SHORT COMMUNICATION

Neuropathology studies of X-linked dystonia parkinsonism

Susan Harris, Betty Thomas

Harris S, Thomas B. From genetics to functional pathways, neurodevelopmental disorders. Neurodev Disord Treat. 2022; 5(1):1-3.

ABSTRACT

Dystonia caused by the X-chromosome Parkinsonism (XDP) is a neurodegenerative ailment that is indigenous to Panay Island in the Philippines. It is a recessive, genetically inherited disease. Dystonia is the first clinical sign, followed by parkinsonian features around 10–15 years. The striatum, in particular, is a focus of XDP neuropathology study because the striatum shows substantial atrophy that correlates with illness development. Thus, XDP shares symptomatology with Parkinson's disease, as well as a genetic propensity and striatal atrophy similar to Huntington's disease. However, more research is needed to learn more about the pathology and disease signs in the XDP brain. For starters, neuronal alterations and neuroinflammation in the XDP brain have only been studied in a few neuropathological studies. Multiple neuroimaging investigations on XDP patients, on the other hand, point to different brain regions that are damaged. Furthermore, molecular pathological studies have revealed that the main genetic cause of XDP is a mutation in the TAF-1 gene, but the exact relationship between this mutation and XDP neuropathology has yet to be determined. As a result, we intend to present a comprehensive review of the current literature showing neuropathological changes in the XDP brain, as well as explore future research directions that will help us better understand XDP neuropathogenesis.

Key word: *X-linked dystonia parkinsonism; Striatum; Caudate nucleus; Putamen Striosomes; Neuropathology; NeuroimagingDystonia; Parkinsonism;*

SHORT COMMUNICATION

The inability to meet cognitive, emotional or motor XDP, commonly known as Lubag, is an X-linked recessive and genetically inherited disease indigenous to the Philippine island of Panay, affecting one out of every 4000 males. Because the illness is inherited in an X-linked recessive pattern, the majority of those affected are men who inherited the faulty chromosomes from their carrier moms. There have been a few cases of affected homozygous females (females) that had a slower disease progression. The early emergence of focal dystonia, which becomes generalised in different body regions over time, is one of the specific clinical hallmarks of XDP [1]. The first XDP report was published in 1969, while the first landmark publication on 'torsion dystonia' was published in 1976 in Panay, Philippines. However, there are now only a few studies on XDP neuropathology, with the 1993 report by C. H. Waters being the first. The caudate nucleus and putamen, which are located in the basal ganglia, show atrophy in these investigations. These findings were discovered by MRI examinations as well as post-mortem tissue evaluation. Patients with severe stages of XDP often have symptoms that are similar to those seen in Parkinson's Disease (PD), such as bradykinesia and tremor (Lee et al., 1991). Huntington's Disease (HD) and Parkinson's Disease (PD) are both neurodegenerative disorders that largely impact the basal ganglia, and pathological comparisons between these two disorders and XDP may offer further light on XDP pathophysiology, clinical symptomatology, and potential disease pathways [2].

In XDP, neuropathological research has primarily focused on the striatum. So far, the data have shown histological and immunohistochemical alterations. The current neuroimaging and neuropathological research of XDP will be outlined in this review, with an emphasis on the basal ganglia and other crucial parts of the human brain.

Patients who have been tested for XDP usually have a history of dystonia and a family history that is compatible with XDP

Editorial Office, Neurodevelopmental Disorders and Treatment, Windsor, Berkshire, England

Correspondence: Susan Harris, Editorial Office, Neurodevelopmental Disorders and Treatment, Windsor, Berkshire, England, e-mail neurodev.treat@gmail.com

Received: 04-Jan-2022, Manuscript No. pulndt-22-4678; Editor Assigned: 06-Jan-2022, PreQC No. pulndt-22-4678(PQ); Reviewed: 18-Jan-2022, QC No. pulndt-22-4678(Q); Revised: 20-Jan-2022, Manuscript No. pulndt-22 -4678(R) Published: 25-Jan-2022, DOI: 10.37532/pulndt.22. 5(1).1-3.

