/YU822.2/01, Ph/HK/FY155/01, Ck/HK/FY150/01, Ck/HK/NT873.3/01) and 1 was not (Ck/HK/YU562/01). This group did extensive sequence analysis of these viruses and found that there was not a common set of mutations that induced neurotropism, suggesting the neurovirulence of the influenza virus is a polygenic trait. They found that multiple basic cleavage sites in the surface

hemagglutinin proteins were necessary, but not sufficient, to make these viruses neurovirulent. In addition, they also suggested that specific changes in polymerase proteins PB2 and PA, which are important in transcription and replication of viral RNAs [131], are also implicated in this process. In addition, several studies have found that mutations in the Mx gene, which regulate GTPase activity [132, 133], and act as an important downstream effector of interferon [134], also regulate Type A influenza neurotropism. MxA protein has also been found to be a component of Lewy Bodies [135-137] and therefore may link influenza to parkinsonism. As an aside, one treatment for influenza, Amantadine which targets the M2 protein channel on the surface of the influenza A virus [138, 139], has also been used as a limited treatment for Parkinson's disease [140, 141].

In terms of how influenza virus enters the CNS, the A/WSN/33 strain has been shown to enter the CNS via the olfactory epithelium [142]. It has also been hypothesized that it can enter the CNS via other cranial nerves including the vagus and trigeminal nerves [143-146]. These three nerves have processes that innervate visceral organs and tissues that would be first contacted by intranasal viral infection including the olfactory epithelium (olfactory nerve, CN I), orofacial mucosa (trigeminal nerve, CN III) and digestive system (vagus nerve, CN X). The basis of this hypothesis- which does not have any direct proof such as isolation of the virus from axons of these nerves- is two-fold. First, examination of the CNS following infection via intranasal routes shows that the virus is first seen in the regions innervated by these nerves. Second, the virus can be detected (indirectly by the presence of immunohistochemical detection of viral nuclear protein, anti NP) in the visceral ganglia [88, 146]. One argument against this route of entry into the CNS is that the A/WSN/33 strain of influenza has affinity for the substantia nigra [87], a neuronal population without any direct anatomical connection to the

cranial nerve system. This suggests that influenza virus may also enter into the CNS via different mechanisms than axonal transport such as through the ependymal cells lining the ventricles and shedding into the CSF where it can freely transmit through the whole neuraxis, through the blood and extravasation from penetrating capillaries in the brain or invasion into the CNS via reductions in the blood-brain-barrier around the circumventricular organs. Braak [147] suggests Parkinson's disease may be caused by an infectious agent based on the location of Lewy bodies and neurites at the earliest stages of the disease including the olfactory bulb and gastrointestinal enteric plexi such as Meissner's plexus ultimately reaching preganglionic parasympathetic motor neurones of the vagus nerve. They call this dual route for entry into the brain of an unknown pathogen a 'dual-hit' hypothesis.

While many studies have been done examining the genetics of the viruses and how they influence neurotropism, little has been done to explore the host genetics in terms of resistance to neurotropism [148]. One method for identifying these inherent genetic factors, in the absence of any specific genes to examine, is the use of quantitative trait loci analysis [149, 150]. The premise behind QTL analysis is that if numerous genetic markers are examined, only those that segregate with a particular phenotype will contain the gene(s) that underlie the trait being examined [151]. QTL analysis in mice has been facilitated in the last ten years by several significant advances. First, thousands of microsatellite markers have been found and mapped to their specific chromosomal region spanning the entire murine genome [152]. This method can identify regions of chromosomes responsible for differences in any measurable trait and has been used to identify genes responsible for susceptibility to a number of neurological phenomenon [149, 153-155] and could easily be used to identify chromosomal regions of interest and ultimately genes that regulate neurotropism sensitivity in the host animal (if they exist). The

identification of these genes could have a significant impact on public health in the event of pandemic flu.

Based on all available evidence, we suggest that viruses, and in particular influenza virus, can be one precipitating factor in the development of Parkinson's disease. Although there is little evidence suggesting that infection by any virus directly induces Parkinson's disease (although there might be some transient parkinsonism associated with direct encephalitis), it is clear that some influenza viruses can both enter the CNS and cause cell death, but more importantly they have been shown to induce a cytokine storm in the brain. The sequelae of cytokine induction, such as activation of microglia, can be long lasting and far exceed the presence of the initiating factor. Further support for this hypothesis is the pattern of viral protein expression in the brain of animals and humans exposed to some influenza viruses [63, 87, 156, 157] that mimics the identified by Braak as regions of disease during early pathogenesis [158]. We suggest that infectious agents may be the first "hit" in a two hit hypothesis, and that this insult sensitizes the brain to a later "hit" that might not have been pathogenic in the absence of an already primed system.

## References

- [1] J. Parkinson, *An essay on shaking palsy*, Sherwood, Neeley and Jones, London, 1817.
- [2] S.K. Van Den Eeden, C.M. Tanner, A.L. Bernstein, R.D. Fross, A. Leimpeter, D.A. Bloch and L.M. Nelson, Incidence of Parkinson's disease: variation by age, gender, and race/ethnicity, *Am J Epidemiol* 157 (2003) 1015-22.
- [3] K. Whetten-Goldstein, F. Sloan, E. Kulas, T. Cutson and M. Schenkman, The burden of Parkinson's disease on society, family, and the individual, *J. Am. Ger. Soc.* 45 (1997) 479-485.
- [4] E. Bertrand, W. Lechowicz, G.M. Szpak and J. Dymecki, Qualitative and quantitative analysis of locus coeruleus neurons in Parkinson's disease, *Folia Neuropathol* 35 (1997) 80-6.
- [5] W.P. Gai, P.C. Blumbergs, L.B. Geffen and W.W. Blessing, Age-related loss of dorsal vagal neurons in Parkinson's disease, *Neurology* 42 (1992) 2106-11.
- [6] K. Wakabayashi and H. Takahashi, The intermediolateral nucleus and Clarke's column in Parkinson's disease, *Acta Neuropathol* 94 (1997) 287-9.
- [7] K. Wakabayashi and H. Takahashi, Neuropathology of autonomic nervous system in Parkinson's disease, *Eur Neurol* 38 Suppl 2 (1997) 2-7.
- [8] D.C. German, K. Manaye, W.K. Smith, D.J. Woodward and C.B. Saper, Midbrain dopaminergic cell loss in Parkinson's disease: computer visualization, *Annals of Neurology* 26 (1989) 507-14.
- [9] J. Jankovic, Parkinson's disease: clinical features and diagnosis, *J Neurol Neurosurg Psychiatry* 79 (2008) 368-76.

