

~||{ **National Parkinson Foundation** }||~~||{ **A World Wide Organization** }||~

## Parkinson Disease at an Early Age

*by Juan Sanchez-Ramos, PhD, M.D., Professor Neurology at the University of South Florida an NPF Center of Excellence*

*edited by Abraham Lieberman, M.D., Medical Director of the National Parkinson Foundation, Professor of Neurology at the University of Miami, Miami, FL*

---

**E**ver since the perpetually young actor Michael J. Fox admitted to the media that he suffers from Parkinson disease (PD) a tremendous interest in PD has been ignited in the public. The stereotype of the tremulous, aged, stooped PD patient has been given a new twist by the news. Because of Mr. Fox's candor, young people, less than age 40 years, realize they're at risk. Parents (and grandparents) are concerned because their children are at risk. And doctors have a new threshold for recognizing and diagnosing PD--the young aren't exempt.

### How Common is Young-Onset Parkinson Disease (YOPD)?

Classical, typical adult-onset PD develops at age 60+ years. It's a common disease with approximately 3500 PD patients per 1,000,000 people. Until recently PD starting before age 40 years was considered rare--except in Japan. Although most studies in North American and Europe report the onset of PD in patients younger than age 40 years as approximately 10 patients per 1,000,000 people some studies report the onset of PD in patients younger than age 40 years as high as 47 patients per 1,000,000 people. At any given moment in North America and Europe, the cumulative number of patients whose PD began before age 40 years is 4-12% of all PD patients. In Japan the cumulative number of patients whose PD began before age 40 years may, in some clinics, be as high as 40% of PD patients!

Patients who develop PD between ages 21-40 years are called young onset PD patients abbreviated as YOPD. Patients who develop PD before age 21 years are called juvenile Parkinsonism patients abbreviated as JP. JP consist is a mix of diseases--hence the designation as Parkinsonism (or Parkinson Syndrome) not Parkinson Disease. One of these diseases is characterized, at autopsy, by the presence of Lewy bodies, the hallmark of PD. And one of these diseases is characterized, at autopsy, by the absence of Lewy bodies. YOPD, on the other hand, resembles adult-onset PD with Lewy bodies--hence the designation PD.

Autopsy studies of brains from YOPD patient reveals loss and degeneration of dopamine nerves cells in the substantia nigra. Inside the cytoplasm of the degenerating cells are Lewy bodies.

### **Differences between Young-Onset PD (YOPD) and Adult-Onset PD**

In 40 YOPD patients in Japan 3 groups are described. Group-1 consists of YOPD patients whose symptoms are similar to adult-onset patients PD except for an earlier-age of onset and marked response to levodopa (Atamet or Sinemet). Group-2 (YOPD) consists of patients similar to Group-1 except their response to levodopa isn't as marked. Group-3 consists of Juvenile Parkinsonism (JP) patients with the earliest onset: ages 6-16 years. In JP patients symptoms usually begins symmetrically in both feet and consists of turning-in (inversion). This differs from adult-onset PD patients whose symptoms begin asymmetrically usually in a hand. JP patients show the most marked response to levodopa-responding to small doses. At autopsy JP patients have preserved, non-degenerated, cells in the substantia nigra. The cells, however, lack pigment (neuromelanin).

Pigment (neuromelanin) is formed within nigral cells as a by-product of dopamine metabolism. Neuromelanin differs from skin pigment. Caucasians, Africans, Orientals and albinos have equal amounts of neuromelanin. Neuromelanin is absent @ birth-in all people. It accumulates after birth. And, In most people, the nigral cells are fully pigmented @ age 16 years. In PD, as nigral cells die, neuromelanin's released, removed, and disappears. And Lewy bodies appear. Tyrosine hydroxylase, the enzyme that regulates dopamine, is reduced more in the striatum (the area to which the nigra projects) than in the nigra of JP patients. This is unlike typical PD or YOPD where tyrosine hydroxylase is reduced equally in the nigra and the striatum.

