

Lubag Syndrome (X-linked Dystonia Parkinsonism) Case Study of Mr G. Infante

Vincent Cheah

Abstract:

Sex-linked dystonia parkinsonism (XDP) also known as Lubag Syndrome is a rare sex-linked genetic progressive movement disorder affecting almost exclusively males from the province of Capiz in the Philippines and their descendants. At the Mater Centre for Neurosciences we have recently treated two patients with XDP utilising Deep Brain Stimulation (DBS) implants. Mr G. Infante was the second patient to be treated, the first being his uncle. Mr G. Infante's case was brought to the attention of the Mater Centre for Neurosciences at South Brisbane after the success of his uncle's treatment two years prior.

In the three years from when Mr G. Infante's dystonia symptoms were first noticed, his condition progressively worsened until he was wheelchair bound. With severe chronic pain, unable to walk, difficulties talking and swallowing, Mr G's quality of life was severely impacted by XDP.

XDP is a movement disorder considered a variation to Parkinson's Disease. The difference being that the XDP starts with a long period of dystonia that eventually evolves into the tremor and associated symptoms typical of Parkinson's Disease. Due to the similarity of the conditions the patient's needs and treatment methods, both medical and surgical, are almost identical. Deep brain stimulation surgery involves implantation of electrodes into specific regions of the brain. The electrodes are then used to deliver finely tuned electrical currents in order to reduce the signs and symptoms of both neuropsychiatric and movement disorders such as Parkinson's and XDP. The high frequency electrical charges sent to deep structures in the brain stimulate or shut down nerve cells around the electrode. The areas of the brain that the electrodes target are thought to participate in the circuitry involved and effectively disrupts these processes and reduces the symptoms of the disease.

This paper presents the journey of Mr G. Infante's XDP and DBS and provides an explanation of how DBS works to improve the quality of life for patients who suffer from XDP.

Key Words: lubag syndrome, x-linked dystonia parkinsonism, deep brain stimulation.

Background:

Lubag syndrome is an extremely rare adult onset neurodegenerative movement disorder first described in Filipino males from the Panay Islands in 1975 (Lee, Maranon, Demaisip, Peralta, Borres-Icasiano, Arancillo & Reyes, 2002). The term 'Lubag' is a broad, meaning 'twisted' in the local Filipino dialect of Ilongo and also used to describe the torsion seen in children with cerebral palsy. Lubag syndrome is known as X-linked dystonia Parkinsonism (XDP) or DYT3 after the gene which produces the mutation causing XDP. XDP presents a higher male incidence as recessive mutation affects the X chromosome.

Males, having only the one X chromosome, are more likely to express the mutation where women, having two chances to obtain a normal dominant X chromosome, are less likely to display the mutation (Dobyns, et al. 2004). Females can be carriers of the defective gene however it is rare for symptoms to be displayed and if present, they appear comparatively mild to male counterparts (Lee, et al. 2002).

Statistics reported in the Philippines state that prevalence amongst the general Filipino population is estimated at 0.34/100,000 with the highest rates being seen in the province of Capiz where approximately one in every 4000 males are affected by XDP (Lee, et al. 2002). The mutation of the gene DYT3 and its effects can be traced back over 2000 years in the Ilongo ethnic group of the Panay islands (Lee, et al. 2002). Filipinos have migrated across the globe and cases identified outside the Philippines show that maternal ancestry traces back to this ethnic group on Panay Islands (Evidente, et al. 2002).

Questions or comments about this article should be directed to Vincent Cheah Registered Nurse Mater Private Hospital, South Brisbane Queensland

vincecheah852@gmail.com

Copyright © 2017ANNA

Mr G Infante's symptoms appeared at age thirty-nine, typical of the disease which begins to effect the individual from age thirty to forty (Lehn, Airey, Olson, O'Sullivan & Boyle, 2014). In a typical case of XDP, as seen with Mr G Infante, the symptoms that lead to a diagnosis include continuous muscle cramping and spasms, postural instability, blepharospasms, difficulties with speaking, swallowing, coordination and walking (Lee, et al. 2002). The sufferer will also develop focal dystonic movement which spreads and generalizes to the whole body within five years of onset (Evidente, et al. 2002). After several years the dystonic movements become less prominent and stiffening of the limbs and trunk occurs (Lehn et al., 2014). This is known as the dystonia/parkinsonism phase. As XDP is a neurodegenerative disease, as the basal ganglia degenerates over time, the symptoms of parkinsonism begin to become more prominent.