- [10] D.D. Truong, R. Bhidayasiri and E. Wolters, Management of non-motor symptoms in advanced Parkinson disease, *J Neurol Sci* 266 (2008) 216-28.
- [11] R.F. Pfeiffer, Gastrointestinal dysfunction in Parkinson's disease, *Clin Neurosci* 5 (1998) 136-46.
- [12] F. Lewy, Zur pathologischen Anatomie der Paralysis agitans., *Deutsche Zeitschrift fur Nervenheilkunde* 50 (1913) 50-55.
- [13] J.E. Duda, V.M. Lee and J.Q. Trojanowski, Neuropathology of synuclein aggregates, *J Neurosci Res* 61 (2000) 121-7.
- [14] S. Gilman, Parkinsonian syndromes, *Clin Geriatr Med* 22 (2006) 827-42, vi.
- [15] G.K. Wenning and N.P. Quinn, Parkinsonism. Multiple system atrophy, *Baillieres Clin Neurol* 6 (1997) 187-204.
- [16] M. Lubarsky and J.L. Juncos, Progressive supranuclear palsy: a current review, *Neurologist* 14 (2008) 79-88.
- [17] H. Arai, T. Furuya, Y. Mizuno and H. Mochizuki, Inflammation and infection in Parkinson's disease, *Histol Histopathol* 21 (2006) 673-8.
- [18] M.A. Mena and J.G. de Yebenes, Drug-induced parkinsonism, *Expert Opin Drug Saf* 5 (2006) 759-71.
- [19] R.J. Smeyne and V. Jackson-Lewis, The MPTP model of Parkinson's disease, *Brain Res Mol Brain Res* 134 (2005) 57-66.
- [20] I. Sibon and F. Tison, Vascular parkinsonism, *Curr Opin Neurol* 17 (2004) 49-54.
- [21] J.H. Bower, D.M. Maraganore, B.J. Peterson, S.K. McDonnell, J.E. Ahlskog and W.A. Rocca, Head trauma preceding PD: a case-control study, *Neurology* 60 (2003) 1610-5.
- [22] S. Bostantjopoulou, Z. Katsarou and A. Petridis, Relapsing hemiparkinsonism due to

- recurrent meningioma, *Parkinsonism Relat Disord* 13 (2007) 372-4.
- [23] D.C. Chang, J.J. Lin and J.C. Lin, Parkinsonism as an initial manifestation of brain tumor, *Zhonghua Yi Xue Za Zhi (Taipei)* 63 (2000) 658-62.
- [24] D.A. Di Monte, The environment and Parkinson's disease: is the nigrostriatal system preferentially targeted by neurotoxins? *Lancet Neurol* 2 (2003) 531-8.
- [25] M.J. Farrer, Genetics of Parkinson disease: paradigm shifts and future prospects, *Nat Rev Genet* 7 (2006) 306-18.
- [26] C. Klein and M.G. Schlossmacher, Parkinson disease, 10 years after its genetic revolution: multiple clues to a complex disorder, *Neurology* 69 (2007) 2093-104.
- [27] A.C. Belin and M. Westerlund, Parkinson's disease: A genetic perspective, *Febs J* 275 (2008) 1377-83.
- [28] J. Hardy, H. Cai, M.R. Cookson, K. Gwinn-Hardy and A. Singleton, Genetics of Parkinson's disease and parkinsonism, *Ann Neurol* 60 (2006) 389-98.
- [29] K. von Economo, Encephalitis lethargica, *Wiener klinische Wochenschrift* 30 (1917) 581-585.
- [30] J.R. Goldsmith, Y.O. Herishanu, M. Podgajetski and E. Kordysh, Dynamics of parkinsonism-Parkinson's disease in residents of adjacent kibbutzim in Israel's Negev, *Environ Res* 73 (1997) 156-61.
- [31] A. Kumar, S.M. Calne, M. Schulzer, E. Mak, Z. Wszolek, C. Van Netten, J.K. Tsui, A.J. Stoessl and D.B. Calne, Clustering of Parkinson disease: shared cause or coincidence? *Arch Neurol* 61 (2004) 1057-60.
- [32] K.A. Menninger, Psychoses associated with influenza, *Arch. Neurol. Psych.* 2 (1919) 291-337.

- [33] K.A. Menninger, Influenza and schizophrenia. An analysis of post-influenzal "dementia precox" as of 1918 and five years later., *Am. J. Psych.* 5 (1926) 469-529.
- [34] R. Lamb and R. Krug. in (Knipe, D.M.a.H., P.M., ed.) *Fields Virology*, Lippincott Williams & Wilkins, Philadelphia 2001, pp. 1487–1532.
- [35] A.S. Monto, S. Gravenstein, M. Elliott, M. Colopy and J. Schweinle, Clinical signs and symptoms predicting influenza infection, *Arch Intern Med* 160 (2000) 3243-7.
- [36] K.G. Nicholson, J.M. Wood and M. Zambon, *Influenza*, *Lancet* 362 (2003) 1733-45.
- [37] C.M. Martin, C.M. Kunin, L.S. Gottlieb, M.W. Barnes, C. Liu and M. Finland, Asian influenza A in Boston, 1957-1958. I. Observations in thirty-two influenza-associated fatal cases, *AMA Arch Intern Med* 103 (1959) 515-31.
- [38] Y. Hayase and K. Tobita, Influenza virus and neurological diseases, *Psychiatry Clin Neurosci* 51 (1997) 181-4.
- [39] M.M. Ryan, P.G. Procopis and R.A. Ouvrier, Influenza A encephalitis with movement disorder, *Pediatr Neurol* 21 (1999) 669-73.
- [40] J. Guarner, C.D. Paddock, W.J. Shieh, M.M. Packard, M. Patel, J.L. Montague, T.M. Uyeki, N. Bhat, A. Balish, S. Lindstrom, A. Klimov and S.R. Zaki, Histopathologic and immunohistochemical features of fatal influenza virus infection in children during the 2003-2004 season, *Clin Infect Dis* 43 (2006) 132-40.
- [41] A. Reid, J. Taubenberger and T. Fanning, The 1918 Spanish influenza: integrating history and biology., *Microbes Infect* 3 (2001) 81-87.
- [42] L. Simonsen, M.J. Clarke, G.D. Williamson, D.F. Stroup, N.H. Arden and L.B. Schonberger, The impact of influenza epidemics on mortality: introducing a severity index, *Am J Public Health* 87 (1997) 1944-50.



