Myalgic encephalomyelitis – a persistent enteroviral infection?

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Summary: Myalgic encephalomyelitis is a common disability but frequently misinterpreted. Amongst 6,000 patients referred for general microbiological diagnosis between 1975 and 1987, 420 cases were recognized. Coxsackie B neutralization tests, in 205 of these, demonstrated significant titres in 103/205 (50%), while of 124 additionally investigated for enteroviral IgM, 38/124 (31%) were positive. This illness is distinguished from a variety of other post-viral states by an unique clinical and epidemiological pattern characteristic of enteroviral infection. Prompt recognition and advice to avoid over-exertion is mandatory. Routine diagnosis, specific therapy and prevention, await further technical advances.

Introduction

Since 1934, myalgic encephalomyelitis (ME) has been increasingly reported from socially developed countries and temperate regions of the world. Endemic prevalence alternates with periodic epidemics, showing a curious predilection for female staff of health care and teaching institutions.1 Maximum incidence in both sexes occurs in the third decade. ME is a multisystem syndrome including nervous, cardiovascular, endocrine and other involvement, distinguished by severe muscle fatigue following trivial exertion. Other characteristics include high morbidity, low mortality, a prolonged relapsing course and variation in intensity of symptoms within and between episodes, tending to chronicity.2,3 Conventional technology is limited in demonstrating abnormalities and this has hitherto permitted misinterpretation of the symptoms as psychogenic.4,5 Historically, a marked similarity to non-paralytic poliomyelitis in respect of prodrome, seasonal and geographical incidence1–3 caused diagnostic confusion. The return of a local family from holiday with a poliomyelitis-like illness (of whom 3 subsequently developed ME), prompted collaboration between the authors.

Patient selection

We adopted the following clinical criteria for investigation of ME: a syndrome commonly initiated by respiratory and/or gastro-intestinal infection but an insidious or more dramatic onset following neurological, cardiac or endocrine disability occurs. The pathognomonic features are: a complaint of general or local muscular fatigue following minimal exertion with prolonged recovery time; neurological disturbance, especially of cognitive, autonomic and sensory functions; variable involvement of cardiac and other systems; a prolonged relapsing course. Four hundred and twenty patients, fulfilling these criteria, were selected for further investigation amongst 6,000 patients with heterogeneous infections referred to one of us (EGD) between 1975 and 1987. Patients with ME comprised approximately 7% per annum of all who attended; 324/420 (77%) were referred from general practice and 96/420 (23%) from other hospital specialties in Essex and South London, including cardiology, endocrinology, neurology and psychiatry.

Clinical investigation

To elicit the essential features of this multisystem syndrome and ensure a comparable history, examination, and investigation for selected patients, a detailed questionnaire was devised with a scoring system weighted for the above diagnostic criteria. When tested on normal adults and clinic patients with other chronic diseases, none achieved scores in the ME range. Cognitive disturbances in patients with ME were readily elicited by failure to complete the questionnaire without assistance. Muscular fatigue was demonstrated by repeated activity such as

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†Dr A.M. Ramsay died on 29 March 1990.
as weight raising on a block or climbing several flights of stairs, and myalgic foci by careful palpation of affected muscles with the finger tip. Standard methods were used to elicit other clinical signs.

**Laboratory investigation**

Tests included: routine haematological and biochemical screening; Paul Bunnell, Monospot or Epstein-Barr virus (EBV) IgM; rheumatoid factor, liver and cardiac enzymes, thyroid function, blood glucose; bacterial and viral culture; serological tests for streptococcal infection, brucellosis, toxoplasmosis, legionella, hepatitis A and B, cytomegalovirus, rubella, respiratory syncytial virus and parvovirus. Specialist technology was introduced as it became available but did not include EBV reactivation.

**Coxsackie B virus (CBV) serology**

Neutralizing tests (NT) to CBV 1–5 were estimated using the Microtitre method described elsewhere. Titres of 512 and above were regarded as indicative and of 256 as suggestive, of recent CBV infection. After 1985, only sera positive by the μ antibody capture ELISA technique were tested by NT.

**Immunology**

Tests for immune complexes were performed as described elsewhere and autoimmune screening by standard immunofluorescence methods.

**Results**

**Epidemiological characteristics**

Age, sex, occupation Of 420 patients with ME, 307 (73%) were female and 113 (27%) male. The average age at onset was 32.3 years (range 7–64 years) – Table I; 172 (41%) were employed in health care or teaching, 109 (26%) in clerical, administrative or other professional posts, 88 (21%) in skilled or unskilled manual occupations and 51 (12%) not gainfully employed, including children, pensioners, housewives. Corresponding figures for other clinic attenders are 4%, 21%, 12% and 63% respectively.