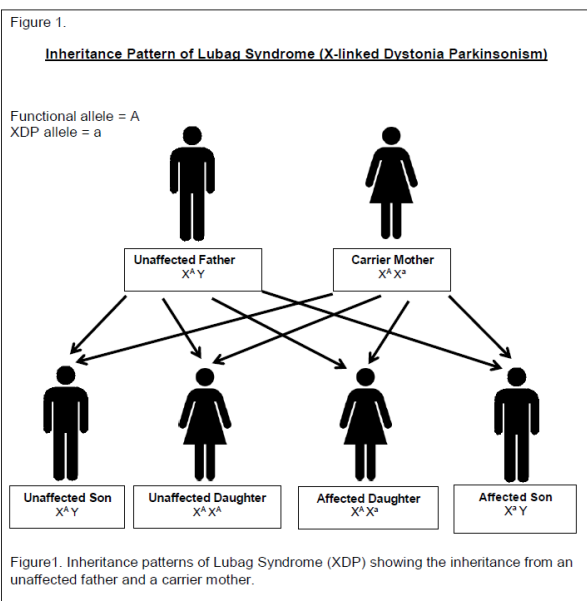
Currently XDP has no cure, treat-

age it is possible for patients to undergo lesioning surgery or deep brain stimulation (DBS).

While the underlying mechanisms of DBS are not yet fully understood, it allows changes in brain activity to be made in a controlled manner (Herrington, Cheng & Eskandar 2016). Prior to DBS surgical lesioning was the primary surgical intervention for Parkinson's Disease (PD) and dystonic conditions. This involves the insertion of a heated electrode into structures within the basal ganglia, destroying cells within a very small area and disrupting electrical brain signals to reduce symptoms. The disadvantage of this procedure is XDP and PD are degenerative diseases that progressively worsen over time and while destroying small parts of the basal ganglia can relieve symptoms, damaging too much can lead to a significant further loss of function. DBS aims to provide the same results as lesioning without permanently destroying brain cells (Okun, Zellman, 2017). DBS consists of 3 elements: electrodes, extension cables and an impulse generator.

The cost of DBS surgery can range from \$35,000 to upwards of \$70,000 for bilateral procedures (Okun, Zellman, 2017). The electrodes are placed in targets within the basal ganglia, the location depending on symptoms. As both PD and XDP affect similar regions the DBS brain targets include the globus pallidus internus, sub-thalamic nucleus (Okun, Zellman, 2017). These structures are targets as they relay the sensory and motor signals to the cerebral cortex. The impulse generator creates a small charge at a high frequency >100 Hz (Beuter, Anne, & Modolo, 2009). This high frequency disrupts electrical activity in the target area creating a 'temporary lesion'.

By interrupting these unwanted signals to the key brain areas DBS is able to alleviate symptoms. Due to the dystonia that is present with XDP after successful implantation and stimulation there is a latency effect or lag that does not occur in those patients with PD. This lag is due to the brain reorganising itself through neuro-modulation, synaptic plasticity and then finally anatomical reorganization (Beuter, Anne, & Modolo, 2009). Another benefit of DBS for XDP is that as symptom progression occurs, frequencies of the impulse generator can be adjusted. Current technological advancements have seen wireless technology incorporated into DBS devices so that medical professionals are able to remotely assess and treat patients.



ment is aimed at alleviating the symptoms to improve quality of life for sufferers. Unfortunately the treatment options, particularly in the Phillipines, are both limited and expensive. It is often the case that sufferers are isolated and unable to access treatment or support due to the financial burdens of both living with the disease and the treatments themselves. In early stages of the disease options include the use of benzodiazepines and anti-cholinergic agents, and Botox injections to relieve focal dystonia. Allied health services including speech, physiotherapy and occupational provide benefits to assist the individual to improve and maintain symptoms and function in daily life. Dependent on the availability of finances, the symptoms and

Case Study: Mr G. Infante

Mr G. Infante is a forty-nine year old Filipino male diagnosed with XDP at forty-six years of age. Mr Infante has a notable family history of XDP with one blood and three half brothers to the same mother, a carrier of the XDP mutation. Mr Infante's father is of German decent and does not carry the XDP mutation. Mr Infante's three half-brothers all suffer from XDP however his biological brother is yet to show any signs. Mr Infante had a normal birth and unremarkable developmental milestones during childhood and early adulthood. At thirty-nine years of age he developed subtle shuffling and slowing of gait. Mr Infante ignored these symptoms at the time, considering them as fatigue related to work.

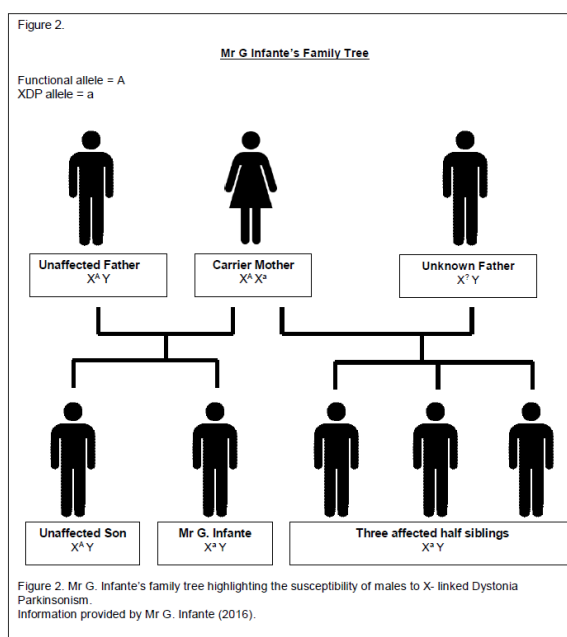
At age forty-one Mr Infante's symptoms worsened and he developed a resting tremor, dystonic posturing of his upper left limb, as well as torticollis; typical of the progression of the disease process. By the age of forty-six, a continued deterioration of symptoms led to constant tongue protrusion causing dysarthria and dysphagia. During this period Mr Infante also suffered worsening chronic back pain, decline in gait with frequent falls, dysphagia that progressed to the point of significant dietary modification and weight loss from 85.7 kilograms to 68 kilograms in three months. When Mr Infante came to Australia for treatment he was wheelchair bound and required maximum assistance for his everyday needs.

The story of how Mr Infante came to the Mater Centre of Neurosciences is quite remarkable. Following successful DBS implantation for XDP, Mr Infante's uncle discussed his case with neurologist Dr Alexander Lehn and neurosurgeon Dr Sarah Olsen to see if they could help to treat his nephew. In a generous humanitarian gesture, the Mater Executive Board approved funding for Mr Infante and his wife to travel from the Philippines to the Mater Private Hospital in South Brisbane for assessment at the Movement Disorder Clinic headed by Dr Lehn. After initial assessments of Mr Infante both Dr Lehn and Dr Olsen wanted to help but were faced with challenges regarding the costs of DBS equipment, theatre time and rehabilitation as Mr Infante was not an Australian citizen. In an incredible stroke of luck, on the day Mr Infante was assessed at the clinic a representative of St Jude Medical, the manufacturers of DBS equipment, was visiting the hospital. Upon hearing of Mr Infante and the struggles that he and his wife had faced while dealing with this debilitating condition, the

representative was moved. Phone calls were made and remarkably the DBS equipment, worth upward of \$30 000, was donated to Mr Infante's cause. Dr Olsen and Dr Lehn had agreed without hesitation to perform the implantation surgery and the Mater Private Hospital Brisbane organised the donation of the theatre time and services of Mater Centre for Neuroscience and associated teams to improve the quality of life for Mr Infante.

Mr Infante was successfully implanted bilaterally into the globus pallidus internus. Following surgery Mr Infante spent a few days in the intensive care unit before returning to the neurosurgical ward. CT scans showed no bleeding and electrode placement was accurate. The first stimulation was around two weeks post-surgery with positive results showing two to three weeks later. Daily physiotherapy, speech therapy and occupational therapy helped Mr Infante make the slow and steady journey towards independence. Through time in the rehabilitation unit Mr Infante slowly regained his ability to walk with minimal assistance, together with improved fine motor skills and speech.

The improvement seen in Mr Infante was remarkable and highlights the significance of DBS therapy in those individuals who suffer from XDP. Mr Infante came to the Mater in a wheelchair and left walking with only minor aid. He is very grateful to the Mater Private Hospital South Brisbane for the DBS treatment that significantly improved his quality of life for himself and his wife. Mr Infante is currently residing at home in the Philippines with regular contact with neurologist Dr Lehn.



References:

- Lee, LV, Maranon, E, Demaisip, C, Peralta, O, Borres-Icasiano, R, Arancillo, J, , Rivera C, Munoz E, Tan K, Reyes MT (2002) 'The natural history of sex-linked recessive dystonia parkinsonism of Panay, Philippines (XDP)', *Parkinsonism & Related Disorders*, vol. 9, no. 1: pp. 29-38.
- Evidente, VGH, Advincula, J, Esteban, R, Pasco, P, Alfon, JA, Natividad, FF, Cuanang J, Luis AS, Gwinn-Hardy K, Hardy J, Hernandez D (2002), 'Phenomenology of "Lubag" or X-linked dystonia-parkinsonism', *Movement Disorders*, vol. 17, no. 6: pp.1271-1277.
- Dobyns, WB, Filauro, A, Tomson, BN, Chan, AS, Ho, AW, Ting, NT, Oosterwijk JC, Ober C (2004), 'Inheritance of most X linked traits is not dominant or recessive, just X linked', *American Journal of Medical Genetics Part A*, vol. 129, no. 2; pp. 136-143.
- Lehn, A, Airey, C, Olson, S, O'Sullivan, JD, and Boyle, R (2014), 'Deep Brain Stimulation for DYT3 Dystonia', *Movement Disorders Clinical Practice*, vol. 1, no. 1; pp. 73-75.
- Okun, M and Zellman. P (2017), 'Parkinson's Disease: Guide to Deep Brain Stimulation Therapy', *National Parkinson Foundation Patient and Family Education*, pp. 1-56.
- Herrington, TM, Cheng, JJ, and Eskandar, EN (2016), 'Mechanisms of deep brain stimulation.', *Journal of Neurophysiology*, vol. 115, no. 1: pp. 19-38.

- Beuter, A, and Modolo, J (2009), 'Delayed and lasting effects of deep brain stimulation on locomotion in Parkinson's disease', *Chaos: An interdisciplinary Journal of Nonlinear Science*, vol. 19, no. 2; pp. 1-11.

Acknowledgements

The author wishes to thank:

Mr G. Infante and his wife Leah Infante for giving permission to present his case at the ANNA 2016 conference. He wishes his name to remain unchanged in hopes more work can be done to help sufferers of Lubag Syndrome.

Neurologist Dr Alexander Lehn for his expertise, professionalism and mentorship.

Joan Crystal Nurse Unit Manager at the Mater Centre for Neurosciences providing the opportunities to present this case at ANNA 2016.

2017 Annual Conference
Building Bridges, Making Connections

Thursday 31 August and Friday 1 September 2017
 Adelaide Convention Centre
 Registrations open 23 February
 Early bird registrations close 1 July