- [43] S. Olgar, T. Ertugrul, K. Nisli, K. Aydin and M. Caliskan, Influenza a-associated acute necrotizing encephalopathy, *Neuropediatrics* 37 (2006) 166-8.
- [44] L. Drago, M.W. Attia, A. DePiero and C. Bean, Influenza A-associated meningoencephalitis, *Pediatr Emerg Care* 21 (2005) 437-9.
- [45] M.D. de Jong, V.C. Bach, T.Q. Phan, M.H. Vo, T.T. Tran, B.H. Nguyen, M. Beld, T.P. Le, H.K. Truong, V.V. Nguyen, T.H. Tran, Q.H. Do and J. Farrar, Fatal avian influenza A (H5N1) in a child presenting with diarrhea followed by coma, *N Engl J Med* 352 (2005) 686-91.
- [46] T. Togashi, Y. Matsuzono, M. Narita and T. Morishima, Influenza-associated acute encephalopathy in Japanese children in 1994-2002, *Virus Res* 103 (2004) 75-8.
- [47] M.O. Chandesris, E. Bernit, N. Schleinitz, C. Nicolino, P. Bensa, D. Tammam, C. Zandotti, V. Veit, G. Kaplanski and J.R. Harle, [A case of Influenza virus encephalitis in south of France], *Rev Med Interne* 25 (2004) 78-82.
- [48] H. Iijima, K. Wakasugi, M. Ayabe, H. Shoji and T. Abe, A case of adult influenza A virus-associated encephalitis: magnetic resonance imaging findings, *J Neuroimaging* 12 (2002) 273-5.
- [49] M. Mihara, K. Utsugisawa, S. Konno and H. Tohgi, Isolated lesions limited to the bilateral substantia nigra on MRI associated with influenza A infection, *Eur Neurol* 45 (2001) 290-1.
- [50] W.H. Bayer, Influenza B encephalitis, *West J Med* 147 (1987) 466.
- [51] G.H. Lawrence and R.A. Jones, Case report; encephalitis as a complication of the influenza, *Mo Med* 54 (1957) 1164 passim.
- [52] J.K. Taubenberger, The origin and virulence of the 1918 "Spanish" influenza virus, *Proc*

- Am Philos Soc 150 (2006) 86-112.
- [53] J.R. Cruchet, Quarante cas d'encéphalo-myélite subaiguë., *Bulletins et Mémoires de la Société Médicale des Hôpitaux de Paris* 41 (1917) 614-616.
- [54] J.A. Vilensky and S. Gilman, Encephalitis lethargica: could this disease be recognised if the epidemic recurred? *Practical Neurology* 6 (2006) 360-367.
- [55] C.P. Maurizi, Why was the 1918 influenza pandemic so lethal? The possible role of a neurovirulent neuraminidase, *Med Hypotheses* 16 (1985) 1-5.
- [56] D.C. Poskanzer and R.S. Schwab, Cohort analysis of Parkinson's syndrome. Evidence for a single etiology related to subclinical infection about 1920., *J. Chronic Dis.* 16 (1963) 961-973.
- [57] R.T. Ravenholt and W.H. Foegen, 1918 influenza, encephalitis lethargica, parkinsonism, *Lancet* 2 (1982) 860-4.
- [58] C.N. Martyn and C. Osmond, Parkinson's disease and the environment in early life, *J Neurol Sci* 132 (1995) 201-6.
- [59] C.N. Martyn, Infection in childhood and neurological diseases in adult life, *Br Med Bull* 53 (1997) 24-39.
- [60] R. Klopffleisch, O. Werner, E. Mundt, T. Harder and J.P. Teifke, Neurotropism of highly pathogenic avian influenza virus A/chicken/Indonesia/2003 (H5N1) in experimentally infected pigeons (*Columba livia f. domestica*), *Vet Pathol* 43 (2006) 463-70.
- [61] M. Rigoni, K. Shinya, A. Toffan, A. Milani, F. Bettini, Y. Kawaoka, G. Cattoli and I. Capua, Pneumo- and neurotropism of avian origin Italian highly pathogenic avian influenza H7N1 isolates in experimentally infected mice, *Virology* 364 (2007) 28-35.
- [62] H. Tanaka, C.H. Park, A. Ninomiya, H. Ozaki, A. Takada, T. Umemura and H. Kida,

- Neurotropism of the 1997 Hong Kong H5N1 influenza virus in mice, *Vet Microbiol* 95 (2003) 1-13.
- [63] E.T. Gamboa, A. Wolf, M.D. Yahr, D.H. Harter, P.E. Duffy, H. Barden and K.C. Hsu, Influenza virus antigen in postencephalitic parkinsonism brain. Detection by immunofluorescence, *Arch Neurol* 31 (1974) 228-32.
- [64] S. McCall, J.M. Henry, A.H. Reid and J.K. Taubenberger, Influenza RNA not detected in archival brain tissues from acute encephalitis lethargica cases or in postencephalitic Parkinson cases, *J Neuropathol Exp Neurol* 60 (2001) 696-704.
- [65] J. Casals, T.S. Elizan and M.D. Yahr, Postencephalitic parkinsonism--a review, *J Neural Transm* 105 (1998) 645-76.
- [66] S.B. Blunt, R.J. Lane, N. Turjanski and G.D. Perkin, Clinical features and management of two cases of encephalitis lethargica, *Mov Disord* 12 (1997) 354-9.
- [67] R.C. Dale, A.J. Church, R.A. Surtees, A.J. Lees, J.E. Adcock, B. Harding, B.G. Neville and G. Giovannoni, Encephalitis lethargica syndrome: 20 new cases and evidence of basal ganglia autoimmunity, *Brain* 127 (2004) 21-33.
- [68] A. Vincent, Encephalitis lethargica: part of a spectrum of post-streptococcal autoimmune diseases? *Brain* 127 (2004) 2-3.
- [69] G. Neumann, T. Watanabe, H. Ito, S. Watanabe, H. Goto, P. Gao, M. Hughes, D.R. Perez, R. Donis, E. Hoffmann, G. Hobom and Y. Kawaoka, Generation of influenza A viruses entirely from cloned cDNAs, *Proc Natl Acad Sci U S A* 96 (1999) 9345-50.
- [70] D. Kobasa, S.M. Jones, K. Shinya, J.C. Kash, J. Copps, H. Ebihara, Y. Hatta, J.H. Kim, P. Halfmann, M. Hatta, F. Feldmann, J.B. Alimonti, L. Fernando, Y. Li, M.G. Katze, H. Feldmann and Y. Kawaoka, Aberrant innate immune response in lethal infection of

