Case Report ISSN 2693-2490

Journal of Psychology and Neuroscience

Dopa Responsive Dystonia with Marked Diurnal Fluctuation (Sagawa Disease) Forty-Five Years of Follow–Up

Natan Gadoth MD

Maynei Hayeshua Medical Center and the Sackler Faculty of Medicine, Tel –Aviv University, Israel.

***Correspondence author**
N. Gadoth MD
Dept. Neurology,
Maynei Hayeshua Med Ctr. 17 Povarsky St. Bnei Barak. Israel.

Submitted : 15 Mar 2024 ; Published : 13 Apr 2024

Citation: N. Gadoth. (2024). Dopa Responsive Dystonia with Marked Diurnal Fluctuation (Sagawa Disease) Forty-Five Years of Follow–Up. J Psychol Neurosci; 6(2):1-3. DOI : https://doi.org/10.47485/2693-2490.1087

Abstract

Objective: *To describe the clinical course and very long personal follow-up of a patient with Segawa Disease*

Methods: *The medical records of the patient since the diagnosis at the age of 9 years until her last follow-up at the age of 55 years were obtained and summarized*

Results: *The long-term follow-up showed an excellent long-lasting response to L-DOPA therapy and also revealed that non-motor psychiatric features are an integral part of the disease rather than an emotional side effect of chronic motor disability.*

Conclusion: *Long term follow-up of Segawa syndrome can provide additional information on prognosis and quality of life in old age, which are not known yet.*

Keywords: dystonia, hereditary, DOPA, serotonin, sleep, Segawa disease, depression, anxiety

Introduction

Childhood onset progressive dystonia with marked diurnal fluctuation of severity responsive to L-Dopa was first described in 2 Japanese siblings by Segawa in 1971 (Segawa et al., 1971). Subsequently, Segawa described a series of 9 patients establishing the hereditary autosomal dominant nature of the disorder and expanding its clinical spectrum (Segawa et al., 1976), which became known somewhat later as Segawa Disease (SD). Negaard coined the term DOPA Responsive Dystonia (DRD) for cases with various forms of dystonia which responded favorably to L-DOPA and included SD in this group (Nygaard et al., 1988). Since 1990 attempt have been made to determine the molecular genetics of SD, until Nygraard and colleagues have mapped the gene for DRD to chromosome 14(14q11.2-q22) (Nygaard et al., 1993). Somewhat later it was confirmed that the gene GTP cyclohydrolase I (GCH1) which is located at that locus is responsible for SD (lchinose et al., 1994).

The gene GCH1 (OMIM #600225), encodes the enzyme GTP (Guanosine -5'-Triphospate) cyclohydrolase I which is involved in the first and rate-limiting step of the de novo biosynthesis of tetrahydrobiopterin (BH4) by catalyzing the formation of dihydroneopterin triphosphate from GTP. BH4 is an essential cofactor required for the activity of various enzymes such as phenylalanine, tryptophane and tyrosine hydroxylases (Thöny et al., 2000). BH4 is essential for the synthesis of dopamine and serotonin, thus, heterozygous point mutations and more rarely, large deletions in GCHI found in patients with SD result in decreased activity of GTP cyclohydrolase I causing dopamine and serotonin deficiency. Indeed, neuropathological and neurochemical studies of SD brains have shown a marked decrease of dopamine in the striatum, mainly in the putamen as well as decreased activity of Tryptophan hydroxylase (Rajput et al., 1994) and also a markedly decreased content of total biopterin and neopterin in the putamen (Furukawa et al., 1996). It should be noted that most of biopterin takes the form of BH4 and neuropterin concentration is an indicator of GCH I activity. DRD and SD in particular are very rare disorders. Females are more affected and estimates of the prevalence of all forms of DRD as 0.5 per 1 million was considered as too low due to underdiagnoses (Nygaard et al., 1991).

Hereditary progressive dystonia with marked diurnal fluctuations which was later given the eponym “Sagawa Disease" is indeed the best and precise description of this form of dystonia, rather than the terms DRD or DYT5 (dystonia type 5), since those terms refer to a variety of disorders characterized by progressive dystonia responsive to DOPA. Thus, it is appropriate to renew the use of Sagawa Disease for such patients as was previously suggested (Lee et al., 2018).

