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Risk Factors in Monomelic Amyotrophy - A Case Control Study

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Abstract

A number of factors were examined for their association with monomelic amyotrophy in a case-control study. Twenty-one cases and 63 control subjects matched for age, gender and place of residence were interviewed using a pretested structured questionnaire. Nature of occupation, handedness, exposure to infectious diseases and toxins, close contact with animals, mechanical and electrical injuries and family history of neurological disorders, were some of the important factors examined. Heavy physical activity emerged as the only factor with a significant odds ratio (OR) of 4.67 (1.44-15.20). Further analysis showed that nature of occupation or injuries resulting from physical activity were not significantly different in cases and controls. Dementia in the family, ($Z=2.37$; $p<0.05$), contact with domestic animals ($z=1.14$; NS) and varicella in childhood (X^2-4.21; $p<0.05$) emerged significant on the univariate statistics between the groups, although they did not attain a significant odds ratio. The frequency of exposure to lead, antecedent history of poliomyelitis and handiness did not differ between cases and controls.

Key words -

Monomelic amytrophy,
Motor neurone disease,
Risk factors,
Aetiology,
Case control study,
Occupation,
Injuries,
Varicella,
Poliomyelitis,

Dementia

Monomelic amyotrophy (MMA) with the characteristic features of wasting and weakness usually restricted to a single upper or lower limb, occurrence in young males, a benign outcome and evidence of lower motor neurone involvement is a well recognised entity [1] [2], [3], [4]. Bulbar cranial nerves, cerebellar, extrapyramidal, pyramidal and sensory systems are spared. The unique geographic distribution to Asia including Japan, India and Sri Lanka has aroused considerable interest [5]. The possible role of viruses and circulatory insufficiency are considered in the aetiopathogenesis of MMA [6], [7]. Several studies have reported the risk factors in motor neurone disease (MND) [8], [9], [10], [11] but none so far on monomelic amyotrophy, a begin a typical form of MND. In the present study, we determined the possible risk factors which may predispose to the development of atrophy of single limb through a case-control design. Since both MND and MMA are chronic anterior horn cell disorders, certain selected antecedent events considered to have a role in the aetiopathogenesis of MND were examined for their association with monomelic amyotrophy.

Methods

Sixty-five patients of MMA were seen in our Institute during the period 1977 to 1991. Among them, 21 patients came from the city of Bangalore and the surrounding rural areas within a radius of 100 kms. In some studies, questionnaires are mailed to the respondents for completing the information. We preferred to personally interview the cases and controls so that reliable data would be obtained and errors in recording the information due to low level of literacy could be avoided. Therefore, the number of cases were restricted to those who could attend the personal interview. Three controls matched for age, gender and place of residence were selected for each case. (Consent of the subjects was obtained before administering the questionnaire).

Selection of patients

Inclusion criteria

Patients who fulfilled all the following criteria were included in the study:

(a) atrophy and weakness confined to a single limb
(b) onset of disease in second to fourth decade
(c) clinical features of lower motor neurone lesion with evidence of neurogenic process on electrophysiology and muscle histopathology and
(d) A normal myelogram/spanial CT scan.

Exclusion criteria

(a) Frank evidence of pyramidal tract involvement as seen by the presence of spasticity, exaggerated tendon jerks and extensor plantar response (brisk reflexes in isolation were not considered as an exclusion criteria) and
(b) involvement of bulbar cranial nerves, sensory system, brain stem, cerebrum, cerebellum and extrapyramidal system.

Selection of controls

Three controls were selected for each patient matched for age (± 3 years), gender and place of residence. Of the 63 controls, 17 were family members and 46 were from the neighbourhood.

Questionnaire

The questionnaire consisted of 90 items covering sociodemographic information and address, personal

habits, occupational history with special reference to exposure to toxins/chemical substances, injuries, sports, childhood infectious diseases, presence of neurological disorders, environmental factors, family history of neurological disorders and exposure to animals.