- macaques with the 1918 influenza virus, *Nature* 445 (2007) 319-23.
- [71] A. Ghoshal, S. Das, S. Ghosh, M.K. Mishra, V. Sharma, P. Koli, E. Sen and A. Basu, Proinflammatory mediators released by activated microglia induces neuronal death in Japanese encephalitis, *Glia* 55 (2007) 483-96.
- [72] K.L. Wu, S.H. Chan, Y.M. Chao and J.Y. Chan, Expression of pro-inflammatory cytokine and caspase genes promotes neuronal apoptosis in pontine reticular formation after spinal cord transection, *Neurobiol Dis* 14 (2003) 19-31.
- [73] J.W. Langston, L.S. Forno, J. Tetrad, A.G. Reeves, J.A. Kaplan and D. Karluk, Evidence of active nerve cell degeneration in the substantia nigra of humans years after 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine exposure, *Ann Neurol* 46 (1999) 598-605.
- [74] I. Mori, Y. Imai, S. Kohsaka and Y. Kimura, Upregulated expression of Iba1 molecules in the central nervous system of mice in response to neurovirulent influenza A virus infection, *Microbiol Immunol* 44 (2000) 729-35.
- [75] S. Dhib-Jalbut, N. Gogate, H. Jiang, H. Eisenberg and G. Bergey, Human microglia activate lymphoproliferative responses to recall viral antigens, *J Neuroimmunol* 65 (1996) 67-73.
- [76] E. Geoffroy. pp. 1-86, L'Institut Colonial de Marseille, Marseille 1895.
- [77] P.F. Fuller and A.J. Benson. (USGS, ed.) 2008.
- [78] R.H. Bromilow, Paraquat and sustainable agriculture, *Pest Manag Sci* 60 (2004) 340-9.
- [79] P.I. Center. 2008.
- [80] L. Michaelis and E.S. Hill, The Viologen Indicators, *Journal of General Physiology* 16 (1933) 859-873.
- [81] J.T. Greenamyre, T.B. Sherer, R. Betarbet and A.V. Panov, Complex I and Parkinson's

- disease, *IUBMB Life* 52 (2001) 135-41.
- [82] C. Gomez, M.J. Bandez and A. Navarro, Pesticides and impairment of mitochondrial function in relation with the parkinsonian syndrome, *Front Biosci* 12 (2007) 1079-93.
- [83] D. Di Monte, M.S. Sandy, G. Ekstrom and M.T. Smith, Comparative studies on the mechanisms of paraquat and 1-methyl-4-phenylpyridine (MPP+) cytotoxicity, *Biochem Biophys Res Commun* 137 (1986) 303-9.
- [84] J.R. Richardson, Y. Quan, T.B. Sherer, J.T. Greenamyre and G.W. Miller, Paraquat neurotoxicity is distinct from that of MPTP and rotenone, *Toxicol Sci* 88 (2005) 193-201.
- [85] M.G. Purisai, A.L. McCormack, S. Cumine, J. Li, M.Z. Isla and D.A. Di Monte, Microglial activation as a priming event leading to paraquat-induced dopaminergic cell degeneration, *Neurobiol Dis* 25 (2007) 392-400.
- [86] A.L. Phinney, G. Andringa, J.G. Bol, E. Wolters, F.L. van Muiswinkel, A.M. van Dam and B. Drukarch, Enhanced sensitivity of dopaminergic neurons to rotenone-induced toxicity with aging, *Parkinsonism Relat Disord* 12 (2006) 228-38.
- [87] M. Takahashi, T. Yamada, S. Nakajima, K. Nakajima, T. Yamamoto and H. Okada, The substantia nigra is a major target for neurovirulent influenza A virus, *J Exp Med* 181 (1995) 2161-9.
- [88] G.F. Rimmelzwaan, D. van Riel, M. Baars, T.M. Bestebroer, G. van Amerongen, R.A. Fouchier, A.D. Osterhaus and T. Kuiken, Influenza A virus (H5N1) infection in cats causes systemic disease with potential novel routes of virus spread within and between hosts, *Am J Pathol* 168 (2006) 176-83; quiz 364.
- [89] A.S. Lipatov, S. Krauss, Y. Guan, M. Peiris, J.E. Rehg, D.R. Perez and R.G. Webster, Neurovirulence in mice of H5N1 influenza virus genotypes isolated from Hong Kong

- poultry in 2001, *J Virol* 77 (2003) 3816-23.
- [90] BloombergNews. Budapest Business Journal 2006.
- [91] D.R. Schultz, J.S. Barthal and G. Garrett, Western equine encephalitis with rapid onset of parkinsonism, *Neurology* 27 (1977) 1095-6.
- [92] M.R. Pranzatelli, S.H. Mott, S.G. Pavlakis, J.A. Conry and E.D. Tate, Clinical spectrum of secondary parkinsonism in childhood: a reversible disorder, *Pediatr Neurol* 10 (1994) 131-40.
- [93] G. Dalldorf, The Coxsackie Group of Viruses, *Science* 110 (1949) 594.
- [94] G. Dalldorf and G.M. Sickles, An Unidentified, Filtrable Agent Isolated From the Feces of Children With Paralysis, *Science* 108 (1948) 61-62.
- [95] C.f.D.P.a. Control, Enterovirus surveillance--United States, 1997-1999, *MMWR Morb Mortal Wkly Rep* 49 (2000) 913-6.
- [96] P. Muir and A.M. van Loon, Enterovirus infections of the central nervous system, *Intervirology* 40 (1997) 153-66.
- [97] P.E. Tam, Coxsackievirus myocarditis: interplay between virus and host in the pathogenesis of heart disease, *Viral Immunol* 19 (2006) 133-46.
- [98] S.Z. Hirschman and G.S. Hammer, Coxsackie virus myopericarditis. A microbiological and clinical review, *Am J Cardiol* 34 (1974) 224-32.
- [99] J. Walters, Postencephalic Parkinson Syndrome After Meningoencephalitis Due to Coxsackie Virus Group-B, Type-2., *New England Journal of Medicine* 263 (1960) 744.
- [100] C.M. Poser, C.J. Huntley and J.D. Poland, Para-encephalitic parkinsonism. Report of an acute case due to coxsackie virus type B 2 and re-examination of the etiologic concepts of postencephalitic parkinsonism, *Acta Neurol Scand* 45 (1969) 199-215.

