REVIEW

Electrical injury and amyotrophic lateral sclerosis: a systematic review of the literature

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Electrical injury may act as a potential precipitating or risk factor for amyotrophic lateral sclerosis (ALS). A systematic review of the literature was undertaken to assess the relationship between electrical injury and the development of ALS. Information for the review was obtained using five medical databases, and from manual searching of individual papers. Patients presenting with a neurological syndrome after electrical injury, including lightning, were included and classified into four categories: ALS; progressive upper motor neurone (UMN) syndrome; progressive lower motor neurone (LMN) syndrome; and non-progressive syndrome. Linear regression and χ^2testing were used for analysis of the data. 96 individuals, comprising 44 with ALS, 1 with a progressive UMN syndrome, 7 with a progressive LMN syndrome and 44 with a non-progressive syndrome, were identified from 31 papers with publication dates between 1906 and 2002. The median interval between electrical injury and disease onset was 2.25 years for all progressive syndromes and just over 1 week for the non-progressive syndrome. The more severe the shock (excluding lightning), the more likely individuals were to have a non-progressive motor syndrome. A non-progressive spinal cord syndrome is associated with more severe electrical injury. Overall, the evidence reviewed does not support a causal relationship between ALS and electric shock.

A supplemental table is available at http://jnnp.bmj.com/supplemental

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Amyotrophic lateral sclerosis (ALS), also known as motor neurone disease (MND), is a progressive, degenerative disorder of the central nervous system characterised by relatively selective damage to corticospinal tract neurones and to α-motor neurones of the brain stem and spinal cord. Although 5–10% of ALS cases have a family history usually indicating an autosomal dominant form of inheritance,[1] about 90% are apparently sporadic. In sporadic ALS, the cause is unknown, although there are many hypotheses.[2] As ALS is a disorder of ageing,[3] epidemiological studies have sought factors that predispose or trigger the disease, but none has been identified. Recent interest has focused on physical activity, exposure to endogenous or environmental toxins, and injury of various sorts including injury from electric shock.[4–7] Kurtzke[8] considered that ''evidence is good that physical trauma, whether mechanical, electrical, or operative, and whether measured by fractures alone or by less severe injury, is the strongest and most consistent risk factor'' for ALS. A systematic review, however, concluded that injury was not definitely associated with risk for ALS.[9] It is possible, nevertheless, that environmental insults including trauma or electrical injury could represent triggers of the pathological process that, once initiated, could activate a molecular cascade leading to progressive loss of motor neurones. It is important therefore to determine whether environmental insults such as electric shock have a pathogenic role in ALS. Unfortunately, it is not easy to answer this question, even using well-designed, population-based samples[9] as retrospective evidence is difficult to acquire and may be unreliable because of recall bias in patients compared with controls.[10] It has been claimed that electricians have a higher risk of developing ALS compared with those in other occupations partly because of exposure to power frequency electromagnetic fields.[11–13]

Before considering prospective studies of electrical injury as a possible trigger for neurodegenerative diseases including ALS, we decided to undertake a systematic review of all the existing literature, which extends back to 1906.

METHODS

Source of papers

The information for this review was obtained using the five medical databases PubMed/Medline (January 1966 to October 2005), Cochrane Database of Systematic Reviews (1993 to October 2005), AMED (January 1985 to October 2005), LILACS (January 1982 to October 2005) and Embase (January 1980 to October 2005); and from manual searching of the individual papers included in the review. The search for relevant articles in the online databases was carried out using the keywords ''MND/ALS and electrical injury/shocks'', ''ALS/MND and lightning'', ''neurological syndromes following electric shocks/injury'', ''neurological syndromes following lightning'', ''spinal/neurological sequelae following electric shocks/injury'' and ''spinal/neurological sequelae following lightning''.

Diagnostic classification

As the clinical data in the papers were often insufficient to classify patients by the original[14] or revised[15] El Escorial Criteria, we devised a modified classification that allowed us to categorise patients according to the certainty of diagnosis, using principles similar to those of the El Escorial Criteria. We sought evidence of combined upper motor neurone (UMN) and lower motor neurone (LMN) signs in several regions, reasonably complete information on supportive evidence (eg electromyography findings) and exclusion of other

Abbreviations: ALS, amyotrophic lateral sclerosis; LMN, lower motor neurone; MND, motor neurone disease; UMN, upper motor neurone

disorders (''ALS mimics''). Four categories were defined: ALS, progressive UMN syndrome, progressive LMN syndrome and non-progressive syndrome. Specifically, patients were considered to be a part of the ALS group if they had a combination of UMN and LMN signs (evidence of LMN involvement on electromyography was accepted) in one or more regions with progression over ⩾6 months and adequate investigations to exclude ALS mimics, had a combination of UMN and LMN signs with progression or had been diagnosed as having ALS by a neurologist. The regions used were cranial, thoracic, cervical and lumbosacral. Patients were considered to have a non-progressive syndrome if they had a non-progressive UMN and LMN syndrome (no progression after 6 months from injury), a pure LMN syndrome without progression, a pure UMN syndrome without progression, or a myelopathy or other neurological condition specified by the authors.

