Journal of the Neurological Sciences 352 (2015) 19–28

Contents lists available at ScienceDirect

Journal of the Neurological Sciences

journal homepage: www.elsevier.com/locate/jns

Review article

Fragile X premutation carriers: A systematic review of neuroimaging findings

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ARTICLE INFO

Article history:
Received 24 July 2014
Received in revised form 16 March 2015
Accepted 18 March 2015
Available online 27 March 2015

Keywords:
Fragile X syndrome
Fragile X premutation
Premutation carriers
FXTAS
Neuroimaging
MRI

ABSTRACT

Background: Expansion of the CGG repeat region of the *FMR1* gene from less than 45 repeats to between 55 and 200 repeats is known as the fragile X premutation. Carriers of the fragile X premutation may develop a neurodegenerative disease called fragile X-associated tremor/ataxia syndrome (FXTAS). Recent evidence suggests that premutation carriers experience other psychiatric difficulties throughout their lifespan.
Methods: Medline, EMBASE and PsychINFO were searched for all appropriate English language studies published between January 1990 and December 2013. 419 potentially relevant articles were identified and screened. 19 articles were included in the analysis.
Results: We discuss key structural magnetic resonance imaging (MRI) findings such as the MCP sign and white matter atrophy. Additionally, we discuss how functional MRI results have progressed our knowledge of how FXTAS may manifest, including reduced brain activation during social and memory tasks in multiple regions.
Limitations: This systematic review may have been limited by the search for articles on just 3 scientific databases. Differing techniques and methods of analyses between research groups and primary research articles may have caused differences in results between studies.
Conclusion: Current MRI studies into the fragile X premutation have been important in the diagnosis of FXTAS and identifying potential pathophysiological mechanisms. Associations with blood based measures have also demonstrated that neurodevelopmental and neurodegenerative aspects of the fragile X premutation could be functionally and pathologically separate. Larger longitudinal studies will be required to investigate these conclusions.

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http://dx.doi.org/10.1016/j.jns.2015.03.031
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1. Introduction

The fragile X-associated tremor/ataxia syndrome (FXTAS) is one of the most prevalent movement disorders with a known single gene causation [1]. FXTAS is a neurodegenerative disease which affects approximately 40% of males and 8–16% of females who carry the premutation allele of the *FMR1* gene [2,3]. At present, there is no evidence based treatment for FXTAS, although symptomatic treatments of associated cognitive, psychiatric and movement disorders have proven useful in a percentage of cases [4].

Premutation status is conferred by an expansion of the non-translated 5′ CGG repeat region of *FMR1* from the normal range, which is less than 45 repeats, to between 55 and 200 repeats. Typically, an expansion of over 200 repeats is associated with DNA methylation and subsequent silencing of *FMR1* leading to a lack of production of a protein called fragile X mental retardation protein (FMRP). This lack of FMRP manifests clinically as the severe neurodevelopmental disorder fragile X syndrome [1]. The premutation allele is unstable and the CGG repeat region is liable to expand through maternal transmission. Thus, a mother with the fragile X premutation is very likely to have a child with fragile X syndrome [5].

1.1. Clinical features associated with the fragile X premutation

The classical clinical presentation of FXTAS is late-onset, usually male and over 50 years of age, with progressive symptoms of tremor, ataxia and cognitive decline. Gait ataxia, kinetic tremor and mild Parkinsonism typically are the first symptoms to appear in FXTAS [6]. Patients begin to experience frequent falls, and eventually become bed bound in the later stages of the disease. Peripheral neuropathy, dysfunction of the autonomic system and endocrine changes also form part of the FXTAS phenotype, however these occur less frequently [7]. Onset of cognitive decline is initially subtle and typically precedes appearance of motor symptoms. Cognitive decline in FXTAS mainly involves deficits in executive function, working memory, inhibition and visuospatial learning and progresses to full dementia in approximately 50% of patients [8,9]. In patients with established FXTAS gross changes to white matter structure can be seen in almost all individuals using magnetic resonance imaging, suggesting that disturbances to brain connectivity underpin the disorder [10]. It is of note that FXTAS symptomatology is both broad and heterogeneous, with similarities to multiple other diseases, likely resulting in under- and misdiagnoses. Psychiatric problems (including, anxiety, irritability and obsessive–compulsive behaviours) and autistic traits have been identified in premutation carriers throughout their lifespan [11]. Such traits are also known to be associated with disturbances to executive function and changes to brain connectivity.