- [101] E.Y. So, M.H. Kang and B.S. Kim, Induction of chemokine and cytokine genes in astrocytes following infection with Theiler's murine encephalomyelitis virus is mediated by the Toll-like receptor 3, *Glia* 53 (2006) 858-67.
- [102] M.J. Turell, M.L. O'Guinn, L.P. Wasieloski, Jr., D.J. Dohm, W.J. Lee, H.W. Cho, H.C. Kim, D.A. Burkett, C.N. Mores, R.E. Coleman and T.A. Klein, Isolation of Japanese encephalitis and Getah viruses from mosquitoes (Diptera: Culicidae) collected near Camp Greaves, Gyonggi Province, Republic of Korea, 2000, *J Med Entomol* 40 (2003) 580-4.
- [103] J.S. Mackenzie, D.J. Gubler and L.R. Petersen, Emerging flaviviruses: the spread and resurgence of Japanese encephalitis, West Nile and dengue viruses, *Nat Med* 10 (2004) S98-109.
- [104] J.P. Luby, S.E. Sulkin and J.P. Sanford, The epidemiology of St. Louis encephalitis: a review, *Annu Rev Med* 20 (1969) 329-50.
- [105] T. Solomon and P.M. Winter, Neurovirulence and host factors in flavivirus encephalitis--evidence from clinical epidemiology, *Arch Virol Suppl* (2004) 161-70.
- [106] M. Diagana, P.M. Preux and M. Dumas, Japanese encephalitis revisited, *J Neurol Sci* 262 (2007) 165-70.
- [107] T. Ishii, M. Matsushita and S. Hamada, Characteristic residual neuropathological features of Japanese B encephalitis, *Acta Neuropathol* 38 (1977) 181-6.
- [108] S.V. Tiroumourougane, P. Raghava and S. Srinivasan, Japanese viral encephalitis, *Postgrad Med J* 78 (2002) 205-15.
- [109] T. Abe, K. Kojima, H. Shoji, N. Tanaka, K. Fujimoto, M. Uchida, H. Nishimura, N. Hayabuchi and A.M. Norbash, Japanese encephalitis, *J Magn Reson Imaging* 8 (1998) 755-61.

- [110] A. Ogata, K. Tashiro, S. Nukuzuma, K. Nagashima and W.W. Hall, A rat model of Parkinson's disease induced by Japanese encephalitis virus, *J Neurovirol* 3 (1997) 141-7.
- [111] F. Cerna, B. Mehrad, J.P. Luby, D. Burns and J.L. Fleckenstein, St. Louis encephalitis and the substantia nigra: MR imaging evaluation, *AJNR Am J Neuroradiol* 20 (1999) 1281-3.
- [112] M.G. Sarngadharan, A.L. DeVico, L. Bruch, J. Schupbach and R.C. Gallo, HTLV-III: the etiologic agent of AIDS, *Princess Takamatsu Symp* 15 (1984) 301-8.
- [113] J.P. Mattos, A.L. Rosso, R.B. Correa and S.A. Novis, Movement disorders in 28 HIV-infected patients, *Arq Neuropsiquiatr* 60 (2002) 525-30.
- [114] W. Tse, M.G. Cersosimo, J.M. Gracies, S. Morgello, C.W. Olanow and W. Koller, Movement disorders and AIDS: a review, *Parkinsonism Relat Disord* 10 (2004) 323-34.
- [115] F.C. Krebs, H. Ross, J. McAllister and B. Wigdahl, HIV-1-associated central nervous system dysfunction, *Adv Pharmacol* 49 (2000) 315-85.
- [116] H. Budka, Human immunodeficiency virus (HIV) envelope and core proteins in CNS tissues of patients with the acquired immune deficiency syndrome (AIDS), *Acta Neuropathol* 79 (1990) 611-9.
- [117] R. Brack-Werner, Astrocytes: HIV cellular reservoirs and important participants in neuropathogenesis, *Aids* 13 (1999) 1-22.
- [118] J.E. Bell, The neuropathology of adult HIV infection, *Rev Neurol (Paris)* 154 (1998) 816-29.
- [119] C. Canto-Nogues, S. Sanchez-Ramon, S. Alvarez, C. Lacruz and M.A. Munoz-Fernandez, HIV-1 infection of neurons might account for progressive HIV-1-associated encephalopathy in children, *J Mol Neurosci* 27 (2005) 79-89.



- [120] J.E. Torres-Munoz, M. Nunez and C.K. Petito, Successful Application of Hyperbranched Multidisplacement Genomic Amplification to Detect HIV-1 Sequences in Single Neurons Removed from Autopsy Brain Sections by Laser Capture Microdissection, *J Mol Diagn* 10 (2008) 317-24.
- [121] E.D. Wheeler, C.L. Achim and V. Ayyavoo, Immunodetection of human immunodeficiency virus type 1 (HIV-1) Vpr in brain tissue of HIV-1 encephalitic patients, *J Neurovirol* 12 (2006) 200-10.
- [122] M. Kaul and S.A. Lipton, Mechanisms of neuronal injury and death in HIV-1 associated dementia, *Curr HIV Res* 4 (2006) 307-18.
- [123] N.A. Brabers and H.S. Nottet, Role of the pro-inflammatory cytokines TNF-alpha and IL-1beta in HIV-associated dementia, *Eur J Clin Invest* 36 (2006) 447-58.
- [124] R. Paul, R. Cohen, B. Navia and K. Tashima, Relationships between cognition and structural neuroimaging findings in adults with human immunodeficiency virus type-1, *Neurosci Biobehav Rev* 26 (2002) 353-9.
- [125] E.H. Aylward, J.D. Henderer, J.C. McArthur, P.D. Brettschneider, G.J. Harris, P.E. Barta and G.D. Pearlson, Reduced basal ganglia volume in HIV-1-associated dementia: results from quantitative neuroimaging, *Neurology* 43 (1993) 2099-104.
- [126] J.M. Castelo, M.G. Courtney, R.J. Melrose and C.E. Stern, Putamen hypertrophy in nondemented patients with human immunodeficiency virus infection and cognitive compromise, *Arch Neurol* 64 (2007) 1275-80.
- [127] C.P. Hawkins, J.E. McLaughlin, B.E. Kendall and W.I. McDonald, Pathological findings correlated with MRI in HIV infection, *Neuroradiology* 35 (1993) 264-8.
- [128] T. Kodama, Y. Numaguchi, F.E. Gellad and N. Sadato, High signal intensity of both

