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Muscular effects in late polio

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ABSTRACT

New or increased muscular weakness, fatigue and muscle and joint pain with neuropathic electromyography (EMG) changes in a person with a confirmed history of polio constitute the cardinal symptoms of the post-polio syndrome. Unusual tiredness or fatigue is a common complaint in late polio subjects as is intolerance to cold. Fatigue in polio subjects can have several explanations: emotional fatigue, central nervous system fatigue, 'general' fatigue and/or neuromuscular fatigue. Some studies indicate central fatigue, but it is unclear how often and to which degree there will be a central muscular fatigue. Polio patients are known to be deconditioned (reduced function because of low activity level), and aerobic power is reduced. Defects in the neuromuscular transmission may be present but are not seen in all post-polio subjects with reduction in force and increased fatigability. The fatigue experienced by late polio patients is most likely an augmented peripheral muscle fatigue. Possible explanations may be an imperfection in the sarcoplasmatic reticulum with altered calcium release mechanisms (activation) or in sliding filament function (contractile properties). This may be a secondary effect to the enlarged muscle fibres. However, the prolonged subjective feeling of fatigue reported despite unchanged maximal voluntary contraction (MVC) remains unexplained.

Keywords biopsy, EMG, endurance, fatigue, postpolio, skeletal muscle, spectroscopy.

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After the introduction of the immunization programme in the mid-1950s, poliomyelitis was rapidly eradicated in developed nations. Sweden has used the Salk vaccine, which requires inoculation. This vaccine is produced from a mixture of types I, II and III virus strains and is heated to kill the viruses. The Sabine vaccine dominates in the rest of the world and is produced by weakening the living viruses and given perorally, thereby theoretically rendering immunity in the gut, which is the entry port for the wild virus. Before the start of the vaccination programme, many people contracted the disease each year, especially during late summer and early fall. Patients with acute polio typically have an acute biphasical viral illness with fever, headache and gastrointestinal symptoms, followed several days later by the rapid development of paralysis. The paralysis is caused by an invasion of neurotrophic polio virus in motor neurones, which is followed by neuronal damage or death. The progression of paralysis usually stops in less than a week, after which there is a period of stability followed by some degree of gradual recovery of function. A main factor for recovery is the result of sprouting and reinnervation of muscle by the surviving motor neurones.

THE POST-POLIO SYNDROME

In survivors of acute paralytic polio, new symptoms occurring decades after the acute illness phase are sometimes referred to as post-polio syndrome (PPS) (Tufvesson 1984). The syndrome encompasses such general complaints as fatigue, cold intolerance, musculo-skeletal manifestations, such as muscle and joint pain, neurological manifestations, such as progressive weakness and atrophy, and sometimes sleep-disordered breathing problems. Criteria for the diagnosis of PPS were outlined first by Halstead & Rossi (1987) and revised by Halstead & Gawne (1996). New or more severe muscular weakness, fatigue and muscle and joint pain with neuropathic electromyography (EMG) changes in a person with a confirmed history of polio constitute the cardinal symptoms of the post-polio syndrome (Halstead & Gawne 1996). Unusual tiredness or fatigue is a common complaint in late polio subjects who report new symptoms many years after the onset of disease (Cosgrove *et al.* 1987). Cold intolerance is an often reported symptom (Halstead 1998, Gandevia *et al.* 2000).

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The occurrence of PPS has been found to relate to older age at the onset of disease (Halstead & Rossi 1985), the severity of the original symptoms (Halstead & Rossi 1985, Agre & Rodriguez 1990) and a longer time to reach recovery (Klingman *et al.* 1988). While a number of aetiologies have been proposed in recent years to explain the pathological changes that cause the symptoms (Jubelt & Cashman 1987), the question remains unanswered.

MUSCULO-SKELETAL SYMPTOMS

Musculo-skeletal symptoms are often the reason why persons with late polio re-establish contacts with the health establishment. Symptoms may include fatigue, increase in skeletal distortions or pain in biomechanically disadvantaged joints. General orthopaedic problems are quite common (Agre *et al.* 1989). About one-third have orthoses that are not functioning properly (Perry & Fleming 1985) or are in need of orthoses to compensate for a weak calf muscle while walking (Perry *et al.* 1995). The impact on the disability level is mainly on mobility-related activities and different physical demands at work and in the home, as paresis seems to be more common in the lower than in the upper extremities (Cosgrove *et al.* 1987, Einarsson & Grimby 1990, Grimby & Thorén-Jönsson 1994).