Season and type of prodromal illness A distinct prodrome occurred in 340/420 (81%) patients, characterized by a respiratory/gastrointestinal or 'flu-like illness in 277/340 (81%) and lymphadenopathy and summer/autumn onset in 218/340 (64%). Alternative prodromal presentations in 63/340 (19%) included: acute neurological, visual or psychotic episodes, myo/pericarditis, pleurodynia, exanthems, enanthems, thyroiditis, orchitis, and mesenteric adenitis. The remaining patients, 80/420 (19%) described an insidious onset, 105/340 (31%) reported a similar illness in family or occupational contacts not invariably followed by ME. In eleven families, an incubation period of 2–5 days for the prodrome was noted, but subsequent recognition of ME varied from a few days to 6 months.

**Clinical characteristics**

**Duration and severity of illness at first attendance of 420 patients** The duration was less than 12 months in 38 patients (9%); 1–2 years in 139 (32%); 3–10 years in 198 (47%); 11–20 years in 33 (8%) and 21–60 years in 17 (4%). Illness was reported to be improving in 130 (31%), fluctuating in 84 (20%), a steady level of disability in 105 (25%) and no remission or worse in 101 (24%).

**Symptoms and signs** (Table II) Symptomatology in ME is characteristically varied between age groups and episodes. Our study includes a number of families followed up from the prodromal illness, when the nature and frequency of symptoms may differ greatly from those recorded in individuals who subsequently develop ME.

**Relapse of ME** Known precipitants included physical and mental stress in all 420 patients (100%), intercurrent infection in 176 (42%), climatic change or hot baths in 50 (12%), surgery, immunization, hormonal disturbance in 38 (9%), psychoactive, antiarthritic or steroid drugs in 21 (5%).

### Table I

<table>
<thead>
<tr>
<th>Age group</th>
<th>Males</th>
<th>Females</th>
<th>Total</th>
</tr>
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<tr>
<td>&lt; 10 years</td>
<td>3</td>
<td>12</td>
<td>15</td>
</tr>
<tr>
<td>11–15</td>
<td>5</td>
<td>14</td>
<td>19</td>
</tr>
<tr>
<td>16–20</td>
<td>15</td>
<td>40</td>
<td>55</td>
</tr>
<tr>
<td>21–25</td>
<td>12</td>
<td>26</td>
<td>38</td>
</tr>
<tr>
<td>26–30</td>
<td>8</td>
<td>30</td>
<td>38</td>
</tr>
<tr>
<td>31–35</td>
<td>22</td>
<td>58</td>
<td>80</td>
</tr>
<tr>
<td>36–40</td>
<td>20</td>
<td>56</td>
<td>76</td>
</tr>
<tr>
<td>41–45</td>
<td>13</td>
<td>33</td>
<td>46</td>
</tr>
<tr>
<td>46–50</td>
<td>6</td>
<td>15</td>
<td>21</td>
</tr>
<tr>
<td>51–55</td>
<td>3</td>
<td>9</td>
<td>12</td>
</tr>
<tr>
<td>56–60</td>
<td>4</td>
<td>10</td>
<td>14</td>
</tr>
<tr>
<td>&gt; 60 years</td>
<td>2</td>
<td>4</td>
<td>6</td>
</tr>
<tr>
<td>Total</td>
<td>113</td>
<td>307</td>
<td>420</td>
</tr>
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</table>
Table II  Symptoms and signs in 420 patients with ME

