LETTER

Tissue atrophy and elevated iron concentration in the extrapyramidal motor system in Friedreich ataxia: the IMAGE-FRDA study

INTRODUCTION

Friedreich ataxia (FRDA) is an autosomal recessive disorder defined by progressive motor incoordination. FRDA results from reduced expression of the protein, frataxin, which is involved in cellular iron homeostasis and metabolism, antioxidant protection, and iron-sulfur cluster biogenesis. Disruption of one or more of these processes putatively underpins the pathology of FRDA, which manifests in processes putatively underpinned by proliferative iron-related pathology and/or degeneration within these extrapyramidal stations may also feature in FRDA. To test this hypothesis, we analysed tissue volume and iron concentration within the dentate nuclei, midbrain (red nuclei, substantia nigra), basal ganglia (caudate, putamen, and pallidum), and thalamus in individuals with FRDA and healthy controls using magnetic resonance imaging (MRI).

METHODS

Data collection

Whole-brain 3 T MRI were acquired from 30 individuals with genetically-confirmed FRDA (35.7±12.2 years; 17 males) and 33 healthy controls (36.9±13.1 years; 18 males; see online supplementary table S1): (1) dual-echo gradient-echo (GRE) images: TA=11.5 min; TR=30 ms, TE1=7.38 ms, TE2=22.14 ms, flip=15°, FOV=230×230 mm, 160 axial slices, 0.9 mm isotropic voxels; (2) T1-weighted magnetisation-prepared rapid gradient-echo (MPRAGE) images: TA=3.5 min; TR=1900 ms, TE=2.19 ms, flip=9°, FOV=256×256 mm, 176 sagittal slices, 1.0 mm isotropic voxels.

To measure motor dexterity, the maximal rate of non-dominant index finger tapping was measured over 10 s, repeated five times. The study was sanctioned by the Monash Health Human Research Ethics Committee. Participants provided written informed consent.

RESULTS

Significantly greater iron concentration in the FRDA cohort, relative to controls, was evident in the dentate nuclei and red nuclei (Bonferroni-corrected; p<0.007), with uncorrected trend increases in the basal ganglia (caudate, putamen, and pallidum). The volume of the dentate nuclei, red nuclei, substantia nigra, pallidum, and thalamus were also significantly smaller in the FRDA cohort (table 1).

Greater iron content in the dentate nuclei significantly correlated with greater disease severity (Friedreich Ataxia Rating Scale (FARS); r27=0.50; p=0.006) and greater triplet repeat length in the smaller FXN allele (GAA1; r27=0.39; p=0.037); online supplementary figure S2a.

Reduced thalamus volume correlated with greater GAA1 (r27=−0.54; p=0.002) and strong trends were evident with the volume of the dentate nuclei (FARS: r27=−0.45; p=0.015; GAA1: r27=−0.46; p=0.013), substantia nigra (FARS: r27=−0.41; p=0.027; GAA1: r27=−0.41; p=0.027), and putamen (GAA1: r27=−0.41; p=0.028); online supplementary figure S2b–e.

Poorer motor dexterity in FRDA correlated with lesser volume in the dentate nuclei (r27=0.60; p=0.001) and substantia nigra (r27=0.57; p=0.001), and at uncorrected levels in the red nuclei (r27=0.46; p=0.013), putamen (r27=0.44; p=0.017), and pallidum (r27=0.41; p=0.027); online supplementary figure S3.

