Quantitative assessment of MRI $T_2$ relaxation time of thigh muscles in juvenile dermatomyositis

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Objective. The aim of the study was to examine the validity and reliability of a quantifiable measure of inflammation using magnetic resonance imaging (MRI) in children with juvenile dermatomyositis (JDM).

Methods. Children with active JDM, inactive JDM and healthy children received detailed assessments of recognized measures of muscle inflammation including muscle strength (manual muscle testing and myometry) and function (Childhood Myositis Assessment Scale, Childhood Health Assessment Questionnaire), the muscle enzymes lactate dehydrogenase (LDH) and creatine kinase (CK) and $T_2$-weighted MRI scans of the thigh muscles, and these values were correlated with each other.

Results. Ten children with active JDM, 10 with inactive JDM and 20 healthy children completed the study. There was no significant difference in ages between the three groups. The MRI $T_2$ relaxation times were significantly increased in active JDM compared with inactive JDM and healthy children ($P = 0.05$), indicating a detectable increase in inflammation within the muscles. There were also good correlations between the MRI scores and the measures of muscle strength and function; however, there was no correlation between the MRI and muscle enzymes.

Conclusions. The MRI $T_2$ relaxation time can be used as a quantitative measure of muscle inflammation and it has good correlations with other measures of disease activity.

Key words: Magnetic resonance imaging, Juvenile dermatomyositis, Childhood Myositis Assessment Scale, Muscle inflammation.

The idiopathic inflammatory myopathies (IIM) are a heterogeneous group of disorders which have in common an autoimmune inflammatory process affecting muscle, skin and internal systems to varying degrees. Juvenile dermatomyositis (JDM) is the most common of these conditions in children. It is thought that the inflammation in JDM primarily affects the blood vessels supplying the muscles and skin, though the precise aetiology is unknown [1, 2]. Both genetic and infectious agents are thought to be important.

The estimated incidence of new cases of JDM in childhood in the UK is approximately 2 per million in children under 16 years of age, according to a British Paediatric Surveillance Unit survey. In the United States, estimates are up to 3 per million [3, 4].

The current accepted diagnostic criteria were defined over 25 years ago by Bohan and Peter [5]. These criteria are clearly defined and are internationally accepted, but they are now partially outdated as clinical practice has changed and new assessment and diagnostic tools, such as magnetic resonance imaging (MRI), have become available.

A diagnosis of definite JDM can be made according to these criteria if rash is present and three out of four of the other criteria are also present. In children electromyography and muscle biopsy are rarely used as they are invasive procedures and diagnosis is often made on clinical features and muscle enzyme elevations. Therefore the full diagnostic criteria are often not met, and the diagnosis of JDM is often made on clinical and laboratory criteria and MRI.

Due to variable clinical features and severity, monitoring of JDM can often prove a challenge. Therefore clinical assessments are used to assess the progression of the disease, and in the assessment of disease activity and damage several of these are internationally recognized and have been shown to have good intra- and inter-rater reliability in children and adolescents. These include muscle strength, muscle function, serum muscle enzyme levels, joint range of movement, physician’s global assessment (PGA) and MRI [6–8].

The recent developments in MRI have shown that it can assess a change in muscle inflammation as well provide an assessment of disease activity and damage [9]. It has been shown that inflammation, characteristic of active JDM, is visible as a high signal intensity on fat-suppressed $T_2$-weighted and short $T_1$ inversion recovery (STIR) MRI images [10] These signals enable the use of MRI as a tool in establishing the diagnosis of JDM, and monitoring the progression of the disease. On $T_2$ MRI images an increase in water content, representing inflammation, appears as white within muscles that should have dark image areas. These areas can be quantified by computer generation of the MRI $T_2$ relaxation times [11–13].

This study looks at the quantifiable measures of MRI $T_2$ relaxation times and correlates them with other measures of muscle inflammation in order to validate the quantification of MRI in assessment and diagnosis of JDM, and compares three groups of children, those with active disease, those with inactive disease and healthy children.

Patients and methods

Patients

Subjects in the study were diagnosed with definite or probable JDM by a consultant paediatric rheumatologist on the basis of the

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Bohan and Peter criteria [5]. Healthy children were recruited from the siblings of the children with JDM and families of staff members. The study was approved by the institutional ethics committee and informed consent was obtained from parents and, where age appropriate, subjects.