- putamina in patients with HIV infection, *Neuroradiology* 33 (1991) 362-3.
- [129] S. Luttmann, I.W. Husstedt, G. Schuierer, G. Kuhlenbaumer, S. Stodieck, M. Riedasch, D. Reichelt and W. Zidek, High-signal lesions in the midbrain on T1-weighted MRI in an HIV-infected patient, *Neuroradiology* 39 (1997) 136-8.
- [130] D.A. Rottenberg, J.R. Moeller, S.C. Strother, J.J. Sidtis, B.A. Navia, V. Dhawan, J.Z. Ginos and R.W. Price, The metabolic pathology of the AIDS dementia complex, *Ann Neurol* 22 (1987) 700-6.
- [131] E. Fodor and G.G. Brownlee. in (Potter, C.W., ed.) *Influenza*, Elsevier, Amsterdam 2002, pp. 1-29.
- [132] P. Staeheli, R. Grob, E. Meier, J.G. Sutcliffe and O. Haller, Influenza virus-susceptible mice carry Mx genes with a large deletion or a nonsense mutation, *Mol Cell Biol* 8 (1988) 4518-23.
- [133] M.A. Horisberger, Interferons, Mx genes, and resistance to influenza virus, *Am J Respir Crit Care Med* 152 (1995) S67-71.
- [134] O.G. Engelhardt, E. Ullrich, G. Kochs and O. Haller, Interferon-induced antiviral Mx1 GTPase is associated with components of the SUMO-1 system and promyelocytic leukemia protein nuclear bodies, *Exp Cell Res* 271 (2001) 286-95.
- [135] M. Takahashi and T. Yamada, A possible role of influenza A virus infection for Parkinson's disease, *Adv Neurol* 86 (2001) 91-104.
- [136] T. Yamada, Further observations on MxA-positive Lewy bodies in Parkinson's disease brain tissues, *Neurosci Lett* 195 (1995) 41-4.
- [137] T. Yamada, M.A. Horisberger, N. Kawaguchi, I. Moroo and T. Toyoda, Immunohistochemistry using antibodies to alpha-interferon and its induced protein,

- MxA, in Alzheimer's and Parkinson's disease brain tissues, *Neurosci Lett* 181 (1994) 61-4.
- [138] C. Wang, K. Takeuchi, L.H. Pinto and R.A. Lamb, Ion channel activity of influenza A virus M2 protein: characterization of the amantadine block, *J Virol* 67 (1993) 5585-94.
- [139] P. Intharathap, C. Laohpongspaisan, T. Rungrotmongkol, A. Loisuangsinsin, M. Malaisree, P. Decha, O. Aruksakunwong, K. Chuenpennit, N. Kaiyawet, P. Sompornpisut, S. Pianwanit and S. Hannongbua, How amantadine and rimantadine inhibit proton transport in the M2 protein channel, *J Mol Graph Model* (2008).
- [140] R. Pahwa, S.A. Factor, K.E. Lyons, W.G. Ondo, G. Gronseth, H. Bronte-Stewart, M. Hallett, J. Miyasaki, J. Stevens and W.J. Weiner, Practice Parameter: treatment of Parkinson disease with motor fluctuations and dyskinesia (an evidence-based review): report of the Quality Standards Subcommittee of the American Academy of Neurology, *Neurology* 66 (2006) 983-95.
- [141] W.H. Oertel and N.P. Quinn, Parkinson's disease: drug therapy, *Baillieres Clin Neurol* 6 (1997) 89-108.
- [142] F. Aronsson, B. Robertson, H.G. Ljunggren and K. Kristensson, Invasion and persistence of the neuroadapted influenza virus A/WSN/33 in the mouse olfactory system, *Viral Immunol* 16 (2003) 415-23.
- [143] T. Iwasaki, S. Itamura, H. Nishimura, Y. Sato, M. Tashiro, T. Hashikawa and T. Kurata, Productive infection in the murine central nervous system with avian influenza virus A (H5N1) after intranasal inoculation, *Acta Neuropathol (Berl)* 108 (2004) 485-92.
- [144] K. Matsuda, C.H. Park, Y. Sunden, T. Kimura, K. Ochiai, H. Kida and T. Umemura, The vagus nerve is one route of transneural invasion for intranasally inoculated influenza a

- virus in mice, *Vet Pathol* 41 (2004) 101-7.
- [145] M. Reinacher, J. Bonin, O. Narayan and C. Scholtissek, Pathogenesis of neurovirulent influenza A virus infection in mice. Route of entry of virus into brain determines infection of different populations of cells, *Lab Invest* 49 (1983) 686-92.
- [146] K. Shinya, A. Shimada, T. Ito, K. Otsuki, T. Morita, H. Tanaka, A. Takada, H. Kida and T. Umemura, Avian influenza virus intranasally inoculated infects the central nervous system of mice through the general visceral afferent nerve, *Arch Virol* 145 (2000) 187-95.
- [147] C.H. Hawkes, K. Del Tredici and H. Braak, Parkinson's disease: a dual-hit hypothesis, *Neuropathol Appl Neurobiol* 33 (2007) 599-614.
- [148] R. Finberg, D.R. Spriggs and B.N. Fields, Host immune response to reovirus: CTL recognize the major neutralization domain of the viral hemagglutinin, *J Immunol* 129 (1982) 2235-8.
- [149] R. Cook, L. Lu, J. Gu, R.W. Williams and R.J. Smeyne, Identification of a single QTL, *Mptp1*, for susceptibility to MPTP-induced substantia nigra pars compacta neuron loss in mice, *Brain Res Mol Brain Res* 110 (2003) 279-88.
- [150] O. Abiola, J.M. Angel, P. Avner, A.A. Bachmanov, J.K. Belknap, B. Bennett, E.P. Blankenhorn, D.A. Blizard, V. Bolivar, G.A. Brockmann, K.J. Buck, J.F. Bureau, W.L. Casley, E.J. Chesler, J.M. Cheverud, G.A. Churchill, M. Cook, J.C. Crabbe, W.E. Crusio, A. Darvasi, G. de Haan, P. Dermant, R.W. Doerge, R.W. Elliot, C.R. Farber, L. Flaherty, J. Flint, H. Gershenfeld, J.P. Gibson, J. Gu, W. Gu, H. Himmelbauer, R. Hitzemann, H.C. Hsu, K. Hunter, F.F. Iraqi, R.C. Jansen, T.E. Johnson, B.C. Jones, G. Kempermann, F. Lammert, L. Lu, K.F. Manly, D.B. Matthews, J.F. Medrano, M. Mehrabian, G.