Identification details including age, gender, birth order, place of residence, level of education, socio-economic status and consanguinity of the parents were recorded. Since right limb is twice often affected as the left, 6 questions were included to determine the handedness. Information on tobacco and alcohol consumption with details of frequency, amount and duration was collected. Specific questions on intake of unboiled milk was included. Details of occupation during the 5 years preceding the onset of illness in the cases and a matched period in controls was obtained. Additional information on nature of work and duration of employment was recorded. Exposure to various toxic metals, pesticides, insecticides, radioactive material at place of work or residence and duration of exposure were noted. Mechanical injuries such as road traffic accidents, fall from height, penetrating injury and surgical procedures and electrical injury along with specific details of site and severity were noted. In cases the interval between injury and onset of illness was recorded. Specific information related to participation in sports particularly those involving severe physical effort like wrestling, boxing, athletics, karate and kabaddi and other games was elicited. History of infectious diseases in childhood like poliomyelitis, mumps, measles, varicella and infections including encephalitis, tuberculosis were enquired. Care was taken to record blood transfusion and exposure to sexually transmitted diseases. The source and nature of drinking water and presence of factories in the vicinity of residence were enquired. Close contact with animals like cow, buffalo, pig, dog, cat and birds in the house or at place of work was recorded. A specific question was included regarding exposure to dead animals in slaughter house or in the villages where such a contact is likely to occur. Special care was taken to elicit history of MMA in the family. Other neurological disorders including MND, dementia, parkinsonism, movement disorders, spinocerebellar degeneration and epilepsy in cases, controls and their family members was recorded.

Data collection

Patients who responded to letters were interviewed in the hospital. Family and neighbourhood controls were identified with the assistance of the patient and accompanying relative. The questionnaire was administered to the controls at their house. A few patients who did not respond to letters due to change in residence were traced with the help of local authorities, neighbours, and colleagues at work place.

Data analysis

Data from cases and controls was analysed using the EPI-INFO 5 package. Odds ratio, Chi-square values, 95% confidence interval limits was obtained for all the factors investigated.

Results

The mean age of the cases (CA) and controls (CO) was 33.43 ± 11.53 and 33.21 ± 10.58 years, respectively. There were 16 males and 5 females among cases and 48 and 15 in the control group respectively, with a male to female ratio of 3.3:1. In the cases, the right upper limb was affected in 10 patients (47.6%), left upper limb in 5 (23.8%) and right lower limb in six (28.6%). All the cases and controls reported that they were right handed.

The results of analysis of various factors are shown in Table I. The place of residence (rural/urban), socio-economic status, literacy level, consanguinity among parents and type of occupation were similar in cases and controls. A further analysis of occupation based on the nature of work in terms of the physical activity revealed that more cases than controls were involved in heavy physical activity and this difference was significant (OR=4.67, 95% CI 1.44-15.20). Consumption of unboiled milk, unsafe water, tobacco and alcohol and sexually transmitted disease were not significantly different among cases and controls. Among the various environmental factors, close contact with animals was significantly ($p<0.05$) more common among cases as compared to controls. Twelve cases and 20 controls reported exposure to animals including cows (CA=6, CO=15), buffaloes (2.:2), pig (2:1) and pet dogs (2:2). Exposure to lead, pesticides and industrial pollutants was not dissimilar in the two groups. Injury due to trauma, electric shock and surgical operations as also sports activity were not significantly different in cases and controls (Table II). Detailed information of the site of injury, interval between injury and onset of illness along with limb affected in cases is shown in Table III. In eleven out of 21 cases there was a preceding history of injury with the interval between injury and onset of symptoms varying from 6 months to 18 years (mean 7.7 years). It is noteworthy that in 7 of them, progressive atrophy occurred in the previously injured limb. Among a number of infectious disease and neurological disorders, a positive association was found only with varicella ($p<0.05$) and dementia in family members ($p<0.05$) (Tables IV and V). Varicella in childhood was reported by 10 cases and 15 controls. The frequency of poliomyelitis was surprisingly low in both cases and controls (CA-1;CO-2). Clinically evident dementia was seen in close relatives of 4 cases (elder brother, grandfather, grandmother) and 2 controls (elder brother and cousin). Other degenerative disorders of nervous system including motor neurone disease, parkinsonism and spinocerebellar degeneration were not reported among cases, controls or their family members.