There are few reports on long term follow-up of patients with SD who have been treated successfully with L-DOPA. Quite recently a large cohort of Spanish patients with DRD was reported, 26 of them with classical SD. As expected, those patients showed an excellent and long lasting response to treatment with L-DOPA during a follow-up period of 3-29 years (mean 14.3), (Fernandez-Ramos et al., 2022).

Case Report

In the present report we will describe in brief the clinical features and details of 45 years of personal follow-up of case 1 our previously reported female patient (Costeff et al., 1987). This 55 year old woman was seen by us for the first time at the age of 9 years. She was the product of a normal pregnancy and delivery. Family history and early development were unremarkable. Since the age of 4 years progressive gait difficulty, frequent stumbling and easy tiring were noted. Somewhat later, emotional instability and decreased, school, performance unchanged with extensive psychotherapy led to her being placed in a "slow-learner" class. The neurological evaluation at the age of 7 years disclosed the presence of obesity, "tiered" facial expression and slow reactions. Her sleep-wake cycle was described as waking up at dawn being able to walk independently. Later in the day, progressive gait difficulty with stiff limbs and pronounced tiredness with prominent sleep urge ended with her falling asleep during the early afternoon hours. Episodes of inability to walk forcing her to crawl were reported. During those episodes which lasted for hours, flexion of neck and arms, wrists and fingers with extended legs and left foot equinovarus were noted. Between the ages 7-9 years a number of specialists referred to her muscle tone as "normal, increased and equivocal". Also noted were absent Babinski sign, ankle clonus, wide based gait and slow rigid movements "most of the time". Extensive evaluation in 5 university affiliated medical centers which included routine blood tests, thyroid functions, EEG, pneumoencephalography, air myelography, visual and auditory evoked potentials, nerve conduction, electromyography, repetitive nerve stimulation, muscle biopsy, serum lactate and pyruvate at rest and during ischemic exercise, ceruloplasmin and Tension test were within normal limits or negative. Muscle biopsy disclosed type 2 fiber atrophy. The following diagnoses were entertained: spastic diplegiaspinocerebellar degeneration, metabolic myopathy and Dystonia Muscularum Deformans. She receives extensive daily physiotherapy away from home. It was noted that during the early morning she could easily get in-and-out of the taxi while after the end of the treatment session at about noon time 2 strong adults were required to get her into the taxi on the way home.