- Mittlemann, B.A. Mock, J.S. Mogil, X. Montagutelli, G. Morahan, J.D. Mountz, H. Nagase, R.S. Nowakowski, B.F. O'Hara, A.V. Osadchuk, B. Paigen, A.A. Palmer, J.L. Peirce, D. Pomp, M. Rosemann, G.D. Rosen, L.C. Schalkwyk, Z. Seltzer, S. Settle, K. Shimomura, S. Shou, J.M. Sikela, L.D. Siracusa, J.L. Spearow, C. Teuscher, D.W. Threadgill, L.A. Toth, A.A. Toyne, C. Vadasz, G. Van Zant, E. Wakeland, R.W. Williams, H.G. Zhang and F. Zou, The nature and identification of quantitative trait loci: a community's view, *Nat Rev Genet* 4 (2003) 911-6.
- [151] W. Crusio. in (Goldowitz D, W., D., Wimer, R.E., ed.) *Techniques for the genetic analysis of brain and behavior.*, Elsevier, Amsterdam 1992, pp. 231-250.
- [152] S.D. Brown, The Mouse Genome Project and human genetics. A report from the 5th International Mouse Genome Mapping Workshop, Lunteren, Holland., *Genomics* 13 (1992) 490-492.
- [153] T.N. Ferraro, G.G. Smith, C.L. Schwebel, F.W. Lohoff, P. Furlong, W.H. Berrettini and R.J. Buono, Quantitative trait locus for seizure susceptibility on mouse chromosome 5 confirmed with reciprocal congenic strains, *Physiol Genomics* 31 (2007) 458-62.
- [154] A. Lorenzana, Z. Chancer and P.E. Schauwecker, A quantitative trait locus on chromosome 18 is a critical determinant of excitotoxic cell death susceptibility, *Eur J Neurosci* 25 (2007) 1998-2008.
- [155] D. Ryman, Y. Gao and B.T. Lamb, Genetic loci modulating amyloid-beta levels in a mouse model of Alzheimer's disease, *Neurobiol Aging* (2007).
- [156] S. Rubin, D. Liu, M. Pletnikov, J. McCullers, Z. Ye, R. Levandowski, J. Johannessen and K. Carbone, Wild-type and attenuated influenza virus infection of the neonatal rat brain, *J Neurovirol* 10 (2004) 305-14.

- [157] K. Shinya, A. Suto, M. Kawakami, H. Sakamoto, T. Umemura, Y. Kawaoka, N. Kasai and T. Ito, Neurovirulence of H7N7 influenza A virus: brain stem encephalitis accompanied with aspiration pneumonia in mice, *Arch Virol* 150 (2005) 1653-60.
- [158] H. Braak, K. Del Tredici, U. Rub, R.A. de Vos, E.N. Jansen Steur and E. Braak, Staging of brain pathology related to sporadic Parkinson's disease, *Neurobiol Aging* 24 (2003) 197-211.
- [159] N. Hemling, M. Roytta, J. Rinne, P. Pollanen, E. Broberg, V. Tapio, T. Vahlberg and V. Hukkanen, Herpesviruses in brains in Alzheimer's and Parkinson's diseases, *Ann Neurol* 54 (2003) 267-71.
- [160] R.J. Marttila, U.K. Rinne, P. Halonen, D.L. Madden and J.L. Sever, Herpesviruses and parkinsonism. Herpes simplex virus types 1 and 2, and cytomegalovirus antibodies in serum and CSF, *Arch Neurol* 38 (1981) 19-21.
- [161] C. Irkec, [The role of viral antibodies in the pathogenesis of degenerative and demyelinating diseases], *Mikrobiyol Bul* 23 (1989) 40-50.
- [162] T.S. Elizan, D.L. Madden, G.R. Noble, K.L. Herrmann, J. Gardner, J. Schwartz, H. Smith, Jr., J.L. Sever and M.D. Yahr, Viral antibodies in serum and CSF of Parkinsonian patients and controls, *Arch Neurol* 36 (1979) 529-34.
- [163] J. Woulfe, H. Hoogendoorn, M. Tarnopolsky and D.G. Munoz, Monoclonal antibodies against Epstein-Barr virus cross-react with alpha-synuclein in human brain, *Neurology* 55 (2000) 1398-401.
- [164] F.O. Bastian, A.S. Rabson, C.L. Yee and T.S. Tralka, Herpesvirus hominis: isolation from human trigeminal ganglion, *Science* 178 (1972) 306-7.
- [165] K. Tomonaga, T. Kobayashi and K. Ikuta, [The neuropathogenesis of Borna disease virus

- infection], *Nippon Rinsho* 59 (2001) 1605-13.
- [166] J. Iwahashi, K. Tsuji, T. Ishibashi, J. Kajiwara, Y. Imamura, R. Mori, K. Hara, T. Kashiwagi, Y. Ohtsu, N. Hamada, H. Maeda, M. Toyoda and T. Toyoda, Isolation of amantadine-resistant influenza A viruses (H3N2) from patients following administration of amantadine in Japan, *J Clin Microbiol* 39 (2001) 1652-3.
- [167] E.T. Gamboa, A. Wolf, M.D. Yahr, H. Barden, C.C. Hsu, P.E. Duffy and D.H. Harter, Influenza A virus as a possible cause of postencephalitic Parkinsonism, *Trans Am Neurol Assoc* 98 (1973) 177-80.
- [168] W.P. Isgreen, A.M. Chutorian and S. Fahn, Sequential parkinsonism and chorea following "mild" influenza, *Trans Am Neurol Assoc* 101 (1976) 56-60.
- [169] C.P. Maurizi, Was a neurovirulent influenza virus the cause of amyotrophic lateral sclerosis and parkinsonism-dementia on Guam? *Med Hypotheses* 23 (1987) 325-6.
- [170] G. Moore, Influenza and Parkinson's disease, *Public Health Rep* 92 (1977) 79-80.
- [171] M. Takahashi and T. Yamada, Viral etiology for Parkinson's disease--a possible role of influenza A virus infection, *Jpn J Infect Dis* 52 (1999) 89-98.
- [172] M.J. Ball, Unexplained sudden amnesia, postencephalitic Parkinson disease, subacute sclerosing panencephalitis, and Alzheimer disease: does viral synergy produce neurofibrillary tangles? *Arch Neurol* 60 (2003) 641-2.
- [173] A.J. Sasco and R.S. Paffenbarger, Jr., Measles infection and Parkinson's disease, *Am J Epidemiol* 122 (1985) 1017-31.
- [174] R.C. Peatfield, Basal ganglia damage and subcortical dementia after possible insidious Coxsackie virus encephalitis, *Acta Neurol Scand* 76 (1987) 340-5.
- [175] S. Kamei, S.M. Hersch, T. Kurata and Y. Takei, Coxsackie B antigen in the central