The impairment in patients' muscles varies from none to severe. Early recovery within a few weeks after the acute phase is probably a result of the revival of affected but not degenerated motor neurons. Recovery within the first year is thought to be accomplished through collateral sprouting, i.e. nerve twigs branching off from surviving motor neurones overlapping the denervated ones. Late compensatory effects are caused by increased size of the remaining innervated muscle fibres (Borg *et al.* 1988) in weak muscles used in daily activities. As a result of this, even normal muscle strength and presumably normal muscle volume can be present despite an estimated loss exceeding 50% of the number of motor neurones. It seems that there is a relationship between the initial degree of involvement and the effect of various compensatory mechanisms and the subsequent clinical picture. The severity of the original paralysis and the degree of recovery have been reported to predict the risk of new weakening (Klingman *et al.* 1988). Two follow-up studies by Grimby *et al.* (1994, 1998) showed evidence of progressive loss of muscle strength in the knee extensors. A comparative study between Swedish and American postpolio subjects reported similar trends (Agre & Grimby 1995). However, in a population-based cohort study in Olmstead county, Minnesota (Windebank *et al.* 1996), no progress in deterioration was noted in muscle strength owing to loss of motor neurones over a 5-year period, although the methods used for testing muscle strength and EMG differed from the earlier mentioned studies and might explain the different findings.

The motor units are enlarged by reinnervation, and the macro motor units' potential can be demonstrated to increase by more than seven-fold in relation to normal values for the age in question (Einarsson *et al.* 1990). Even muscles that are clinically not weak are often affected (Luciano *et al.* 1996). The consequence of this is that the drop-out of such a large motor unit has a much greater functional impact than that of a motor unit of normal size (Stålberg & Grimby 1995, Grimby *et al.* 1996, Grimby *et al.* 1998). There is evidence of unstable neuromuscular connections in the periphery, as suggested by increased jitter and blocking of nerve transmission, as detected by EMG signals (Wiechers & Hubbell 1981, Einarsson *et al.* 1990). Electromyography and muscle biopsy evidence of ongoing denervation cannot yet distinguish between stable and unstable polio patients (Cashman *et al.* 1987, Ravits *et al.* 1990).

In weak muscles, the fibres adapt with hypertrophy (Grimby & Einarsson 1987). Examination of muscle biopsies from the tibialis anterior in patients with excessive overuse showed that almost all were type I fibres (Borg *et al.* 1988). Muscle fibre transformations occur in polio patients, which seem to depend on the functional demand on the muscle (Borg *et al.* 1989). These results were confirmed in another study whose results show that contractile properties of the overused muscle did not change in parallel with fibre type (Tollbäck *et al.* 1992).

FATIGUE

Many individuals with late effects of polio complain of fatigue that they describe as 'increasing physical weakness', 'a sensation of loss of strength during exercise' and 'heavy sensations in the muscles' (Berlly *et al.* 1991). This common complaint in polio subjects can have several explanations, i.e. emotional fatigue, central nervous system fatigue, 'general' fatigue and/or neuromuscular fatigue (Basmaijan 1978). There is a chain of command for muscular contraction involving a number of steps from the brain to the spinal cord and the peripheral nerve all the way to the actin-myosin cross bridges within the muscle fibres (Edwards 1983). Briefly, central fatigue may occur as a malfunction of nerve cells or inhibition of voluntary effort.

Muscular fatigue can be defined (Edwards 1981) as a failure to maintain the required or expected force. This fatigue may be either because of central or peripheral performance elements. Electromyography can be used to evaluate fatigue. Alterations of the EMG signal over

time, expressed as Root Mean Square (RMS), will mainly reflect changes in muscle activation, such as firing rate, and number of active motor units.

Central fatigue is defined as a voluntary or involuntary failure of neural drive resulting in (a) a reduction in the number of the functioning motor units and (b) a reduction in motor unit firing frequency. Reduction of the RMS during maximal voluntary activation may indicate central fatigue. In a study carried out by our group, however, we could not demonstrate a change in the RMS signal at repeated MVC (maximal voluntary contraction) with successively increasing ramp levels of isometric contractions (Sunnerhagen *et al.* 2000). This finding would indicate a lack of central fatigue in this particular set-up, where the required force at each step was in proportion to the individual MVC.

Peripheral fatigue may occur either at the neuromuscular junction and cell membrane (excitation), the calcium release mechanism (activation) or at the sliding filaments (contractile processes). A progressive spectral compression of the EMG signal towards lower frequencies has been suggested to be related to peripheral fatigue during sustained contractions (Lindström *et al.* 1970). Thus, muscle fatigue can be studied by means of the mean power frequency (MPF).

GENERALIZED FATIGUE

'General' fatigue can be caused by cardiorespiratory deconditioning (reduced function because of low activity level). Polio patients are known to be deconditioned, and aerobic power is shown to be reduced (Owen & Jones 1985, Owen 1991). This has more recently been reconfirmed in both Norway (Stanghelle *et al.* 1993) and Sweden (Willén *et al.* 1999). The explanation is probably muscular impairment, which limits the patients' ability to be active enough to put demands on the cardiorespiratory system. This can theoretically be normalized through exercise aimed at influencing the cardio-respiratory system, for instance with a modified walking programme (Dean & Ross 1988), aerobic exercise (Jones *et al.* 1989, Dean & Ross 1991), endurance training (Ernstoff *et al.* 1996) or pool exercise with an emphasis on endurance (Willén *et al.* 2001). For some patients, ventilatory capacity may be a limiting factor leading to fatigue of the respiratory system (Stanghelle *et al.* 1993, Sinderby *et al.* 1996).