When seeing her for the first time at the age of 9 years she was overweight, with "frozen", course facial features, protruding tongue, drooling. Speech melody, rhythm and intonation were impaired (dysprosody). She stood on a wide base with flexed neck and could walk with short steps mainly on her toes with "winging" movements of her right arm. Muscle tone was increased without additional neurological impairment. The severity of gait and posture was milder when examined in the morning and dramatically worsened when seen in the late afternoon. Two consecutive nocturnal polysomnographic studies disclosed increased body movements during REM sleep with otherwise normal sleep architecture. A diagnosis of SD was entertained and daily L-DOPA /DC inhibitor (Dopicar^{R}), 1.5 mg. /Kg. was promptly started. Almost immediately a dramatic decrease in motor disability and increase in alertness was noted. Subsequently, she lost weight and returned to a normal sleep cycle, however, increased body movements during REM sleep were still present as evident in a repeated sleep study. Three months later she appeared as a happy and normally mobile girl without neurological impairment. Weight loss of 20 Kg. was recorded. She did well in school after being placed in a regular class. During the next 7 years she was maintained on 200/50 L-DOPA /DC inhibitor (Sinemet CR^{R}), during which neither side effects nor loss of treatment response were noted. She tried several times to discontinue drug treatment which resulted in a prompt reappearance of dystonia. The clinical diagnosis was confirmed by genetic molecular testing showing a single mutated allele (loss of function mutation type) in the GCH1 gene. This mutation is known as pathogenic for SD according to the American College of Medical Genetics. During the following years the follow-up consisted of annual phone calls reporting a stable normal condition as long as the drug treatment was continued. She returned to the clinic at the age of 45 years. During the years since her last clinic evaluation, she managed to graduate from high school being an average student. She considered herself as emotionally unstable with bouts of depressed mood and low self-esteem. Her general health was described as satisfactory as long as she was in relationship with a number of boyfriends. She held a permanent job requiring shift work and was still unmarried. She experienced brief transient bouts of dystonia involving tongue and eyelids with rare bouts of generalized dystonia. The dose of Sinement^{R} was increased in accordance with her weight. She complained of significant insomnia which could be related partially to shift work. Cognitive behavioral therapy for insomnia was recommended. She was seen again a year later and reported on attacks of focal or less frequently generalized dystonia especially during the late afternoon accompanied by profound anxiety which was ameliorated by Lorazem (Lorivan^{R}). The characteristic diurnal fluctuation of dystonia with marked worsening during the evening was still evident. One milligram of Lorivan^{R} before bedtime was prescribed. During the next two years she reported on several bouts of dystonia which became progressively more frequent especially during a strict dietary regimen and subsequent bariatric surgery. She also tried to decrease the dose and frequently skipped a dose of Sinemet CR^{R}. Insomnia and daytime fatigue worsened. During the last 2 years her social life deteriorated concomitantly with frequent phone calls to the author for help even during the night complaining of attacks of disabling dystonia in spite of increase or decrease dose of either Dopicar^{R} or Sinemet CR^{R} and a short trial of add-on of Trihexyphenidyl (Rodenal^{R}). This unexpected course of events was considered as very atypical for classical SD. Since all those events happened at home, we have asked to receive a video clip of a typical event. The clip showed a hyperkinetic

event accompanied by hyperventilation and marked sweating typical marked anxiety attack. Treatment with Lorivan[R] 1 mg. TID was very effective and markedly reduced the frequency of those events.

Discussion

The present case repot provides a unique opportunity to learn about the long-term course, treatment response and prognosis of SD patients due to more than 40 years of follow-up by the same physician who arrived at the correct diagnosis after 5 years of a variety of misdiagnoses. Such a delay in diagnosis and the appearance of non-motor psychiatric morbidity as patients grow older are quite typical. The long term excellent response to low dose DOPA+DC without ill side effects is an additional proof that SD is a metabolic deficiency disorder unlike Parkinson disease in which long term DOPA/DC inhibitor treatment requires a progressive increase of dosage leading to tardive dyskinesia as expected from a degenerative disease with progressive nigrostriatal cell loss. One could quite easily attribute the psychiatric non-motor symptoms in our patients to being affected with a chronic "mysterious" disease requiring daily drug administration, together with personal life frequent crises. Indeed, the earlier views on the lack of non-motor signs were expressed by Sagawa stating that in "classical autosomal dominant GTP cyclohydrolase I deficiency there are no mental of psychological abnormalities". (Sagawa et al., 2003). Subsequently, it was recognized that while this is true during childhood, significant psychiatric morbidity appears during adulthood mainly in the form of depression and anxiety which "are part of the phenotype of the disease and not a secondary phenomenon of living with motor disability (Timmers et al., 2017).

It will of interest to find out if the excellent therapeutic response to DOPA replacement to our patient and similar patients elsewhere is going to persist at old age.