The progression of symptoms in YOPD and JP patients differs from adult-onset PD in being slower. In addition, in YOPD and JP patients symptoms start symmetrically. In adult-onset PD symptoms start asymmetrically. In YOPD and JP patients the principal symptoms are rigidity, slowness of movement, and dystonia(with painful spasms)--of the feet. In JP patients, unlike YOPD and adult-onset PD, tremor is usually absent. In YOPD (but not necessarily JP), mental changes: intellectual decline and cognitive impairment are usually absent. And in YOPD (but not necessarily JP), autonomic symptoms are usually absent.

The obvious difference between YOPD, JP, and adult-onset PD patients is in YOPD and JP patients there's a marked response to levodopa. Many YOPD and JP patients respond dramatically to a single dose of levodopa. In addition, on levodopa, YOPD and JP patients are more likely than adult-onset PD patients to develop fluctuations: "wearing-off" and "on-off" effects. And on levodopa, YOPD and JP patients are more likely to develop involuntary twisting movements (dyskinesias). In YOPD and JP patients, fluctuations and dyskinesias appear within a few months of starting levodopa. In typical, adult-onset PD patients fluctuations and dyskineses appear within 3-5 years of starting levodopa.

In a study from England of 149 YOPD patients starting before age 40 years 10 patients (7%) had onset before age 21 years. The remaining 139 patients had onset between ages 21 - 40 years. This age distribution is similar to that reported in other studies in North America and Europe, but differs from Japan.

Whereas in North America and Europe onset before age 21 years is uncommon, in Japan, onset before age 21 years is common.

In Japan, unlike in North America and Europe, YOPD and JP patients are more likely to have a family history of Parkinsonism. In Japan approximately 40% of YOPD patients (and almost all JP patients) have a family history of Parkinsonism. In Japan, the inheritance of YOPD, and especially the inheritance of JP, is recessive-it skips or spares some generations.

A note of caution. JP patients are identified as JP because their symptoms are recognized before age 21 years. Usually, patients so-identified represent a single disease, a disease with, at autopsy, distinct changes in the brain. YOPD patients are identified as YOPD because their symptoms are recognized after age 21 years but before age 40 years. Patients so-identified represent two disease. One disease is JP--it starts, in the brain, before age 21 years. But it doesn't manifest itself, or isn't diagnosed till after age 21 years. The changes in the brain of JP diagnosed after age 21 years are identical to the changes in the brain of JP diagnosed, after age 21 years. These changes consist of a loss of cells in the substantia nigra unaccompanied by Lewy bodies. These changes are different from those in the brains of YOPD patients. In YOPD patients, as in adult onset PD patients, there's a loss of cells in the substantia nigra accompanied by Lewy bodies.

In North America and Europe only 16% of YOPD patients have a family history of PD. This figure's similar to that in adult-onset PD patients. This suggests that in YOPD patients in North America and Europe, unlike in Japan, genetic factors are similar to adult-onset PD patients. However, in North America and Europe in YOPD patients who are identical twins (from a single-egg), there's a higher incidence of PD than among YOPD patients who are non-identical twins (twins from two eggs). This suggests subtle but as yet undetermined genetic factors.

In Japan, JP is different from YOPD with the exception of those JP patients misdiagnosed as YOPD (because their disease wasn't recognized until after age 21 years). JP patients are more likely to have a family history of Parkinsonism. JP patients are more likely to have onset of symptoms symmetrically. And JP patients are more likely to have onset of symptoms in their feet--with dystonia.

Dr. Y Mizuno (and his group) at the NPF Center of Excellence at Jutendo University in Tokyo studied several JP patients. They identified on chromosome-6 an abnormal gene. The gene codes for a protein they identified and named, parkin. Parkin, like the related protein, ubiquitin, is a scavenger-protein. A scavenger-protein's one that "cleans-up" accumulations or deposits of other proteins. If there's a problem with the scavenger, the scavenger, as well as the protein the scavenger's meant to "clean-up"--accumulates.

Parkin, like ubiquitin, accumulates in Lewy bodies in YOPD and adult-onset PD patients. In addition, in YOPD and adult-onset PD patients, another protein, alpha-synuclein, deposits and accumulates in Lewy bodies. Alpha-synuclein,

unlike parkin and ubiquitin, isn't a scavenger. Alpha-synuclein, like most proteins, is "manufactured" inside the cell's nucleus or in a nearby area called the endoplasmic-reticulum. Alpha-synuclein, like most proteins, is then transported through a system of tubules, or "tunnels", into another nearby area called the Golgi-apparatus. In the Golgi-apparatus proteins are "modified" to perform specific tasks. The proteins are then, again, transported through a system of "tunnels" to their final destination. Alpha-synuclein's final destination is the synaptic vesicles, granular particles that store chemicals. Dopamine is stored on synaptic vesicles.