Methods

The assessments detailed below were completed before the MRI and included muscle strength assessments, the Childhood Myositis Assessment Scale (CMAS) [6], the Childhood Health Assessment Questionnaire (CHAQ) [14], joint range of movement and physician’s global assessment (PGA). Muscle strength was evaluated using a combination of two methods, the Manual Muscle Test (MMT) [15] and a hand-held myometer [16]. The myometer used was the CITEC 3001 produced by CIT Technics BV, which measures strength in newtons. The muscle groups assessed were the neck flexors, shoulder abductors, hip abductors, quadriceps and hamstrings.

The CHAQ and CMAS were completed by all children in the study. Serum creatine kinase (CK) and lactate dehydrogenase (LDH) were measured in patients. No blood samples were taken from control subjects. All were seen by the specialist physiotherapist and their joint range of movement (ROM) was assessed. The PGA was completed on all patients and the results were recorded on a visual analogue scale (VAS) on a 10 cm line. Patients with a VAS score $\leq 2.0$ were classified as inactive, and those with a score of $>2.1$ were considered to have active disease.

MRI sequences

The sequences undertaken by all patients to quantify the $T_2$ relaxation time included a gradient echo $T_1$-weighted (multiplanar) localizer and a spin echo $T_2$-weighted 16-echo mapping sequence.

The magnet used was a 1.5 T Siemens Symphony with an inbuilt body coil, and standardized protocols of imaging were used in the imaging of both thighs [17,18].

The $T_2$ relaxation mapping sequence, or Carr–Purcell–Meiboom–Gill sequence, provides the data that allow the objective assessment of signal abnormality [19]. Eight image slices throughout the thigh were gained at each scan, with the first slice positioned at the level of the base of the greater trochanters and the final slice positioned at the level of the superior aspect of the condyles. The other six slices were automatically positioned between these two, equidistantly throughout the thigh.

For any given $T_2$ map slice image, the positioning of a region of interest (ROI) within the image results in a value in milliseconds (ms), which represents the average $T_2$ relaxation time of the tissue within this ROI. Data from two consecutive slices at the positions of the fourth and fifth slices on the left leg were taken enable any changes to be evaluated over a global rather than localized volume of muscle. To enable accurate measurement, slices chosen contained the largest area of visible muscle tissue and had good muscle compartment differentiation.

Each of the three thigh muscle groups examined (anterior, posterior and medial) is made up of various individual muscles; operator-defined regions of interest (ROI) were placed in specific muscles in each group and then the mathematical mean of these individual muscle readings was used to gain an average value of relaxation time for that particular muscle group. In cases of patients with very active disease where muscle wastage was severe, the placement of the ROIs presented difficulties. In all cases, readings were made from visible muscle tissue (avoiding completely wasted muscle regions) to avoid a skew of the readings and allowing false muscle relaxation times to be recorded. For continuity, where possible anatomically identical ROIs were used on successive slice images and from patient to patient. These ROIs were determined and positioned by the radiographer who was blinded to the clinical findings and disease status of the children.

Statistics

The analyses were carried out using the SPSS 10.1 for Windows program. The data were normally distributed and the samples were drawn from a population of equal variance. Pearson’s correlation coefficients were used to analyse the values of the MRI $T_2$ relaxation times at two levels (4 and 5) in the correlations of these scores against the other measures of disease activity. A one-way analysis of variance (ANOVA) using an a priori approach was chosen in the analysis of the mean MRI $T_2$ relaxation times between the different groups. Statistical significance was taken as $P < 0.05$.

Results

Forty-four children were recruited to the study over 6 months. Twenty-two children had been diagnosed with JDM and 22 were healthy children with no other underlying diagnosis. Two children with JDM withdrew from the study as they were unable to tolerate the MRI scanning due to fear of the machine. The siblings of these two children were also withdrawn to minimize the stay in hospital for the family. Twenty children with JDM and 20 healthy children completed the study.

