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Case Report

From stroke mimic to genetic enigma: diagnostic challenges in neuronal intranuclear inclusion disease associated with FMR1 premutation

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ABSTRACT

Neuronal intranuclear inclusion disease (NIID) is a rare progressive neurodegenerative disorder characterized by eosinophilic hyaline intranuclear inclusions in neurons, glial cells, and visceral organs. Recently, NIID has been genetically linked to GGC repeat expansion in the 5′-UTR of the NOTCH2NLC gene. Interestingly, overlapping imaging and clinical features have been observed with fragile X-associated tremor/ataxia syndrome (FXTAS), caused by fragile X messenger ribonucleoprotein 1 (FMR1) premutation. A 52-year-old male with long-standing diabetes and hypertension presented with multiple recurrent episodes of transient loss of consciousness over 12 years, mimicking vertebrobasilar transient ischemic attacks. He later developed transient quadriplegia and dysarthria with complete recovery within hours. Initial MRI showed diffusion restriction in the right corona radiata, reported as acute infarct. Repeat MRI and CT angiogram revealed diffusion restriction and FLAIR hyperintensities in the frontoparietal white matter at corticomedullary junctions, corpus callosum, and bilateral middle cerebellar peduncles. Skin biopsy showed intranuclear inclusions in sweat gland cells. Genetic analysis confirmed FMR1 premutation with 99 CGG repeats, establishing the diagnosis of FXTAS with overlapping features of NIID. This case emphasizes the diagnostic challenge in distinguishing NIID from FXTAS, both of which share overlapping clinical and MRI features. Genetic testing for FMR1 mutations should be considered in patients with stroke-like or episodic neurogenic events showing corticomedullary DWI hyperintensities and intranuclear inclusions on biopsy.

Keywords: Neuronal intranuclear inclusion disease, Fragile X-associated tremor/ataxia syndrome, FMR1 premutation, Stroke mimic, Leukoencephalopathy

INTRODUCTION

Neuronal intranuclear inclusion disease (NIID), also referred to as neuronal intranuclear hyaline inclusion disease (NIHID) or intranuclear inclusion body disease (INIBD), is a slowly progressive neurodegenerative disorder characterized by eosinophilic hyaline intranuclear inclusions within cells of the central, peripheral, and autonomic nervous systems, as well as various visceral organs.[1] The first case of NIID was reported in 1968.[2]

A major recent breakthrough in understanding NIID pathogenesis was the discovery that a GGC repeat expansion in the 5′ untranslated region of the NOTCH2NLC gene is the causative mutation, establishing a clear genetic basis for the disorder.[3] Pathologically, NIID/NIHID is defined by intranuclear inclusions in neuronal and glial cells, and reported cases can be categorized into three clinical subgroups based on age at onset and disease duration, each demonstrating distinct phenotypic patterns.[4]

The neuronal intranuclear inclusions (NII) characteristic of NIID are ubiquitinated, and intriguingly, their prevalence is inversely correlated with neuronal loss-supporting the hypothesis that NII formation may represent a neuroprotective response mediated through the ubiquitin–proteasome proteolytic pathway.[4] With the increasing

number of diagnosed cases, the recognized clinical spectrum of NIID has expanded substantially to include cognitive impairment, parkinsonism, tremor, autonomic dysfunction, peripheral neuropathy, myopathy, encephalitic and stroke-like episodes, epileptic seizures, fluctuating disturbances of consciousness, cerebellar ataxia, headache, and vision loss.[5]

Parallel to clinical expansion, characteristic MRI features have been delineated. Among these, corticomedullary junction hyperintensity on diffusion-weighted imaging (DWI) has emerged as a hallmark radiological sign of NIID. Additional imaging findings include focal cortical edema or enhancement, and white matter lesions involving the paravermian region, middle cerebellar peduncles, and corpus callosum.[5]

FXTAS is a late-onset neurodegenerative disorder occurring in carriers of premutation expansions in the FMR1 gene. Despite harboring the premutation, only 40-75% of male carriers and 16-20% of female carriers develop clinically manifest FXTAS.[6] Clinical presentation of FXTAS is heterogeneous and may include intention tremor, cerebellar ataxia, neuropathic pain, deficits in memory and executive function, parkinsonian features, and neuropsychiatric symptoms, such as depression, anxiety, and apathy.[6]

Importantly, overlapping neuroimaging findings, especially corticomedullary junction hyperintensities on DWI, have been reported in both NIID and FXTAS, presenting a diagnostic challenge in some patients.

Here, we report a case of recurrent, transient neurological deficits mimicking stroke, in whom the final diagnosis was FXTAS with NIID-like radiological features.

CASE REPORT

A 52-year-old male, known diabetic and hypertensive for 20 years, presented with multiple episodes of loss of consciousness (LOC) over 12 years. About 12 years ago, he experienced his first episode of LOC while travelling on a motorcycle; although he did not sustain any head injury, he remained unconscious for approximately one hour and recovered fully without any focal neurological deficits. A second episode occurred 2 years ago during hospitalization for hip replacement, when he had a brief LOC lasting 5 minutes without any tonic-clonic movements or postictal deficits. Two months later, he developed a third episode of LOC lasting about one hour, again without features suggestive of seizures or any subsequent neurological deficit. Six weeks prior (on 23 July 2023), he experienced another episode of LOC while walking, resulting in a fall; he remained unconscious for one hour and was unusually drowsy for the next 12 hours before returning to baseline. Nine days prior to presentation (on 2 September 2023), he woke up in the morning with sudden inability to get out of bed, complete immobility of all four limbs, dysarthria, and right facial deviation. The right-sided weakness improved within one hour, and full neurological recovery occurred within five hours, with no residual deficits thereafter.