Statistical methods

Some individuals were recorded as having had more than one shock. In these cases we used the median age at shock for calculations. Similarly, for disease in more than one area, the highest area was used. Four categories of shock strength were used: <300 V, 301–1000 V, >1000 V and lightning strike. Data were analysed using Microsoft Excel 2003 and SPSS for Windows V.11.01. We assumed that the risk of disease onset was linear with time from shock. Linear regression was used to assess the relationship between shock strength and disease onset. χ^2 Testing was used to test the hypothesis of no association between the nature of the neurological syndrome and shock strength.

RESULTS

Papers

Thirty one papers were identified, with publication dates between 1906 and 2002. A single case of ALS with a history of recent electrical trauma was identified from the database in the department.

Diagnostic classification

Ninety six individuals were described (see supplementary table at http://jnnp.bmj.com/supplemental). Of these, 44 could be classified as having ALS, 44 a non-progressive syndrome, 7 a progressive LMN syndrome and 1 a progressive UMN syndrome. There were 89 males (93%) and 7 females (7%). Two of the females had ALS and five a non-progressive syndrome. Only three cases had pathologically confirmed ALS at autopsy (table 1). The clinical description of these cases fulfilled the criteria for ALS according to our classification criteria.

Time between shock and disease onset

For 78 individuals no data were available on the delay between shock and onset of a motor syndrome. For ALS, there were 35 individuals with a range of approximately 2 weeks to 45 years and a median of 3 years. Including all those with any progressive motor syndrome increased the number of individuals with data to 40, with a range of a few days to 45 years and a median of 2.25 years from electrical injury to onset of the neurological syndrome. For those with a non-progressive syndrome ($n = 38$), the range was 0–2 years and the median was just over 1 week.

Shock and clinical presentation

In the ALS group, 18 had disease onset in the upper limbs, 6 in the lower limbs and 1 had bulbar onset. For the remainder with a progressive motor syndrome, six had upper limb onset, one lower limb onset and one had bulbar onset. For those with a non-progressive syndrome, 21 had onset in the lower limbs, 10 in the upper limbs and 1 had bulbar onset. For the remaining cases, this information was not available.

Only 2 of the 19 cases in the ALS group for whom there was information had a site of onset that was different from the entry or the exit point of the current. Details were lacking for the individual with a progressive UMN syndrome, but for those with a progressive LMN syndrome, only one of the six with information had a site of onset that was different from the entry or the exit point of the current. In the non-progressive syndrome group, only 3 of the 17 with sufficient information available had a site of onset that was different from the entry or the exit point of the current.

Shock and pattern of disease

In general, the more severe the shock, the more likely the individuals were to have a non-progressive motor syndrome (table 1, excluding lightning: $\chi^2 = 26$, $df = 2$, $p = 2\times10^{-6}$). Numbers were insufficient to be sure if this trend was true for lightning strike.

In general, the more severe the shock (including lightning), the shorter the interval between shock and disease onset, but this was a weak relationship ($r^2 = 0.12$, $p = 0.004$). In addition, age at shock predicted delay in disease onset, with a younger age at shock weakly but significantly predicting a longer delay in disease onset ($r^2 = 0.15$, $p<0.001$). This effect of age at shock was true even for non-progressive syndromes considered in isolation and was not therefore an effect of the later age at onset of ALS ($r^2 = 0.17$, $p = 0.010$). There was no relationship between age at shock and current strength, and, when both variables were included in a regression model, the model was still significant, as were the individual factors ($r^2 = 0.22$, model $p<0.001$, age at shock $p = 0.005$, current strength $p = 0.016$).

DISCUSSION

The evidence from this systematic review clearly indicates that there is a syndrome of non-progressive spinal cord damage after electrical injury. This syndrome is often associated with site of onset at the entry or exit point of the current, and is associated with more severe electrical injury. Patients with non-progressive syndromes may recover partially or completely (table 1). Severe electrical injury, including lightning strike, is predictive of a more rapid onset of symptoms and signs for all syndromes. Severe electrical injury predicted non-progressive syndromes whereas cases with progressive syndromes including ALS reported in the literature had mild electrical injury. The most parsimonious explanation is that stronger shocks result in myelopathy, and the ALS cases associated with mild shock are then a result of recall and publication bias. Furthermore, age at shock predicted delay in disease onset, with a younger age at shock associated with a longer delay in disease onset. This effect of age at shock was also true for non-progressive syndromes and was therefore not an effect of the later age at onset of ALS. The explanation of the relationship between younger age at shock and longer interval between shock and disease onset is uncertain and may be related to the altered vulnerability of the ageing nervous system. Further, for 35 of the 44 cases with ALS, for whom there was information, the median age at onset of ALS after the electrical injury was 36 years. This earlier age at onset of ALS is most probably related to occupational bias, as young men are more likely to be employed as electricians and experience electric shocks at work.