The distribution of the groups, age range and clinical data are shown in Table 1. There was no statistically significant difference of mean age at diagnosis of the JDM or mean age at MRI between the groups, though the inactive JDM groups had their disease for about 1 yr longer than the active JDM group.

MRI $T_2$ relaxation times measured at two different levels, known as slice 4 and slice 5, showed that the mean scores were significantly higher in children with active JDM when compared with either the inactive JDM group or the healthy controls (Figs 1 and 2). There was no significant difference between inactive JDM group and healthy children. In the combined muscle (anterior, medial and posterior) the mean MRI $T_2$ relaxation times in children with active disease was 86 ms, though this value was reflective of the high values in the anterior muscle groups. When each muscle group (anterior, posterior and medial) was

| Table 1. The distribution of the subject groups, their mean ages and other clinical data |
|-------------------------------------------|----------------------------------|-----------------|-----------------|
|                                         | Active JDM (PGA > 2.1)           | Inactive JDM (PGA < 2.0) | Control         |
| Number of children                      | 10                               | 10               | 20              |
| Mean age at onset of JDM (yr) (range)   | 6.6 (3.8–11.8)                   | 6.9 (2.7–13.3)   | 6.6 (2–13.3)    |
| Mean disease duration (yr) (range)      | 2.2 (0.3–6.7)                    | 1.3–8.0         | N/A             |
| PGA (range: 0–10)                       | 4.52 (2.4–6.9)                   | 1.1 (0.2–2.0)   | N/A             |
| CMAS (range: 0–53)                      | 36 (19–50)                       | 44 (24–53)      | 50 (46–53)      |
| CHAQ (range: 0–3)                       | 1.71 (0.125–3.0)                 | 0.712 (0–2.0)   | 0.06 (0.0–0.375) |
| Manual neck strength (range: 0–5)       | 2.9 (1–4.5)                      | 4.8 (3.0–5.0)   | 4.8 (4.5–5.0)  |
| Myometry of neck (N) (range: 0–100 N)   | 10.1 (0–32)                      | 28.9 (3–55)     | 36.7 (20–82)    |

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analysed separately there were small differences between the groups (Figs 3 and 4). The anterior muscle groups showed the greatest diversity in scores and appeared to show the most inflammation (highest relaxation time). The difference between active JDM and inactive JDM and the healthy controls was evident in each muscle group at either slice.

Correlations between the MRI T2 relaxation scores and the other measures of disease activity

The pre-exercise MRI T2 relaxation times were correlated with the standard assessments of disease activity. Table 2 shows the correlations of the average total scores of the relaxation time of all muscle groups at slice 4 and slice 5 with other measures of disease activity. Correlations were also performed between each muscle group (anterior, posterior and medial) at both slices with these other measures with very similar results to those of the combined scores.

The MRI scores correlated strongly with each other (Table 2). These scores also had good correlations with the PGA, the CMAS, the CHAQ, the number of contractures and the measures of muscle strength. These data suggest that an increase in the T2 relaxation time correlates with an increase in disease activity. There were good negative correlations between the MRI scores and the manual muscle testing and myometry of all muscle groups taken
at slice 5 and good negative correlations at slice 4 except for the myometry values for shoulder abduction and quadriceps. The negative correlations are due to the fact that the weakest muscles, which indicate increased disease activity, have a lower score, and the higher MRI $T_2$ relaxation time represents increased inflammation.

There was no statistically significant correlation between the MRI $T_2$ relaxation times and the levels of CK or LDH, or between the MRI scores and the age of onset, age at MRI and the duration of the disease (data not shown).

**Discussion**

In this study we have demonstrated statistically significant differences between the MRI $T_2$ relaxation time of children with active JDM when compared with those with inactive disease or healthy controls, and have demonstrated the power of the MRI $T_2$ relaxation time as a measure of active muscle inflammation in JDM.