He was admitted locally and investigated. The initial MRI brain performed after the first episode revealed diffusion restriction in the right corona radiata and gangliocapsular region. Echocardiography showed concentric left ventricular hypertrophy, stage 2 diastolic dysfunction, and aortic sclerosis. Holter monitoring captured a single episode of non-sustained tachycardia with a heart rate of 112 bpm. Audiometry demonstrated bilateral mild hearing loss. Routine blood tests including CBC, LFT, RFT, and thyroid profile were normal, while LDL was elevated and glycemic control was poor.

Two months later, during an admission for bronchopneumonia, repeat MRI brain and CT angiography showed diffusion restriction and FLAIR hyperintensities involving frontoparietal white matter at corticomedullary junctions, corpus callosum, and bilateral middle cerebellar peduncles-an imaging pattern suggestive of NIID/FXTAS. A skin biopsy demonstrated intranuclear eosinophilic inclusions within sweat gland cells on H and E staining. Genetic testing confirmed an FMR1 premutation with 99 CGG repeats, establishing the diagnosis of FXTAS.

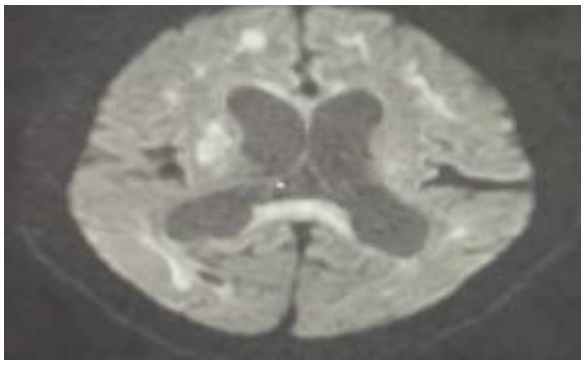

Figure 1: MRI brain DWI showing diffusion restriction along corticomedullary junctions.

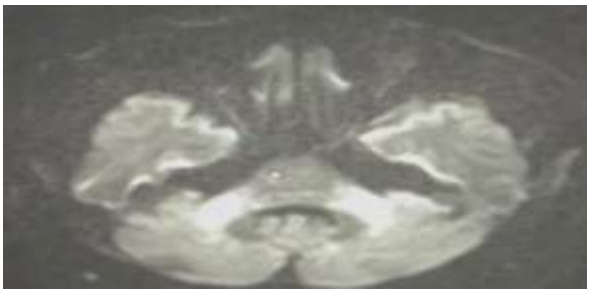

Figure 2: MRI brain FLAIR showing frontoparietal white matter hyperintensities.

DISCUSSION

FXTAS is a late-onset neurodegenerative disorder that occurs in older carriers of the FMR1 premutation (55-200

CGG repeats). In individuals with the premutation, elevated levels of FMR1 mRNA exert a toxic gain-of-function effect, leading to RNA-mediated toxicity, mitochondrial dysfunction, and subsequent neurodegeneration.[7] NIID and FXTAS are both rare neurodegenerative diseases characterized by the presence of intranuclear inclusions and leukoencephalopathy on MRI.[8] GGC repeat expansion in NOTCH2NLC has been identified in a variety of neurologic diseases, including Alzheimer disease, Parkinson disease (PD), frontotemporal dementia, amyotrophic lateral sclerosis, essential tremor (ET), multiple system atrophy (MSA), leukoencephalopathy, oculopharyngodistal myopathy (OPDM), and Charcot-Marie-tooth disease.[9]

These findings indicate that the clinical manifestations of NIID are highly heterogeneous, and the diagnosis of NIID is challenging. High DWI signals along the corticomedullary junction are considered pathognomonic for NIID, corresponding to spongiotic degeneration near subcortical U-fibers.[10] Similar radiological findings may occur in FXTAS, leading to diagnostic confusion. Our case fits into the episodic neurogenic event-dominant type of NIID phenotype,[5] but the presence of FMR1 premutation confirms FXTAS, suggesting an overlap between these entities. Skin biopsy revealing ubiquitin- or p62-positive intranuclear inclusions supports the diagnosis in both diseases, but definitive distinction requires genetic testing.[11]

Management of FXTAS is multifaceted and involves comprehensive evaluation of the patient's neurological and systemic deficits, symptomatic treatment, and timely referral for appropriate support services, particularly genetic counseling. Current therapeutic approaches remain largely empirical, guided by anecdotal evidence and extrapolated from treatments used for symptoms shared with other neurodegenerative disorders. FXTAS continues to be underrecognized, in part because it was first formally described only in 2001 and because its clinical presentation is highly variable, often consisting of nonspecific signs commonly attributed to aging. Nevertheless, establishing an accurate diagnosis is essential-not only for optimizing patient care, but also for informing family members of their genetic risks, reproductive implications, and potential health concerns associated with FMR1 premutation carrier status.[12]

CONCLUSION

This case highlights the diagnostic overlap between NIID and FXTAS, both presenting as stroke mimics with characteristic MRI findings. Genetic testing for FMR1 premutation should be included in the evaluation of atypical leukoencephalopathies and unexplained recurrent neurogenic events to avoid misdiagnosis and guide management.

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