1.2. Molecular changes associated with the fragile X premutation

Unlike in fragile X syndrome, where the expansion exceeds 200 CGG repeats, the premutation allele remains unmethylated, and as such encodes a functional transcript of FMRP. FMRP is expressed at highest concentrations in the brain and is a transcriptional regulator with a diversity of functions. Most importantly it is heavily involved in the regulation of synaptic maturation and plasticity [1,12]. In carriers of the premutation, production of *FMR1* mRNA increases up to 8-fold the normal level, likely due to changes in expansion size altering chromatin structure and giving increased access to transcriptional modulators of the FMRP gene [13]. In addition, FMRP levels have been observed to be slightly lower in some individuals with the premutation, especially at the high end of the CGG repeat range [13–15]. The causation for this is debated, but it has been suggested that a fall in FMRP could arise from deficits in the mRNA translational efficiency [13]. It is possible that this small decrease in FMRP may contribute to increased rates of neurodevelopmental abnormalities in premutation carriers, including autistic behaviours. However, it is widely accepted that the high level of *FMR1* mRNA in premutation carriers is the major causative factor in the molecular pathology of FXTAS [16]. Indeed, studies have shown that intranuclear inclusions in neurones and astrocytes, which are a pathological hallmark of FXTAS, are still formed without the FMRP coding region of the gene, and do not form without the CGG repeat expansion [17]. It seems that the mRNA has a toxic gain-of-function effect, which proceeds to disrupt numerous cellular pathways to cause neuronal damage or death. In particular, intranuclear inclusions containing *FMR1* mRNA are present throughout the brain and brainstem. The exact mechanism of their formation is not fully understood, however the favourable theory is that an excess of *FMR1* mRNA begins to sequester mRNA binding proteins such as histones, heat shock proteins and cytoskeletal proteins. In particular, neurofilament isoforms lamin A/C have been shown to often be involved in inclusion formation, which is likely to initiate neurofilament dysregulation and may be a major cause of peripheral neuropathy in FXTAS patients. These intranuclear inclusions likely not only cause physical blockages to cellular functions, but have knock-on effects through the sequestering and therefore inhibition of mRNA binding proteins [1,18]. Repeat Associated Non-AUG initiated (RAN) translation has also been implicated in the pathogenesis of FXTAS. The CGG repeat region of the *FMR1* gene has been shown to trigger translation of the polyglycine-containing protein FMRpolyG, despite being outside of the open reading frame. This protein has been demonstrated to be toxic in human cell lines, and to accumulate in intranuclear inclusions in cell culture, mouse models and human FXTAS patients. Given that intranuclear inclusions in FXTAS are ubiquitin-positive, it seems likely that the FMRpolyG protein may significantly contribute to neurodegeneration and it is suggested that in FXTAS, RNA and protein toxicity be additive or synergistic. Similar cases of RAN translation have also been implicated in multiple neurodegenerative diseases, such as ALS and frontotemporal dementia [19]. The antisense transcript AS*FMR1*, which overlaps the CGG repeat region of the *FMR1* gene and is transcribed in an antisense orientation, has also been suggested to contribute to phenotypic variations associated with *FMR1* gene repeat expansions. In a similar way to *FMR1* expression, AS*FMR1* mRNA is upregulated by the premutation allele and silenced by the full mutation. In the premutation, the gene is also alternatively spliced, which also indicates its possible association with FXTAS [20]. Despite the exact mechanisms of *FMR1* mRNA gain-of-function toxicity, pathogenic RAN translation and antisense transcripts being unclear, it is probable that combined down-stream effects cause oxidative stress in neurones and consequent cell damage and apoptosis. Fig. 1 summarises the processes by which the *FMR1* premutation may lead to the clinical features with which it is associated.

Several studies have examined whether CCG repeat length and FMRP levels correlate with the physiological, physical and psychiatric manifestations of the fragile X premutation. It has been identified that in patients with FXTAS, increased CGG repeat sizes are seen to correlate with increased severity of FXTAS symptoms [21]. This has prognostic value as identification of larger CGG repeat size may serve as a risk factor for a more severe form of FXTAS. The relationship between FMRP levels and *FMR1* mRNA levels or the CGG repeat expansion remains unclear, although it is recognised that the *FMR1* protein is modestly reduced

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