Our results show that the MRI $T_2$ relaxation time correlates closely with measures of muscle strength (MMT and myometry),
Table 2. The correlations of the MRI T2 relaxation times produced against other measures of disease activity

<table>
<thead>
<tr>
<th>Outcome measures</th>
<th>MRI slice 4</th>
<th>MRI slice 5</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Pearson’s correlation coefficient (R²)</td>
<td>Significance (two-tailed) (P value)</td>
</tr>
<tr>
<td>MRI slice 4</td>
<td>1</td>
<td>0.000</td>
</tr>
<tr>
<td>MRI slice 5</td>
<td>0.834</td>
<td>0.002</td>
</tr>
<tr>
<td>CMAS</td>
<td>-0.476</td>
<td>0.002</td>
</tr>
<tr>
<td>PGA</td>
<td>0.608</td>
<td>0.004</td>
</tr>
<tr>
<td>CHAQ</td>
<td>0.489</td>
<td>0.001</td>
</tr>
<tr>
<td>Contractures</td>
<td>0.434</td>
<td>0.005</td>
</tr>
<tr>
<td>MMT neck flexors</td>
<td>-0.477</td>
<td>0.002</td>
</tr>
<tr>
<td>MMT shoulder</td>
<td>-0.436</td>
<td>0.005</td>
</tr>
<tr>
<td>MMT hip abductor</td>
<td>-0.439</td>
<td>0.005</td>
</tr>
<tr>
<td>MMT quadriceps</td>
<td>-0.523</td>
<td>0.001</td>
</tr>
<tr>
<td>MMT hamstrings</td>
<td>-0.481</td>
<td>0.002</td>
</tr>
<tr>
<td>Myometry—neck</td>
<td>-0.374</td>
<td>0.017</td>
</tr>
</tbody>
</table>

Significance is taken when P<0.05.

muscle function (CMAS) and general function (CHAQ) as well as the PGA and the number of joint contractures present.

Note that children with the very severe JDM were not included within this study. The reason for this was that the children with very active disease frequently had muscles that were below grade 3 MMT in strength and were not able to function against gravity, and they were therefore unable to have their strength tested with the myometer. However, this exclusion of the severe end of the spectrum of disease may have led to an underestimate of the values of MRI T2 relaxation time in the active JDM group.

The MRI T2 relaxation time is a measure of the inflammation within the muscle fibres but it does not take into account other changes occurring within and around the muscle. In JDM these can include replacement of muscle with fat and a change in blood vessels. These were not assessed within this study. Thus MRI is able to provide more information about the disease than the MRI T2 relaxation time alone, including information about replacement of muscle with fat, atrophy of muscle and extramuscular inflammation [20, 21].

In the assessment of some children with active JDM, the vastus medialis muscle of the quadriceps group was so atrophied that it was impossible to place an ROI within the muscle in order to measure the MRI T2 relaxation time. This therefore excluded the most affected muscle from analysis. If it had been possible to assess this muscle then it is likely that the difference between the score of the children with active JDM and the other groups would have been even greater. This highlights the limitations of this method of quantification of MRI and therefore MRI T2 relaxation time should not be used as the only method of assessing MRI images [22].

These results suggest that in our analysis a child with an MRI T2 relaxation time of more than 86 ms is highly likely to have active inflammation within their muscles.

The reliability of the MRI T2 relaxation time was shown by the strong correlation between the scores at different levels of the thigh muscle, indicating that these measurements were gained from any scan of the thigh at two separate levels. The reliability was also supported as individual muscle groups were also analysed and showed the same patterns of results.

This study showed that there was no correlation between the MRI T2 relaxation time and the muscle enzyme levels in serum, casting further doubt on the effectiveness of these measures for monitoring disease activity [23]. It has been reported before that muscle inflammation in JDM is patchy, both within the muscle itself but also between muscle groups, with anterior muscles thought to be the most common muscle groups affected [24]. In this study it was apparent that the anterior muscle groups in both children with JDM and healthy children have a higher MRI T2 relaxation time than the posterior and medial muscle groups.

Normal children have not been studied in this way before; the difference that occurs in the anterior muscles compared with the posterior and medial muscle groups also occurs in healthy children, and may have been overinterpreted in previous studies that did not include healthy children [12].

We conclude that MRI T2 relaxation time can be used as a reliable and valid quantitative measure of inflammation within muscles in children with JDM. This value correlates well with other standard measures of disease activity and can reliably be used as a measure of disease activity. This study also shows that a MRI T2 relaxation time greater than 86 ms can indicate active inflammation within muscles in children with JDM.

The authors have declared no conflicts of interest.

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