In most cases classified as ALS for which information was available, the site of onset of the disease was either at the entry or exit point, suggesting a causal relationship between injury and neurological disease. It is, however, difficult to explain the significance of this observation, as in 25 of the 44 cases in this group sufficient information was lacking, and this relationship was also true for non-progressive syndromes. Thus no firm

Table 1 Distribution of cases with progressive and non-progressive syndromes with different strengths of electrical injury including lightning

	No of cases			
	<300V	301–1000V	>1000V	Lightning
Progressive	21	12	7	6
Non-progressive	3	5	25	4

conclusions can be drawn about the relationship between site of injury and type of syndrome (ALS vs non-progressive disease).

For all progressive motor neurone syndromes, the median interval between electrical injury and disease onset was 2.25 years. This contrasts with the non-progressive syndromes in which the median delay between electrical injury and the onset of disease was only just over 1 week. This suggests that the patients classified with progressive syndromes are heterogeneous. In non-progressive cases in which neurological deficits follow electrical injury within a few days or a week, a causal relationship is likely.

Another striking, but predictable observation is that there is a strong male predominance (93% male, 7% female), which may reflect an occupational bias. Of greater interest is the paucity of patients with bulbar onset in the progressive syndrome group. For 33 patients with a progressive syndrome for whom information on site of onset was available, only 2 had bulbar onset. In most clinic-based and population-based studies, the proportion of bulbar-onset ALS cases is about 25%.[16] The rarity of bulbar onset in the progressive group may be related to the sex ratio in cases reviewed here, as elderly women are more likely to have bulbar-onset ALS,[17] but this cannot be the complete explanation. This apparent under-representation of bulbar-onset disease was also evident in the non-progressive syndromes, most likely because the neurological syndrome is related to the site of injury, which is usually in the limbs.

Unfortunately, there is relatively little information on neuropathological changes associated with electric shock as related to the syndromes described in this study. Furthermore, among all the cases we have reviewed, in only three was ALS pathologically proved (<3%). A variety of mechanisms, including excitotoxicity and microglial activation, might contribute to ongoing damage if electrical injury were acting as a trigger factor for ALS.[2 18 19] Electrical injury may cause a wide range of morphological changes in the central nervous system.[20–25] Cellular changes include neuronal chromatolysis, neuronophagia and neuronal loss. Microglial activation, which is an early event in central nervous system damage,[26] is prominent, as is infiltration of blood-borne macrophages and neutrophils.[27] Electrical injury might thus be expected to trigger a cascade of cellular damage in individuals at risk of developing ALS—for example, those carrying SOD1 gene mutations. Even sporadic ALS may be associated with genetic risk factors,[28 29] and the increased risk of ALS in military personnel or other occupational groups[30] might be related to genetic selection.[31] Thus, the notion that injury might trigger a cascade of neuronal damage is applicable to both familial and sporadic ALS. The fact that our review does not support this concept is therefore somewhat surprising, but may suggest that such cascades are intrinsically generated and propagated and are not significantly influenced even by major focal insults.

Two population-based case–control studies found no association between electric shock and ALS [32 33]; in particular, in the study conducted in Western Washington State[32] no statistically significant association was found and this quality of finding was deemed to be high in a subsequent review.[9] Similarly, the Scottish Motor Neurone Disease Register Case–Control Study demonstrated no significant difference between patients and controls in number of electric shocks [33]; however, the quality of these findings were rated lower owing to lack of actual numbers and confidence intervals.[9] These studies highlight the difficulties in designing a case–control study to provide high-quality evidence in support of risk factors affecting a small number of patients because, apart from an increased likelihood of bias, small patient numbers do not lead to generation of reliable dose–response data.

Unquestionably, the most comprehensive review of the neurological sequelae of electrical trauma to date is that of Panse,[24] but this does not provide a systematic analysis of the relationship between electrical injury and ALS. Panse noted that ALS is extremely rare in victims of electrical accidents and quotes Pietrusky (quoted by Panse) who studied the records of 797 victims of electric accidents and found only one relevant case. Panse quotes that ''certainly, this harvest of spinal atrophic sequelae with a progressive course and (usually) spastic components culled from the whole world literature is not very impressive''; he, however, believed that he could not exclude a causal relationship between electric trauma and a syndrome identical with ALS.

Our systematic review of the literature on the relationship between ALS and electrical injury indicates that a syndrome of non-progressive spinal cord damage, often with both LMN and UMN components, is strongly linked to more severe shock, and that the onset of disease is closely related to time from the injury. A well-defined entry or exit point is common in such cases.

The relationship between electric injury and ALS is less certain, and the evidence reviewed does not support a causal relationship between ALS and electric shock. Only systematic prospective studies could resolve this, but epidemiological evidence, although incomplete, does not suggest that electrical trauma is associated with increased risk of developing ALS. However, ALS is a heterogeneous disorder and it is possible that in some individuals electrical trauma (or other forms of trauma) could trigger the disease process.

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