- nervous system of a patient with fatal acute encephalitis: immunohistochemical studies of formalin-fixed paraffin-embedded tissue, *Acta Neuropathol* 80 (1990) 216-21.
- [176] L. Horta-Barbosa, D.A. Fuccillo and J.L. Sever, Chronic viral infections of the central nervous system, *Jama* 218 (1971) 1185-8.
- [177] N.M. Nielsen, K. Rostgaard, H. Hjalgrim, P. Aaby and D. Askgaard, Poliomyelitis and Parkinson disease, *Jama* 287 (2002) 1650-1.
- [178] B.P. Hersh, P.R. Rajendran and D. Battinelli, Parkinsonism as the presenting manifestation of HIV infection: improvement on HAART, *Neurology* 56 (2001) 278-9.
- [179] P. Maggi, M. de Mari, A. Moramarco, G. Fiorentino, P. Lamberti and G. Angarano, Parkinsonism in a patient with AIDS and cerebral opportunistic granulomatous lesions, *Neurol Sci* 21 (2000) 173-6.
- [180] S.M. Mirsattari, C. Power and A. Nath, Parkinsonism with HIV infection, *Mov Disord* 13 (1998) 684-9.
- [181] J. de la Fuente-Aguado, J. Bordon, J.A. Moreno, B. Sopena, A. Rodriguez and C. Martinez-Vazquez, Parkinsonism in an HIV-infected patient with hypodense cerebral lesion, *Tuber Lung Dis* 77 (1996) 191-2.
- [182] G.J. Wang, L. Chang, N.D. Volkow, F. Telang, J. Logan, T. Ernst and J.S. Fowler, Decreased brain dopaminergic transporters in HIV-associated dementia patients, *Brain* 127 (2004) 2452-8.
- [183] E. Koutsilieri, S. Sopper, C. Scheller, V. ter Meulen and P. Riederer, Parkinsonism in HIV dementia, *J Neural Transm* 109 (2002) 767-75.
- [184] R.L. Robinson, S. Shahida, N. Madan, S. Rao and N. Khardori, Transient parkinsonism in West Nile virus encephalitis, *Am J Med* 115 (2003) 252-3.



- [185] M. Minami, N. Hamaue, M. Hirafuji, H. Saito, T. Hiroshige, A. Ogata, K. Tashiro and S.H. Parvez, Isatin, an endogenous MAO inhibitor, and a rat model of Parkinson's disease induced by the Japanese encephalitis virus, *J Neural Transm Suppl* (2006) 87-95.
- [186] N. Hamaue, A. Ogata, M. Terado, K. Ohno, S. Kikuchi, H. Sasaki, K. Tashiro, M. Hirafuji and M. Minami, Brain catecholamine alterations and pathological features with aging in Parkinson disease model rat induced by Japanese encephalitis virus, *Neurochem Res* 31 (2006) 1451-5.
- [187] U.K. Misra, J. Kalita, S. Pandey, V.K. Khanna and G.N. Babu, Cerebrospinal fluid catecholamine levels in Japanese encephalitis patients with movement disorders, *Neurochem Res* 30 (2005) 1075-8.
- [188] M. Nishimura, I. Mizuta, E. Mizuta, S. Yamasaki, M. Ohta, R. Kaji and S. Kuno, Tumor necrosis factor gene polymorphisms in patients with sporadic Parkinson's disease, *Neurosci Lett* 311 (2001) 1-4.
- [189] A. Ogata, K. Tashiro and S. Pradhan, Parkinsonism due to predominant involvement of substantia nigra in Japanese encephalitis, *Neurology* 55 (2000) 602.
- [190] T. Haraguchi, H. Ishizu, S. Terada, Y. Takehisa, Y. Tanabe, T. Nishinaka, K. Kawai, S. Kuroda, Y. Komoto and M. Namba, An autopsy case of postencephalitic parkinsonism of von Economo type: some new observations concerning neurofibrillary tangles and astrocytic tangles, *Neuropathology* 20 (2000) 143-8.
- [191] H. Shoji, M. Watanabe, S. Itoh, H. Kuwahara and F. Hattori, Japanese encephalitis and parkinsonism, *J Neurol* 240 (1993) 59-60.
- [192] K. Miyasaki and F. Takayoshi, Parkinsonism following encephalitis of unknown etiology, *J Neuropathol Exp Neurol* 36 (1977) 1-8.

[193] M.G. Reyes, J.J. Gardner, J.D. Poland and T.P. Monath, St Louis encephalitis.

Quantitative histologic and immunofluorescent studies, Arch Neurol 38 (1981) 329-34.

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Table 1

## Association of Virus and Parkinsonsim

Virus	Family	Species	References
DNA	Herpesviridae	Herpes simplex virus	[159-162]
		Epstein-Barr virus	[163]
		Cytomegalovirus (CMV)	[160, 162]
		Varicella zoster virus (VZV)	[164]
RNA	Bornaviridae	Borna disease virus	[165]
	Orthomyxoviridae	Influenza virus Type A	[57, 63, 65, 135, 166-171]
	Paramyxoviridae	Measles	[172, 173]
	Picornaviridae	Coxsackie virus	[99, 100, 174, 175]
		Echo virus	[176]
		Polio Virus	[177]
	Retroviridae	Human Immunodeficiency Virus (HIV)	[178-183]
	Flaviviridae	West Nile virus	[184]
		Japanese encephalitis B virus	[110, 166, 185-192]
		St. Louis Virus	[92, 111, 193]