In YOPD or adult-onset PD patients, a defective alpha-synuclein accumulates inside the cell. The accumulation occurs between the nucleus, where alpha-synuclein's "manufactured", and the synaptic vesicles. The accumulation occurs in Lewy bodies and is associated with deposits of parkin and ubiquitin.

Alpha-synuclein may accumulate because it's genetically-defective making-it excessively "sticky." This may be the situation in the large Italian-family, the Contursi-family, described by Drs. Duvoisin and Golbe. Here an abnormal gene on chromosome-4, a gene discovered by Dr. M Polymeropoulos, through a grant from the NPF, codes for a defective (and "sticky") alpha-synuclein. This, however, accounts for less-than 1% of PD patients. In most YOPD and adult-onset PD, the defect in alpha-synuclein (making-it "sticky") probably occurs after it's "manufactured."

Alpha-synuclein and ubiquitin also accumulate on the plaques that occur in Alzheimer disease. Understanding how alpha-synuclein's "manufactured" and transported, and understanding why it becomes "sticky"--how it curls and coils, is crucial to understanding PD and Alzheimer disease.

### **Dopa-Responsive Dystonia (DRD): A Different Disease**

Not all patients diagnosed as JP or YOPD have Parkinsonism or PD. There's a disorder, relatively uncommon, characterized by dystonia and slowness of movement called Dopa-Responsive Dystonia (abbreviated DRD). DRD manifests itself before age 10 years. However, it may-be go unrecognized, or be mistaken for JP. Because of increased awareness (in the public and among doctors) DRD is being recognized more frequently. DRD is also called Dystonia With Diurnal Variations. DRD was first described by Dr. M. Segawa, of the Segawa Clinic, in Tokyo, a NPF Center of Excellence. DRD is often called "Segawa's disease" to honor Dr. Segawa.

In DRD the initial symptoms are "turning-in" of one foot (or both feet). The initial symptoms are similar to JPD and YOPD. Unlike JP or YOPD, the symptoms grow markedly worse towards evening. And, unlike JP or YOPD, the symptoms disappear after a night's sleep. DRD patients like JP and many YOPD patients respond dramatically to low doses of levodopa. There are also reports of DRD patients without diurnal fluctuations. In all DRD-patients the disease is probably inherited.

In DRD patients symptoms may begin in the right-foot, spread to the right-arm, then the left-foot, then the left-arm. Or, symptoms may begin in the right-foot, spread to the left-foot, then the right-foot, then the right-arm. In DRD patients dystonia's appreciated as increased resistance to stretch (similar to PD rigidity). However, in DRD patients, unlike PD patients, the rigidity's "gravity or motion dependent" increasing (or decreasing) in certain positions or after certain movements. Thus, in DRD patients, the dystonia increases as the patients sits or stands and is relieved when he lies down. And, it's worsened by stress.

DRD patients usually develop pes equinovarus ( from the Latin "horse's foot"): an abnormal posture in which the foot assumes a "high-arch" forcing the patient to walk on the ball of his foot. Most DRD patient (when untreated) walk with their head-and-trunk bent @ a 45 degree angle to their legs. Low doses of levodopa (Atamet or Sinemet) completely abolish all symptoms. And most DRD patients, who before levodopa had diurnal fluctuations, can be maintained for years on levodopa without developing the fluctuations or dyskinesias that plague YOPD or adult-onset PD patients.

DRD is inherited as a dominant-trait, each generation's affected. DRD results from a mutation in a gene that codes for a protein: GTP-cyclohydrolase. The protein, GTP-cyclohydrolase, is the rate-limiting enzyme for the synthesis of tetra-hydrobiopterin. Tetra-hydrobiopterin is a necessary factor for activation of tyrosine hydroxylase, the protein that's the rate-limiting enzyme for dopamine synthesis. Among DRD patients a decrease in tyrosine hydroxylase activity results in decreased levels (20% of normal) of dopamine. Although JP, YOPD, and adult-onset PD are characterized by a dopamine deficiency (less than 20% of normal), the deficiency isn't associated with a mutation in GTP-cyclohydrolase. In DRD there's no loss or degeneration of dopamine cells in the substantia nigra. However, the cells are unable to make dopamine. The process that affects these cells is enough to limit their ability to make dopamine, but not enough to destroy them.