Table I - Monomelic amytrophy: Socio-demographic, personal and environmental factors

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Table II - Monomelic amyotrophy: Injuries in cases and controls

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Table III - Monomelic amyotrophy: Site of injury interval and limb affected in cases

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Table IV - Monomelic amyotrophy: Antecedent illnesses

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Table V - Monomelic amyotrophy: Neurological disorders in cases, controls and family members

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All the significant risk factors in monomelic amytrophy are listed in Table VI. Heavy physical activity

emerged as the most significant contributory factor with an elevated odds ratio. Contact with animals, antecedent infection with varicella and dementia in family did not have an increased odds ratio but were statistically significant.

Table VI - Monomelic amyotrophy: Significant risk factors

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Discussion

The present report is the first study to identify risk factors in monomelic amyotrophy. The data clearly show that heavy physical activity was the most significant factor present with a greater frequency in cases as compared to controls. Injuries and type of occupation (farmer, labourer etc.) when examined separately did not show a significant difference between the two groups. The preponderance of young men (76.2%) in our present study and previous report [2] as well as other series [12], [13] could be attributed to the greater involvement of young men in heavy physical work than older individuals and women. It is possible that the nature of activity had led to excessive physical or mechanical strain of the affected limb with consequent vascular and metabolic changes in the corresponding anterior horn cells. Focal cord atrophy ipsilateral to the affected limb seen on computed tomographic myelography and MRI and supported by a single autopsy report have suggested the role of vascular insufficiency of the spinal cord in the pathogenesis of single limb atrophy [7], [14], [15], [16]. Trauma, electrical injury and major surgical operations were more frequently observed in cases of MMA, but were not statistically significant. It is noteworthy that in 7 out of 11 cases who reported antecedent injury, the atrophic limb was previously injured. In the classical motor neurone disease, some case control studies have suggested that heavy physical work, mechanical trauma and electrical injury were significant risk factors [17], [18] while in others a similar association was not observed [19], [20], [21]. Several studies focussing on the nature of occupation found a greater number of farmers among cases as compared to controls [11], [18].

Since the right upper limb was affected twice as common as the left one, special effort was made to determine the handedness. All the cases and controls reported that they were right handed. It is possible that some of them were left handed in early childhood period and because of strong cultural influences might have changed to right hand. Among the infections reported prior to the onset of the symptoms in the index case and corresponding period in the controls, varicella was the only significant illness. The frequency of poliomyelitis, mumps and measles did not differ in cases and controls. In motor neurone disease, poliomyelitis has been found to occur with greater frequency by some [22] while others did not find it significant [17]. No mention has been made about varicella in the literature. Surprisingly, recurrent infections disease were found to be more frequent in controls in a recent study of MND [23]. Varicella is known to cause cerebellar ataxia, encephalitis, Guillain-Barre syndrome, myelitis, optic neuritis but no association has yet been reported with anterior horn cell involvement due to persistence of varicella virus [24]. Further work in this area is warranted to establish an association of varicella infection and chronic anterior horn cell disorder.

Close contact with animals particularly cows and buffaloes was reported more frequently in our cases. In many parts of India, it is a fairly common practice to rear cows and buffaloes for the purpose of

dairy products. The cow sheds are in close proximity to the human dwelling. Although this is more common in rural areas, in the towns and cities also such a practice is seen. Exposure to pets such as dogs, cats, has been reported to be a risk factor in MND in a few studies [25] while others did not find any association [23], [26]. