X-Linked Dystonia Parkinsonism: Clinical Phenotype, Genetics and Therapeutics

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Declaration of Interest
Dr. Rosales does consulting agreements and speaking engagements for Ipsen Pharmaceuticals. He has performed clinical researches sponsored by Ipsen and Allergan through a contract with the University of Santo Tomas and the CNS of Metropolitan Medical Center in Manila. As president of the Movement Disorders Society of the Philippines, he has worked with and developed collaborative projects with the XDP study group, which are intended for the XDP cause. The author alone is responsible for the content and writing of the manuscript.

Prevalence

From the latest account (as of February 2010) of Lee and cohorts, there are now 505 cases from 253 families in the registry of the XDP study. They estimate that the present prevalence rate for the entire Philippines is 0.31 per 100,000 population. For the island of Panay, their estimated prevalence is 5.74 per 100,000, with the province of Capiz having the highest rate (23.66 per 100,000 estimate), followed by the provinces of Aklan, Iloilo, Antique and Guimaras, in that order. Whilst these figures are estimates, additional XDP cases have been found in the other islands of the three main regions of the Philippines (e.g., Bicol, Mindoro, Masbate, Romblon and Palawan provinces of the Luzon region; Negros, Samar and Leyte provinces of the Visayas region; and Davao and Cotabato provinces of the Mindanao region, among other places). People are quite known to migrate outside the country due to petitions and employment needs, hence it is not unusual to find these affected Filipinos with XDP in countries like the USA, Canada, Germany, UK and Japan. Endeavors to further trace the an-
cestries of these other XDP patients to the island of Panay were possible in some, but certainly not all of them. Hence, this gap in epidemiology is a piece of a puzzle that may be needed in our understanding of XDP in terms of ancestry, migration and the possible “gene-environment interaction.”

**Clinical phenotype**

Maintaining a national registry, Lee and coworkers of the XDP study group\(^1\)\(^-\)\(^3\) gave detailed clinical accounts, and with the recent updated data consisting of 505 cases from 253 families, they were quick to conclude that the clinical picture and natural course of XDP only slightly changed.\(^2\) Age of onset is usually 39-40 years (range 12-64 years), mean duration of illness is 16 years, and mean age at death is 55.6 years. To date, five affected females have been identified, giving a male/female gender ratio of 100 : 1. All the female cases have affected brothers and most likely with carrier mothers as evidenced by the presence of affected relatives in both parents.\(^2\)\(^,\)\(^6\) Independent clinical XDP reviews from elsewhere have likewise alluded to parallel findings.\(^3\)^\(^-\)\(^10\)

Compared to parkinsonian traits as onset symptoms, more than 90% of XDP cases initially present with focal dystonia, when evident, parkinsonism typically manifests with slow and periodic resting tremor, bradykinesia, micrographia, hypomimia and shuffling gait. The more prevalent focal dystonia present in the following descending order of occurrence: Lower extremities (31%) > craniofacial area (28%) > neck & shoulder (23%) > upper extremities (14%) and trunk (2.6%).\(^2\) The following are the common clinical manifestations of the dystonias per region, roughly arranged in order of frequency: Big toe dorsiflexion (“striatal toe”), foot extension/flexion/inversion, toe fanning and knee extension/flexion (-lower extremities); jaw opening/closing/deviation, tongue protrusion/rolling/retraction, blepharospasm, twitching of the face, mouth pursing, snout-like movements of lips and adductor laryngeal dysphonia (-craniofacial region); rotational (torticollis), laterocollis, retrocollis, anterocollis, (or a combination thereof), with and without shoulder elevation (-neck and shoulder regions); wrist extension/flexion, writer’s cramp involving fingers, and elbow extension/flexion (-upper extremities); spinal flexion/extension/lateral deviation (or a combination thereof) and flexion at the pelvis or camptocormia (-truncal region)(Figure 1).

Regardless of the first site of regional involvement, the initial focal dystonia in XDP spreads in 97% of the time and generalizes within 5 years in 84%,\(^3\) some of whom may be segmental in the interim. With disease progression, the predominant phenotype is one of nearly constant, severe dystonic movements usually affecting the axial areas, with prominent oromandibular involvement such as jaw opening and tongue protrusion. “Geste antagonistique” may initially abolish the oromandibular, lingual, cervical and truncal dystonias, but eventually fail as the dystonia progresses in time and in regional involvement.

Typically between the 2\(^{nd}\) to the 7\(^{th}\) year of illness, the dystonic phase predominate, however, as early as the second year, parkinsonian traits may appear. As the illness reaches the 7\(^{th}\) to the 10\(^{th}\) year, both dystonia and parkinsonism now co-exist: labeled as the combined dystonia- parkinsonian phase. By the 15\(^{th}\) year of illness, the predominant picture is one of parkinsonism manifesting as tremors, bradykinesia, masked facies, hypomimia and drooling; labeled as the parkinsonian phase. About 68% of the patients on the average are predominantly dystonic throughout and only 18.6% are predominantly parkinsonian. The small number of cases who reach the parkinsonian phase may be due to the shortened life span (mean of 51 yrs) of XDP cases.\(^3\) Aerodigestive dysfunction leading to malnutrition and aspiration pneumonia are the usual causes of demise in XDP, however, the growing number of suicides, whether independent, or within families, has become a new challenge to treating physicians. Important personal and social factors to consider are family history of suicide, depression, anxiety, disfigurement, sleep impairment, “catastrophizing” (thus impending severe disability and death), “stigmatization” (thus social withdrawal and isolation), family separation/disintegration and loss of employment (i.e., men being in the most productive ages of their working careers).

In recognition of the aforementioned phases, the XDP study group proposed an XDP Disease Staging that categorizes extent and severity of the condition by grading patients based on three parameters: 1) The clinical presentation (whether the movement disorder involves a part or several parts of the body and whether the patient manifests dystonic or parkinsonian features or both); 2) The degree of functional impairment in performance of activities of daily living, and 3) the need for caregiver assistance or being independent. Thus, for Stage I: focal dystonia or one parkinsonian component, with no functional impairment and is independent; for Stage II: segmental dystonia or one parkinsonian component, with no functional impairment and is independent; for Stage III: Multifocal dystonia or any dystonia plus parkinsonian component(s), with mild functional impairment and still independent; for Stage IV: Generalized dystonia or any dystonia plus parkinsonian component(s), with
moderate to severe functional impairment and is dependent; and for Stage V: Any combination of dystonia and parkinsonism components, bedridden and highly dependent. In case any of the three components is of a more advanced stage, the final overall stage of the illness will be the stage where the most severe component belongs.2

Regarding manifesting females with XDP, an initial report alluded to a milder course and that they do not present with dystonia, or if they do, the dystonia is usually focal, non-progressive, and non-disabling.6 A scrutiny on the clinical profile of the affected females in the XDP registry indicate that their clinical presentation do not significantly vary from their male counterparts. In fact, an affected female in the family we have carefully followed up had severe manifestations of progressive dystonia, including parkinsonism, as were her two affected brothers.

Pathophysiology and genetics

Imaging and neuropathology help us shed light into the interplay of pathophysiology and genetics in XDP. Cranial MRI in XDP shows hyperintense putaminal rim during both dystonic and parkinsonian phases, and atrophy of the caudate head or putamen during the parkinsonian phase.11 Neuropathology confirms an atrophy of the caudate nucleus and putamen, with mild to severe neuronal loss and gliosis.12 During the dystonic phase of XDP, the neostriatum shows involvement of striosomes, but with matrix sparing, whilst during the parkinsonian phase, matrix involvement occurs as well. During the dystonic phase, the loss of striosomal inhibitory projections lead to disinhibition of nigral dopaminergic neurons, likely resulting to a hyperkinetic state; whilst in the parkinsonian phase, severe and critical reduction of matrix-based projection may result in extranigral parkinsonism.13

It is believed that XDP originated ancestrally in the Philippines, particularly in the Panay Islands through a founder mutation some 50 meiotic generations (-1,000 years) ago.5,10 Two genes are associated with XDP: /DYT3/ and /TAF1/ (TATA binding protein-associated factor-1).14,15 Gene sequencing of the XDP critical region in Xq13.1 revealed an SVA retrotransposon insertion in an intron 32 of /TAF1/. This phenomenon may effectively reduce neuron-specific expression of the /TAF1/ isoform in the caudate nucleus, and subsequently interfere with the transcription of many neuronal genes. The caveat is that analysis of /TAF1/ is not easy, as the gene contains many alternative splicing isoforms and is a member of a larger complex (hence it was previously regarded as multiple transcript system), transcription factor IID (TFIID). TFIID is a DNA-binding complex required for RNA polymerase II and plays a role in the initiation of transcription as it binds to the TATA element. SVA retrotransposon insertions are thought to be active in the human genome and to alter the expression level of adjacent genes that cause diseases. Furthermore, the SVA retrotransposon has a high GC content (approximately 70%) and a large number of CpG sites (more than 150 sites) in its nucleotide sequence, so that it is frequently hypermethylated in its insertion site (May Christine Macidan, personal communication). The entire pathomechanism of this disease still remains enigmatic. It has been proposed that differential neuronal death might cause an imbalance in activity of striatosomal and matrix-based pathways thus giving rise to abnormal movement. Whilst in XDP, the decreased expression of the neuron-specific TA14-391 isoform and probably other /TAF1/ isoforms, may result in transcriptional dysregulation of many neuronal genes, including that which encodes dopamine receptor, /DRD2/, a robust evidence is awaited to demonstrate this matter.

At the moment, the function of /TAF1/ remains to be elaborated, and how it leads to disease can only be answered by in-depth studies using cultured cell models and animal models. Likewise, though the groups of Makino15 and Nolte14 have found “disease specific” nucleotide variants in /DYT3/, a robust functional evidence remains wanting. Moreover, /DYT3/ is still a putative gene at the moment and the protein product has not been purified. At this time, what can be said is that patients carry Disease specific Single nucleotide Changes (DSC) in /DYT3/. Nolte and colleagues14 have also found a 48bp deletion in exon 4 of /TAF1/, but this has not been replicated by other groups. Although it is possible to identify DSCs haplotype and SVA retrotransposon insertion, which may be used as a routine molecular genetic diagnosis of XDP cases, blood /TAF1/ and gene /CXCR3/ expression profiling may not reliable surrogate markers for this disorder.16 Finally, in regard to the affected females in XDP, the implication of a possible co-dominant disorder or extreme X-inactivation mosaicism is possible (albeit the fact that one symptomatic woman was homozygous for the mutation).1,6,17,18

Challenges in therapy

Oral medications

Published data using various oral medications for XDP are very scarce. Of the reported 28 cases from the then known as “Torsion Dystonia of Panay,” 20 cases have been tried on of anti-parkinsonian drugs, anti-histaminics, and phenothiazines. Whilst no mention to which specific symptoms and to which extent of improvement occurred, one case each reported partial response to levodopa/carbidopa and to haloperidol.1 Virtually, oral medications in the form of benzodiazepines (e.g., clonazepam, diazepam), anticholinergic agents (e.g., biperiden, trihexyphenidyl), antipsychotic agents (e.g., haloperidol) and antihistamines (e.g., diphenhydramine), including anti-parkinsonian medications (e.g., levodopa/carbidopa), have failed to show convincing efficacy in XDP.2 Milacemide (top dose of 4,800 mg/day) given in one XDP case with severe freezing of gait (case 8 from the reported 10 cases with various neurode-
generative conditions), failed to show benefit and despite having on board diazepam (30 mg/ day), trihexyphenidyl (30 mg/ day), and levodopa (300 mg/day).19

Perhaps to date the only drug showing potential benefit in XDP is zolpidem. Zolpidem, an imidazopyridine, is a nonbenzodiazepine hypnotic with a selective agonist effect for GABA type A receptors. The binding sites for zolpidem are most abundant in the output structures of the basal ganglia (i.e., globus pallidus pars interna or GPi and substantia nigra pars reticularis).20 In movement disorders, zolpidem improves akinesia, dystonia and dyskinesia in advanced Parkinson’s disease,21 improves parkinsonism in progressive supranuclear palsy,22 and oppose dopaminergic-induced dyskinesia.23 A study of zolpidem in three cases of XDP indicated its usefulness once dystonia becomes multifocal or generalized, and where polypharmacy offers only partial relief.24 In predominantly phasic type of generalized dystonic movements, zolpidem may induce nearly 100% improvement of dystonia for a few hours. The clinical effect of zolpidem may last six to eight hours per 10 mg dose in the first few weeks. Subsequently, the effect becomes progressively shorter, decreasing to two to three hours.10 Addition of zolpidem may induce cross-tolerance in instances where adverse events of drugs may be an issue in view of initial use of benzodiazepines.25 Clinical trials on zolpidem are underway involving larger XDP cohorts, including the awaited final stages of levodopa/cabidopa trial.

Chemodenervation

Chemodenervation in XDP has been reported applying muscle afferent block (MAB) and botulinum toxin type A (BoNT-A), especially during the focal, multifocal and segmental stages of the dystonia. The aims of the therapy are geared toward the disabling dystonia and associated pain. MAB was previously performed in an open-label study of 30 XDP cases injecting 0.5% lidocaine and 95% ethanol, in a volume ratio of 10 : 1.26 Electromyography (EMG)-guided injections of MAB were administered to the dystonic tongue, jaw, neck, trunk, upper and lower limb muscles. Depending upon injected muscle size, the dose ranged from 5-20 mL MAB, care being taken that the total lidocaine dose per patient, per day, did not exceed 1 mL/kg body weight. Employing predetermined outcome assessments, there was an overall improvement in the EMG turns parameters and a moderate improvement in the subjective scales. Mean onset of MAB effect was 27.3 minutes, and the mean duration of effect lasted 7.9 days. Transient and non-serious adverse events were seen in 11/30 cases that included dizziness and injection site pain, bleeding and erythema. Blocking muscle afferents with diluted lidocaine (MAB) to effectively abolish cervical dystonia (CD) and writer’s cramp in non-XDP cases have been reported.27,28 The local anesthetic effect of lidocaine is expectedly fast but short acting, thus, the effects on the muscle may be prolonged by combining concentrated ethanol into the regimen (i.e., volume ratio of 10 : 1). MAB is a relatively safe procedure, however, patients complain of some dizziness and injection pain, secondary to ethanol effects. Ideally, it is better to monitor potential cardiac and central nervous effects of lidocaine, as quite a volume and dose of lidocaine are injected per muscle, with a number of muscles being targeted in a session.

In 1995,29 we reported BoNT-A (onabotulinumtoxinA, Botox®) effects in 5 cases of XDP having CD. Four weeks following a total of 200 units Botox®, the Toronto Western Spasmodic Torticollis Rating Scale (TWSTRS)30 showed marked improvement of the CD. This was followed by a larger series involving 25 cases of XDP with various types of CD.31 Following EMG-guided BoNT-A (abobotulinumtoxinA, Dysport®), dose range of 500-1,000 units) injections, we observed the following findings: 1) significant improvement in the TWSTRS scores 4 weeks post-injection; 2) significant VAS pain reduction 4 weeks post-injection, and 3) transient dysphagia in 4/25 cases, mainly in mixed CD given 1,000 units total dose of Dysport®.31 BoNT-A blocks cholinergically innervated extrafusal and muscle spindle intrafusal fibers, thus modulating the sensory-motor circuitry of dystonia.32-34 Coupled to this phenomenon is the secondary effect of muscle weakening on the corresponding tendon and joint receptors.34

From 1993 to 2003, we did a prospective, single-blind (independent scale assessors) study on 44 XDP cases, belonging to 24 families, to compare efficacy and safety of single-cycle BoNT-A versus MAB injections in CD.35 Consecutive XDP cases, irrespective of type of CD, were randomly distributed to the three interventions (i.e., Dysport®, Botox® and MAB). Per muscle EMG-guided injections of BoNT-A (Dysport® or D and Botox® or B) were as follows, respectively: For sternocleidomastoid, D=125 u (75-150 u); B=50 u (25-75 u); for splenius capitis, D=150 u (50-200 u); B=60 u (40-80 u) for trapezius, D=100u (50-100 u); B= 40 u (30-60 u), and for levator scapula, D=50 u (25-75 u); B=20 u (10-30 u). A revised MAB protocol was used with lidocaine 1%, mixed with 95% ethanol (10 : 1 volume ratio), care being taken not to exceed 3-5 mg/kg body weight of total lidocaine injection per session. The primary outcome results comparing the 3 subscales of TWSTRS pre- and post-injection at week 4 indicated that both Dysport® and Botox® significantly improved in dystonia severity, disability and pain. MAB in CD did not show significant effects in any of the TWSTRS subscales. However, MAB showed modest improvement in the overall subjective dystonia rating scale at week 1, but this effect did not last longer than 2 weeks. Mean duration of the BoNT-A effects were in the order of 11 weeks, but not different between Dysport® and Botox® significantly improved in week 4 indicated that both Dysport® and Botox®. Overall TWSTRS response scale of BoNT-A was significantly better than MAB, but not different between Dysport® and Botox®. Adverse events with BoNT-A were noted in weeks 1-3, and mainly in occasions of bilateral sternocleidomastoid injections for anterocollis.
Dysphagia prevailed among the adverse events for BoNT-A (Dysport®: 3/15 cases; Botox®: 2/15; not significantly different from each other). For MAB, 8/14 XDP cases experienced nausea and dizziness, including pain on injection in 11/14 cases. Nevertheless, MAB is a cheap and rapid procedure, which can be performed while patients await funds for BoNT-A therapy.

Injections with BoNT-A for disabling oromandibular, lingual and laryngeal dystonias should be performed cautiously, in view of the high rates of silent and overt aspiration in these XDP cases who may be in a malnourished state. The injection technique must require EMG guidance, expert choice of muscle targeting and BoNT-A low dosing with low dilution so as to prevent toxin spread. On the other hand, BoNT-A injections into the disabling limb and truncal dystonias of XDP may require higher toxin dosing and dilution to increase radius of spread and even reach those muscles with “overflow” of movements. From the aforementioned studies we performed, there seems to be a dichotomy of BoNT-A effects between the way the toxin relieves pain early and significantly compared to its effects upon the severe muscle spasms and dystonic posturing. It is also possible that, unlike cases of certain spasticity, the toxin relieves pain early and significantly compared to its effects upon the severe muscle spasms and dystonic posturing. Early intervention with BoNT-A in dystonias of a neurodegenerative nature (e.g., XDP), may not be as beneficial.

Illustrative case

Herein, we depict XDP in a family, highlighting the challenging aspects of the disease from phenomenology, therapy, social impact and his eventual demise. The illustrative case is a 44 year old male XDP, whose maternal ancestry belonged to Roxas city of Capiz, and whose manifestations and course were shortened. His elder brother in a brood of 5 (4 males, one female in a family proband) was also diagnosed to have XDP. This elder brother had an onset of oromandibular and cervical dystonia at age 40 years. The dystonia eventually became generalized at age 44 years of this brother. On our examination at age 45 years, this brother also had rest tremors and bradykinesia, in addition to the oromandibulo-lingual, cervical, truncal and limb dystonias. Unable to continue employment as a seafarer and “stigmatized” at his hometown, he isolated himself. At age 47 years, this brother committed suicide one day, by hanging himself, having lost hope due to severe, disabling symptoms with relentless progression. A maternal uncle was also diagnosed to have XDP (though not examined by us, we had information that he had cervical and jaw-opening and tongue protrusion dystonias) at age 40 years. This maternal uncle succumbed to aspiration pneumonia at age 51 years, barely able to feed and had become slowed in movements.

In regard to the illustrative case, he initially developed focal upper limb dystonia, with right wrist extension at age 39 years. Being right-handed and an able-bodied seaman, the focal dystonia started to impede work. The first consult was triggered by the focal upper limb dystonia and localized pain in the same area, physical trauma having been ruled out. His wrist extensors initially responded to MAB with lidocaine-ethanol but efficacy would only last 2 weeks. Thus, BoNT-A was injected to the extensor carpi ulnaris/radialis (each with 100 Dysport®) and extensor digitorum communis (75 units Dysport®), providing significant relief of muscle spasms, posturing and especially pain for at least 3 months. A year later, he developed blepharospasm and jaw-closing dystonia, which together with the limb dystonia, again responded well to BoNT-A. In the absence of available tetrabenazine and trihexyphenidyl, dose escalating doses of clonazepam was started (initially at 0.5 mg/day and moved up to 4 mg/day) and later combined with an anticholinergic agent (biperiden, final total dose of 12 mg/day). Baclofen (up to 30 mg/day) was added into the regimen on his 3rd year, when dystonia became generalized. However, tolerability issues led him to retain the clonazepam and
biperiden doses only. These oral medications became the maintenance medications over time, as he could not fend for the increasing doses BoNT-A injections. He was unable to maintain his seafaring job that led to his depression. Sertraline (up to 20 mg/day) was tried for 3 months but was eventually discontinued, as he noted confounding sedative and intolerance effects of the medication. On his 3rd year of the illness, he noted slowness in movements and periodic slow rhythmic rest hand tremors, in addition to the generalized dystonia. Levodopa-carbopoda (final total dose of 750 mg/day) provided initial relief of the parkinsonism features, but this same medication was discontinued because of eventual loss of efficacy. The course of the illness changed, when he was admitted as an emergency for “status dystonicus,” with severe generalized dystonia, including involvement of his respiratory muscles and laryngeal stridor. His serial total creatine kinase levels were elevated 10x the normal, an elevated creatinine (3x the normal) and hemoglobinuria. Diazepam bolus followed by an intravenous drip (total 60 mg/day) was given and was gradually reduced as his dystonic spasms lessened. Tracheostomy was performed, whilst requiring a respirator. The wife reported that the patient lost hope of the possibility of DBS for financial reasons, that lead to his abrupt discontinuation of his clozanepam and biperiden, five days prior to his confinement. In the hospital, zolpidem monotherapy was initiated and escalated (initially at 10 mg/day and moved up to 30 mg/day in 3 divided doses), that appeared to have improved his dystonia. He was gradually weaned from the respirator and maintained on zolpidem upon discharge after two months in the hospital. He apparently tolerated over a period of 4 weeks the daytime sleepiness associated with zolpidem. Two weeks from discharge, we learned that the patient succumbed in his sleep as he purposely refused to continue treatment, having lost any hope of cure and “catastrophized” by the moribund nature of the illness.

Conclusion

Whilst the clinical phenotype of XDP appears to be straightforward, certain gaps need to be resolved in the future. Phenomenologically, XDP cases in families have been identified whose ancestries cannot be traced from the Panay island. Variability of disease onset, clinical manifestations and disease duration between affected members within families require a revisit into the XDP phenotype. Occurrence of manifesting females with XDP will require a revisit to the genetic profile of the disease. /DYT3/ is still a putative gene at the moment and the protein product has not been purified. At the moment, in depth studies into the function of /TAF1/ and how it leads to disease need to be elaborated. Apart from expense limiting DBS, new pharmacotherapeutic strategies are desired in view of the shortcomings of current regimen for dystonia, especially when XDP enters into a combined phase with parkinsonism. Finally, there is urgency for us to address these issues because our XDP cases are losing hope and have started to take their lives away themselves.

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