<table>
<thead>
<tr>
<th>Commonly found ( &gt; 50%)</th>
<th>No.</th>
<th>%</th>
<th>Less commonly found ( &lt;50%)</th>
<th>No.</th>
<th>%</th>
</tr>
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<tr>
<td>Muscle fatigue</td>
<td>420</td>
<td>100</td>
<td>Gastrointestinal symptoms****</td>
<td>205</td>
<td>49</td>
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<tr>
<td>Emotional lability†</td>
<td>411</td>
<td>98</td>
<td>Disturbance of micturition§</td>
<td>160</td>
<td>38</td>
</tr>
<tr>
<td>Myalgia††</td>
<td>336</td>
<td>80</td>
<td>Recurrent lymphadenopathy §§</td>
<td>152</td>
<td>36</td>
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<tr>
<td>Cognitive disturbance††</td>
<td>323</td>
<td>77</td>
<td>Arthralgia</td>
<td>118</td>
<td>28</td>
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<tr>
<td>Headache</td>
<td>310</td>
<td>74</td>
<td>Orthostatic tachycardia</td>
<td>88</td>
<td>21</td>
</tr>
<tr>
<td>Giddiness, disequilibrium</td>
<td>302</td>
<td>72</td>
<td>Recurrent abacterial conjunctivitis</td>
<td>68</td>
<td>16</td>
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<tr>
<td>Autonomic dysfunction†††</td>
<td>289</td>
<td>69</td>
<td>Orchiis/prostatism in young males</td>
<td>15/113</td>
<td>13</td>
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<tr>
<td>Auditory disturbances*</td>
<td>260</td>
<td>62</td>
<td>Seronegative polyarthritis</td>
<td>42</td>
<td>10</td>
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<tr>
<td>Reversal of sleep rhythm</td>
<td>268</td>
<td>64</td>
<td>Vasculitic skin lesions</td>
<td>42</td>
<td>10</td>
</tr>
<tr>
<td>Visual disturbances**</td>
<td>260</td>
<td>62</td>
<td>Myo/pericarditis</td>
<td>34</td>
<td>8</td>
</tr>
<tr>
<td>Parasthaesia, hypo &amp; hyperasthaesia</td>
<td>256</td>
<td>61</td>
<td>Positive Romberg sign</td>
<td>25</td>
<td>6</td>
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<tr>
<td>Intercostal myalgia/weakness</td>
<td>247</td>
<td>59</td>
<td>Thyroiditis in female patients</td>
<td>15/307</td>
<td>5</td>
</tr>
<tr>
<td>Fasciculation, spasm, myclonus</td>
<td>239</td>
<td>57</td>
<td>Mesenteric adenitis §§§</td>
<td>5</td>
<td>1</td>
</tr>
<tr>
<td>Clumsiness***</td>
<td>235</td>
<td>56</td>
<td>Paresis and muscle wasting</td>
<td>3</td>
<td>1</td>
</tr>
</tbody>
</table>

†Includes frustration, elation, depression; ††characteristically affects limbs, shoulder girdle, spinal muscles; †††memory, concentration, anemia, dyslexia; ††††especially circulation and thermoregulation; *hyperacusis, deafness, tinnitus; **mainly loss of accomodation, photophobia, nystagmus; ***usually due to impaired spatial discrimination; ****nausea/disturbance of intestinal motility; §frequency incontinence, retention; §§enlargement, recurrent after prodrome; §§§surgical intervention for abdominal pain.

Laboratory results

Haematology and biochemistry  Screening tests were normal with the following exceptions: 55/420 (13%) had leucocyte counts below normal range (3,500 × 10^9/l) with occasional atypical lymphocytes and 22/420 (5%), abnormal liver function tests, of whom two had hepatitis A. Two further patients had undiagnosed persistent hyperbilirubinaemia.

CBV serology  The sera of 205 patients with diagnostic features of ME seen before 1985, were tested by NT: 68/205 (33%) had titres indicative and 35/205 (17%) suggestive of recent CBV infection. Subsequently, 124 patients were additionally tested by the enteroviral IgM ELISA system. Applying the diagnostic criteria established by McCartney et al.,38/124 (31%) had evidence of recent/active enteroviral infection. Sixteen patients in our study, who were retested annually for three years, showed persistently raised CBV NTs and intermittently positive enteroviral IgM.

Other viral investigations  Intercurrent viral infections occurred in 12 patients with positive enteroviral serology (not serological cross reactions). EBV IgM was positive in three patients; hepatitis A, respiratory syncytial virus and parvovirus in two cases each; influenza B, varicella, rubella, one case each.

Immunology  128/276 (46%) of patients tested had evidence of circulating immune complexes, but only 15/420 (4%), antinuclear, thyroid or muscle antibodies.

Discussion

Differentiation of the ME syndrome from other forms of post-viral debility

In our opinion, two major errors are responsible for the present confusion surrounding the case definition, aetiology and diagnosis of ME. First, there has been a failure to distinguish the syndrome from post-viral debility following Epstein-Barr mononucleosis, influenza and other common fevers. Compared with ME, these lack the dramatic effect of exercise upon muscle function, the multi-system involvement, diurnal variability of symptoms and prolonged relapsing course. Laboratory tests can distinguish chronic mononucleosis and other infections which, as our results show, may occasionally co-exist with ME and, by their immunosuppressive effect, precipitate relapse. Second, there has been a failure to recognize the unique epidemiological pattern of ME, which, from earliest accounts, has lead to confusion with non-paralytic poliomyelitis.

The epidemiological features of ME require explanation

Polio viruses (Types 1–3) are the best known examples of a group of 69 enteroviruses which, by faecal/oral spread, commonly lead to asymptomatic childhood infection. The epidemiology of poliomyelitis remained enigmatic until virus isolation from carriers demonstrated the link between paralytic cases. In 1948, the non-polio enteroviruses (NPEV) were shown to be causative agents of illness previously designated as ‘non-paralytic
poliomyelitis’. Reports of NPEV isolation from individual cases or serological evidence of NPEV infection occur in many published accounts of ME. Our study also supports association of the ME syndrome with NPEV. Thirty three per cent of 205 patients tested had CBV NTs indicative of infection – a figure comparable with that for enterovirus – associated myocarditis. Seasonal distortion was excluded by the observation that 37/75 (49%) of those attending in winter and spring had significant CBV NT compared with 66/130 (51%) of those attending in summer and autumn. Moreover, 31% of our patients tested had positive enteroviral IgM tests compared with 12% of normal blood donors tested simultaneously in South London by the same technique.