### **Distinguishing DRD from JP and YOPD**

DRD and JP are diagnosed because of the appearance of dystonia and Parkinson symptoms before age 16 years. And both respond to levodopa. In time, over several years, DRD and JP can be distinguished from each other. But, initially, how can they be distinguished? Positron-emission tomography (PET-scan) using radiolabelled fluoro-dopa (a precursor to dopamine) is one method. Fluorodopa PET-scan were performed in 10 DRD and 18 YOPD patients. Fluorodopa-uptake was significantly lower in the striatum of YOPD versus normal age-matched controls. The decreased uptake matched the severity of PD. By contrast DRD patients had normal fluorodopa uptakes. These results support the concept that DRD and YOPD (and by inference JP) result from different mechanism. At autopsy DRD and YOPD (and JP) are characterized by a deficiency of dopamine in the striatum. But, as demonstrated by PET-scanning, in DRD (but not YOPD) dopa is taken-up and converted to dopamine--normally.

### Editor's Note

JP, but not YOPD, is different from adult-onset PD. JP, in Japan, results from a mutation of a gene on chromosome-6, a gene that codes for a protein: parkin. At autopsy, brains of JP patients reveal degeneration of nigral cells unassociated with Lewy bodies. At autopsy, brains of YOPD (like adult-onset PD) reveal degeneration of nigral cell associated with Lewy bodies and accumulation of a protein, alpha-synuclein. JP, YOPD, and adult-onset PD differ from DRD. DRD arises from a mutation of a gene that codes for a protein, GTP-cyclohydrolase.

YOPD have a vital, self-serving interest in understanding the biology of those proteins that are accumulating in their brain. And they have a vital, self-serving interest in raising public awareness to secure funds for research. Till now, understanding how proteins are "made", processed, shaped, transported, and stored--was esoteric, removed from day-to-day life. But, only such understanding will lead to cures for PD and Alzheimer disease.

Our current treatments enable YOPD to live long-lives. The treatments, however, are symptomatic. And as the underlying disease progresses, as proteins accumulate, the quality of life diminishes--markedly. This is unlike the situation in adult-onset PD. Relieve, for 10 years, the symptoms of a 75 year old with PD and he'll outlive his disease. Relieve, for 10 years, the symptoms of a 30 year man with PD, and he's a 40 year old Michael J Fox with the rest of his life to lead--accompanied by PD--a most unwelcome companion.

### References

- Kitada, T., Asakawa, S., Hattori: 1998. Mutations in the parkin gene cause autosomal recessive juvenile parkinsonism. *Nature* 392: 605-8.
- Polymeropoulos, M. H., Lavedan, C., Leroy, E: 1997. Mutation in the alpha-synuclein gene identified in families with Parkinson's disease. *Science* 276: 2045-2047.
- Quinn, N., Critchley, P., and Marsden, C. D. 1987. Young onset Parkinson's disease. *Movement Disorders* 2: 73-91.
- Schrag, A., Ben-Shlomo, Y., Brown. 1998. Young-onset Parkinson's disease revisited--clinical features, natural history, and mortality. *Movement Disorders* 13: 885-94.
- Segawa, M., Hosaka, A., Miyagawa, H. 1976. Hereditary progressive dystonia with marked diurnal fluctuation. *Advances in Neurology* 14: 215-33.
- Snow, B. J., Nygaard, T. G., Takahashi, H. 1993. Positron emission tomographic studies of dopa-responsive dystonia and early-onset idiopathic parkinsonism. *Annals of Neurology* 34: 733-8.
- Yokochi, M., Narabayashi, H., Iizuka, R. 1984. Juvenile parkinsonism--some clinical, pharmacological, and neuropathological aspects. *Advances in Neurology* 40: 407-13.

---

<b>GO BACK</b>
----------------

<b>HOME</b>
-------------