References

1. Segawa, M., Ohmi, K., Itoh, S., Aoyama, M., & Hayakawa, H. (1971). Childhood basal ganglia disease with remarkable response to L-dopa. "*hereditary basal ganglia disease with marked diurnal fluctuation*". Therapy, 24, 667-672.
2. Segawa, M., Hosaka, A., Miyagawa, F., Nomura, Y., & Imai, H. (1976). Hereditary progressive dystonia with marked diurnal fluctuation. In: Eldridge, R., & Fahn, S., (Eds.), *Adv Neurol*. 14, (pp. 215-233). New York, Raven Press.
3. Nygaard, T. G., Marsden, C. D., & Duvoisin, R. C. (1988). Dopa-responsive dystonia. In: Fahn, S., Marsden, C. D., & Calne, D. B., (Eds.), *Adv Neurol*. 50, (pp. 377–384). New York: Raven Press.
4. Nygaard, T. G., Wilhelmsen, K. C., Risch, N. J., Brown, D. L., Trugman, J. M., Conrad Gilliam, T., Fahn, S., & Weeks, D. E. (1993). Linkage mapping of dopa–responsive dystonia (DRD) to chromosome 14q. *Nature Genetics, 5*(4), 386–391. DOI: 10.1038/ng1293-386
5. Ichinose, H., Ohye, T., Takahashi, E., SekI, N., Hori, T., Segawa, M., Nomura, Y., Endo, K., Tanaka, H., Tsuji, S., Fujita, K., & Nagatsu, T. (1994). Hereditary progressive dystonia with marked diurnal fluctuation caused by mutations in the GTP cyclohydrolase I gene. *Nature Genetics, 8*(4), 236–242. DOI: 10.1038/ng1194-236
6. Thöny, B., Auerbach, G., & Blau, N. (2000). Tetrahydrobiopterin biosynthesis, regeneration and functions. *Biochem J, 347*(Pt1), 1-16. Retrieved from https://pubmed.ncbi.nlm.nih.gov/10727395/
7. Rajput, A. H., Gibb, W. R., Zhong, X. H., Shannak, K. S., Kish, S., Chang, L. G., & Hornykiewicz, O. (1994). Dopa-responsive dystonia: pathological and biochemical observations in a case. *Ann Neurol, 35*(4), 396-402. DOI: 10.1002/ana.410350405
8. Furukawa, Y., Shimadzu, M., Rajput, A. H., Shimizu, Y., Tagawa, T., Mori, H., Yokochi, M., Narabayashi, H., Hornykiewicz, O., Mizuno, Y. & Kish, S. J. (1996). GTP-cyclohydrolase I gene mutations in hereditary progressive and dopa-responsive dystonia. *Ann Neurol, 39*(5), 609-617. DOI: 10.1002/ana.410390510
9. Nygaard, T. G., Marsden, C. D., & Fahn, S. (1991). Dopa-responsive dystonia: long-term treatment response and prognosis. *Neurology, 41*(2 (Pt 1)), 174–181. DOI: 10.1212/wnl.41.2_part_1.174
10. Lee, W. W., Jeon, B., & Kim, R. (2018). Expanding the Spectrum of Dopa-Responsive Dystonia (DRD) and Proposal for New Definition: DRD, DRD-plus, and DRD Look-alike. *J Korean Med Sci, 33*(28), e184. DOI: 10.3346/jkms.2018.33.e184
11. Fernández-Ramos, J. A., De la Torre-Aguilar, M. J., Quintáns, B., Pérez-Navero, J. L., Beyer, K., & López-Laso, E. (2022). Spanish Segawa Disease Research group. Genetic landscape of Segawa disease in Spain. Long-term treatment outcomes. *Parkinsonism Relat Disord*. 94, 67-78. DOI: 10.1016/j.parkreldis.2021.11.014
12. Costeff, H., Gadoth, N., Mendelson, L., Harel, S., & Lavie, P. (1987). Fluctuating dystonia responsive to levodopa. *Arch Dis Child, 62*(8), 801-804. DOI: 10.1136/adc.62.8.801
13. Segawa, M., Nomura, Y. N., & Ishiyama, N. (2003). Autosomal dominant guanosine triphosphate cyclohydrolase I deficiency (Segawa Disease). *Annal Neurol, 54*(suppl 6), S32-S45. DOI: 10.1002/ana.10630
14. Timmers, E. R., Kuiper, A., Smit, M., Bartels, A. L, Kamphuis, D. J., Wolf, N. I., Poll-The, B. T, Wassenberg, T., Peeters, E. A. J., de Koning, T. J., & Tijssen, M. A. J. (2017). Non-motor symptoms and quality of life in dopa-responsive dystonia patients. *Parkinsonism Relat Disord*, 45, 57-62. DOI: 10.1016/j.parkreldis.2017.10.005