The geographical epidemiology of entero viral infection depends entirely upon the interaction of climate and hygiene. Virtually all children born in hyperendemic tropical areas lacking sanitation, acquire immunity in early life. Conversely, many adults in temperate zones with seasonal and hygienic limitation of enterovirus circulation, lack immunity. Post-pubertal infections tend to be severe and lead (as in poliomyelitis) to the paradox of overt adult infection and epidemics in affluent societies with cool climates. It is only in these geographical areas that epidemic ME has been described. Sixty four per cent of our patients with a prodrome reported summer/autumn onset, while in 34/420 (8%), travel to an endemic area at any season was an antecedent factor. The peak incidence of ME is in the third decade and Table I indicates that a minority of our patients developed ME before puberty or after 45 years (when a less hygienic childhood may have afforded natural immunity). In this country, asymptomatic children, especially when diaphoresed, are the main dispersers of infection. Male infants are more susceptible than female and possibly acquire earlier immunity. These factors do much to explain the sex ratio of ME, the earlier onset and higher incidence in women (Table I), the secondary cases in family and school contacts and the curious predisposition of health care and teaching staff.

Multi-system clinical involvement in patients with ME

Most enteroviral infections are biphasic. A non-specific prodromal illness precedes, by an interval, infection of target organs. Host factors, such as age, physical and mental stress, climatic change, hormones, immunosuppression, anti-inflammatory drugs, surgery and immunization, contribute to this outcome. The onset of illness and relapse in our patients was significantly associated with similar events. Enteroviruses exhibit an extensive cell tropism. Symptoms are protean within the family and community, depending upon the age and susceptibility of the host as well as the strain and virulence of the virus. Enteroviral syndromes which range from trivial to severe, include: respiratory, gastrointestinal, muscular and neurological infections, exanthems, enanthems, conjunctivitis, arthritis, diseases of endocrine and lymphatic glands. All of these are encountered in the prodrome of ME. In autumn 1976, at the beginning of our survey, 488/814 (60%) of all viruses associated with neurological manifestations notified to the Public Health Laboratory Service, were identified as NPEVs. This could well explain the common neurological and encephalitic features of ME. The psychological disturbances in our patients differed from classical depression in that all but three patients had a normal premorbid personality, volition was preserved, weight and appetite disturbance minimal and treatment with antidepressant drugs ineffectual in 123/420 (29%) of patients in whom it had been tried. Moreover, neurophysiological research using cognitive event-related potentials has shown prolonged latencies in ME – an abnormality not present in patients with depression.

Exercise related morbidity in ME

Coxsackie viruses are characteristically myotropic and entero viral genomic sequences have been detected in muscle biopsies from patients with ME. Exercise related abnormalities of function have been demonstrated by nuclear magnetic resonance and single fibre electro-myoography including a failure to coordinate oxidative metabolism with anaerobic glycolysis causing abnormally high intracellular acidosis, consistent with the early fatigability and the slow recovery from exercise in ME.

Coxsackie viruses can initiate non-cytolytic persistent infection in human cells. Animal models demonstrate similar entero viral persistence in neurological disease, myopericarditis and the deleterious effect of forced exercise on persistently infected muscles. These studies elucidate the exercise-related morbidity and the chronic relapsing nature of ME.

Diagnostic pitfalls in entero virology

Asymptomatic enteroviral carriage is common (it is the rationale for oral polio vaccine) and caution is required in the interpretation of conventional laboratory tests or case/control studies. Virus isolation (unless from a sequestered site) may lack significance and the difficulty is compounded by an early and abundant neutralizing response. Acid dissociation of the virus from neutralizing antibody has been used to permit direct culture and the
production of a monoclonal antibody (5 D 8/1), directed against a viral protein component (VPI) exclusive to enteroviruses, has demonstrated persistent bowel infection leading to systemic disease with VPI antigen, free or bound to antibody, in the circulation of patients with ME. Of 40 patients in our study referred for VPI testing, 20 had positive results.

Conclusions

Clinical, laboratory, and epidemiological data support the suggestion that ME is a complication in non-immune individuals of widespread subclinical NPEV infection.

ME predominantly affects the most socially and economically active section of society. Misinterpretation of this common illness as psychogenic delays the early recognition mandatory for modification of life style which may avoid progression to chronic disability. Other forms of therapy are disappointing. Despite the use of prophylactic anti-enteroviral drugs in animal research, the control of enteroviral infection in humans still depends upon immunization and measures to improve public hygiene.

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