Fatigue that may be related to changes within the central nervous system has received interest. Post-mortem studies have showed the presence of polio virus lesions in the midbrain reticular formation, posterior hypothalamus, thalamic nuclei, putamen and globus palladus (Bodian 1949, Bruno *et al.* 1991). Magnetic resonance imaging of the brain has also shown hyperintensive signals in approximately the same areas in survivors who reported fatigue (Bruno *et al.* 1994). There is no clear-cut evidence that emotional fatigue or depression is more common in polio patients than others (Liechty 1995).

In the literature, it is reported that individuals with late polio use their muscles in many daily activities close to the maximum capacity (Borg *et al.* 1988, Willén & Grimby 1998, Nollet *et al.* 1999), indicating a correlation between muscle overuse and fatigue (Borg *et al.* 1988, Perry *et al.* 1988).

Reduced capillarization may be expected, especially in relation to the very large fibre area, but no conclusive results have been reported. Borg & Henriksson (1991) found relatively few capillaries in the tibialis anterior in relation to the large fibre area. A reduction in capillarization over an 8-year follow-up period has been reported (Grimby *et al.* 1998), although the values were not significantly different from controls. Also, there were low values of citrate synthetase.

A defect in the neuromuscular transmission has been discussed, and Trojan *et al.* (1993a) reported defects in neuromuscular transmission in patients with post-polio fatigue, which led to trials with acetylcholinesterase inhibitors to reduce the development of fatigue. However, a multi-centre trial showed no significant difference between acetylcholinesterase inhibitor and placebo (Trojan *et al.* 1999) in measures of quality of life, isometric strength or fatigue (Trojan *et al.* 1999). In the studies by Stålberg & Grimby (1995) and Grimby *et al.* (1998), jitter and blocking were reported but not such that could explain the reduction in force to any large extent. Defects in neuromuscular transmission as a major cause of muscular fatigue could not be suggested on the basis of findings in studies using electrical stimulation of the peroneal nerve (Sunnerhagen *et al.* 2000).

RECOVERY AFTER FATIGUE

The recovery period after exercise has raised special attention in polio victims both because of the patient history of prolonged fatigue and some experimental results. Agre & Rodriguez (1990) demonstrated a reduced recovery rate of MVC after sustained submaximal isometric contractions until fatigue. They also demonstrated that performance increased when sufficient rest periods were given between the contraction periods (Agre & Rodriguez 1991). An interesting but unexplained finding is that the perception of fatigue remains for days in polio victims after a fatiguing exercise but without reduction in MVC (Agre *et al.* 1998). One possible explanation is low frequency fatigue, which is characterized by a substantial

reduction of tension at low frequencies of stimulation (Edwards *et al.* 1977). A feature of this low frequency fatigue is that it can take more than 1 day for full recovery and this may contribute considerably to the feeling of weakness in muscle groups after intense exercise. From studies of isolated single fibres of mouse skeletal muscle, we know that tetanic calcium is reduced in low frequency fatigue (Westerblad *et al.* 1993), which is probably caused by a reduction in Ca^{2+} release from the sarcoplasmatic reticulum.

In our own studies using a protocol with increasing intermittent work (Sunnerhagen *et al.* 2000, H. Ljungberg, K.S. Sunnerhagen, B. Uikhoff-Baaz *et al.*, unpublished), no differences were found in the metabolic changes in the tibial anterior muscles as shown by MR phosphorous spectroscopy between a group of polio patients with a moderate reduction in the tibialis anterior volume and strength (median 58% of control values) and healthy controls of similar ages. Differences between the polio and the control groups could be noted during the recovery phase, and the recovery half time for Pi (inorganic phosphate) was significantly longer for the patients than for the healthy control group (Ljungberg *et al.* unpublished). In general, the polio group showed a larger individual variation in the results from the MR spectroscopy both with respect to metabolite concentrations and pH values after exercise, which may be explained by the heterogeneity of fibre type proportions and muscle enzyme levels in the polio patients.

CONCLUSIONS

Fatigue is a complex phenomenon or many complex phenomena. Part of the difficulty in identifying fatigue is the lack of a clear definition of the word itself. The relative workload is different for different muscles in everyday activities, and thus limiting weakness in one leg is often described as fatigue. Some studies indicate central fatigue in patients with the post-polio syndrome (Bodian 1949, Bruno *et al.* 1994), but it is unclear how often and to what degree there will be central muscular fatigue. Defects in neuromuscular transmission might be present in post-polio patients (Trojan *et al.* 1993b) but will probably not explain the reduction in force that is present and the development of fatigue to any major degree (Stålberg & Grimby 1995, 1998). There is most likely a development of augmented peripheral muscle fatigue in polio patients. Possible explanations may be an imperfection in the sarcoplasmic reticulum with altered calcium release mechanisms (activation) or in the sliding filaments (contractile properties). This might be a secondary effect to the enlarged muscle fibres. The prolonged subjective feeling of fatigue reported despite unchanged MVC (Agre *et al.* 1998) may be because of low frequency fatigue.

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