DISCUSSION

Subcortical tissue atrophy and iron dysregulation in individuals with FRDA encompass not only regions of established pathology in the cerebellum, but also extend to midbrain and cerebral structures. The clinical relevance of tissue

Table 1 Iron Concentration and Volume (normalised with respect to a standard template) in the Subcortical Regions-of-Interest in Individuals with FRDA (n=30) and Healthy Controls (n=33)

<table>
<thead>
<tr>
<th>Region</th>
<th>Iron concentration (ppm±SD)</th>
<th>Normalised volume (mL±SD)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>FRDA Control F1.59 p Value</td>
<td>FRDA Control F1.59 p Value</td>
</tr>
<tr>
<td>Dentate N.</td>
<td>0.078±0.023 0.050±0.025 25.4</td>
<td>0.08±0.09 0.05±0.01 20.3</td>
</tr>
<tr>
<td>Red N.</td>
<td>0.114±0.026 0.089±0.028 19.3</td>
<td>0.096±0.01 0.06±0.00 14.4</td>
</tr>
<tr>
<td>Sub. Nigra</td>
<td>0.125±0.023 0.121±0.024 0.38</td>
<td>0.96±0.11 0.10±0.01 41.7</td>
</tr>
<tr>
<td>Thalamus</td>
<td>0.013±0.007 0.013±0.005 0.03</td>
<td>0.10±0.10 0.06±0.10 29.5</td>
</tr>
<tr>
<td>Caudate</td>
<td>0.054±0.011 0.051±0.011 3.07</td>
<td>0.16±0.14 0.14±0.03 0.1</td>
</tr>
<tr>
<td>Putamen</td>
<td>0.050±0.015 0.045±0.020 5.60</td>
<td>0.13±0.11 0.10±0.13 7.3</td>
</tr>
<tr>
<td>Pallidum</td>
<td>0.132±0.021 0.124±0.018 2.86</td>
<td>0.10±0.09 0.10±0.12 8.1</td>
</tr>
</tbody>
</table>

BOLDFACE p values are significant after Bonferroni-correction for multiple comparisons (p<0.007); F-values derived from one-way ANCOVA controlling for age, white matter QSM (for iron analyses), and ICV (for volume analyses). ANCOVA, analysis of covariance; FRDA, Friedreich ataxia; QSM, quantitative susceptibility mapping.
atrophy in the extrapyramidal system is supported by associations with disease severity, extent of genetic abnormality and motor dexterity.

Increased iron concentration in the dentate nuclei has been reported using MRI when measures are averaged across its grey and white matter components (eg, ref. 2 and herein), but not when the grey matter is isolated.3 These results suggest that iron dysregulation in the dentate may be relatively focal. Outside of the cerebellum, we additionally observe iron concentration increases in the red nuclei, with trends throughout the basal ganglia. This finding is comparable to another recent MRI study that also reports significant iron changes in the dentate nuclei, but not in the substantia nigra, caudate, or putamen (the red nucleus was not investigated).2 The pathophysiological mechanisms underlying this relatively targeted dysregulation remain unclear; however, potential differences in the basal rates of frataxin expression in different extrapyramidal structures presents one compelling hypothesis.

Notably, QSM cannot distinguish between iron redistribution, accumulation, or deposition; nor disambiguate extracellular from intracellular, or cytosolic from mitochondrial iron content. Histological reports in FRDA do provide some guidance on this topic, with total quantity of measured dentate iron in FRDA equivalent to healthy controls, but redistribution of that iron within the structure.1

Volume loss in the dentate nuclei is also consistently reported in FRDA.1 3 We additionally detect volume reductions in midbrain, thalamus and basal ganglia structures. Critically, tissue loss was observed regardless of co-localised robust iron dysregulation (dentate and red nuclei), potentially more subtle dysregulation (pallidum), or in the absence of iron changes (substantia nigra; thalamus). Animal models similarly suggest that the pathological consequences of frataxin deficiency do not directly depend on iron accumulation. As such, iron dysregulation may not be necessary for neurodegeneration in FRDA.

This report indicates that subcortical brain pathology extends beyond the cerebellum. The relevance of tissue volume (and iron concentration to a lesser extent) throughout the extrapyramidal system to individual disease status indicates its potential utility as a (set of) biomarker(s) sensitive to disease expression, progression, or treatment monitoring. Longitudinal studies will be necessary to further gauge this potential.2

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Contributors IHH and PR conducted statistical analyses and wrote the paper, MBD, LAC, ES, NG-K, and GFE conceptualised the project and edited the paper; MRS conducted data collection and edited the paper.

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