inheritance. For the first 10–15 years after symptom onset, the dystonic phase of XDP dominates the patient's life, before parkinsonian symptoms take over. According to previous research, the average age of onset for men is 39 years, with a range of 12 to 64 years. Women, on the other hand, have a median age of onset of 52 years, with a range of 26 to 75 years. Blepharospasm (eyelid muscle spasms), neck dystonia, oromandibular dystonia, truncal dystonia, limb dystonia, and postural and gait abnormalities are common early symptoms in the dystonic period for the majority of patients. Slowing saccades and a reduced oculomotor range are two oculomotor abnormalities seen in XDP-dystonic patients [3]. In 84 percent of individuals, dystonia evolves from focal to widespread as the disease progresses. Between the second and seventh years of sickness, the dystonic phase predominates, whereas the parkinsonian phase may emerge in the second year of illness and gradually develop in prominence until the fifteenth year of illness, when parkinsonian symptoms are most prominent. In addition to the prevalence of significant depression and anxiety problems in some XDP patients, cognitive impairment related to abstract thinking is suspected [4].

The Burke-Fahn-Marsden Dystonia Rating Scale (BFMDRS) for dystonia, the Unified Parkinson's Disease Rating Scale (UPDRS, Part III) for Parkinsonian motor symptoms, and the Mini Mental State Examination (MMSE) or the Montreal Cognitive Assessment-Filipino version (MoCA-P) for cognitive function have all been used in previous clinical and imaging studies in XDP patients. More recently, a scale for the clinical assessment of XDP patients was created in collaboration with the Movement Disorder Society of the Philippines (MDSP). The new scale (the XDP-MDSP scale) is a five-part assessment with 37 components. I-dystonia, II-parkinsonism, III-non-motor characteristics, IV-activities of daily living (IV-ADL), and V-global impression are the components. The MoCA was recently successfully translated, culturally adapted, and validated using Hiligaynon, the Panay Island language. As a result, the assessment is more culturally acceptable for the Panay Island community.

While males account for the bulk of XDP cases, female patients with localised, non-progressive dystonia, shuffling gait, and tremor can also be impacted. Recent advances in pallidal Deep Brain Stimulation (DBS) as a treatment for XDP have been made. While these treatments are likely to help with dystonia, pallidal DBS has been less effective in treating XDP's parkinsonian symptoms. Anticholinergic drugs, benzodiazepines, baclofen, chemodenervation with botulinum toxin, and levodopa are currently the only treatments that can achieve mild symptomatic relief. However, essential parts of the disease remain unknown, and it is hoped that a better knowledge of XDP's disease mechanisms may lead to more effective treatment options [5].

In 2001, the first known MRI study of XDP patients was published, involving 16 XDP patients. T2 weighted, T1 weighted, and infrared pictures were used to analyse MRI signal intensity parameters. For each patient, the MRI data were associated with numerous parameters such as disease duration and the existence of dystonic or parkinsonian characteristics. None/mild atrophy of the caudate nucleus and putamen was detected in the individuals classified as being in the early stages of the disease (10 of the 16 patients). Dystonia frequently predominates in the early stages of Parkinson's disease, and parkinsonian symptoms are usually absent. A bilateral, symmetrical, moderate to severe atrophy was detected in the head of the caudate nucleus and putamen in the remaining 6 patients (categorised as being in the later stages of disease) [6,7]. Parkinsonism was the most common symptom in the later stages of the disease, and it was occasionally observed to coincide with dystonia in XDP patients. In XDP research, genome-editing experiments have also begun, with the goal of turning results into therapeutic effects. Recently, a study looked at whether using CRISPR/Cas9-based genome editing to remove the SVA insertion in XDP cell lines (iPSCs, cortical neurons, and spiny projections neurons) may rescue TAF1 expression [8]. These studies were carried out on cells taken from XDP sufferers and healthy people. QPCR was used to assess changes in total TAF1 and nTAF1 expression. The scientists discovered that deletion of the sequence at the SVA insertion site did not result in a substantial change in total TAF1 expression in control iPSCs. However, after removing the SVA insertion from XDP-derived iPSCs, a substantial increase in total TAF1 expression was found [9]. TAF1 protein levels in parental, edited, and unedited iPSCs from control and XDP sources were also measured. The findings revealed that trends in protein expression matched those in mRNA expression data. Following that, mRNA expression in edited and unedited cortical neurons from control and XDP sources was compared, but no differences in total TAF1 or nTAF1 expression were seen in XDP-derived cortical neurons after SVA excision. Excision of the SVA insertion increased total TAF1 and nTAF1 expression levels in MSNs, but this increase was not statistically significant. The authors hypothesised that while the SVA deletion had no influence on the expression of TAF1 or nTAF1 mRNA in iPSC-derived cortical or MSN neurons, the variability in iPSC differentiation into mature neurons could reduce the effects of the SVA excision. Second, the authors speculated that the SVA insertion effect on TAF1 expression is typical of progenitor cells like iPSCs, but that the effect fades in postmitotic cells, such as adult neurons [10].

CONCLUSION

Current neuropathological research using XDP human brain tissue is mostly limited to case studies with small sample sizes and little quantification. Furthermore, the majority of previous XDP neuropathological investigations did not involve comparisons of XDP cases to relevant control cases. To yet, no reliable stereological studies have been conducted, and no high-throughput pathology screening tests on XDP diseased tissue have been conducted. This opens up a plethora of neuroanatomical and molecular biology possibilities, including a full investigation of the role of neuronal and non-neuronal cells in the striatum and other nuclei of the basal ganglia, as well as other parts of the diseased XDP brain. The pre- and post-synaptic dopamine systems in the XDP basal ganglia would thus be relevant and pathologically beneficial. Finally, because XDP shares clinical parallels with PD symptomatology and a distinct genetic inheritance pattern similar to HD, researchers anticipate that research into XDP will yield clues and insight not just for XDP patients, but also for individuals with Parkinson's and Huntington's disease.

REFERENCES

1. Ackermann H, Riecker A. The contribution of the insula to motor aspects of speech production: a review and a hypothesis. Brain Lang. 2004; 89(2): 320-328

2. Adrian T, Allen J, Bloom S, et al. Neuropeptide Y distribution in human brain. Nature. 1983;306(5943): 584-586.

3. Aneichyk T, Hendriks WT, Yadav R, et al. Dissecting the causal mechanism of X-linked dystonia-parkinsonism by integrating genome and transcriptome assembly. Cell. 2018;172(5): 884-891.

4. Berg D, Roggendorf W, Schröder U, et al. Echogenicity of the substantia nigra: association with increased iron content and marker for susceptibility to nigrostriatal injury Arch Neurol. 2002; 59(6): 999-1005.

5. Berg D, Godau J, Walter U, et al. Transcranial sonography in movement disorders. Lancet Neurol. 2008; 7(11): 1044-1055.

6. Berg D, Godau J, Riederer P, et al. Microglia activation is related to substantia nigra echogenicity. J Neural Transm. 2010; 117(11): 1287-1292.

7. Bernardo-Alilíng NA, Rivera A, Jamora RDG. Translation, cultural adaptation and validation of the Hiligaynon Montreal cognitive assessment tool (MoCA-Hil) among patients with X-linked dystonia parkinsonism (XDP). Front Neurol. 2019;10: 1249.

8. Bertrand C, Benhamed M, Li YF, et al. Arabidopsis HAF2 gene encoding TATA-binding protein (TBP)-associated factor TAF1, is required to integrate light signals to regulate gene expression and growth. J Biol Chem. 2005; 280:1465-1473.

9. Beste C, Mückschel M, Rosales R, et al. Striosomal dysfunction affects behavioral adaptation but not impulsivity—evidence from X-linked dystonia-parkinsonism. Mov Disord. 2017; 32(4): 576-584.

10. Bhattacharya K, Saadia D, Eisenkraft B, et al. Brain magnetic resonance imaging in multiple-system atrophy and Parkinson disease: a diagnostic algorithm. Arch Neurol. 2002; 59(5): 835-842.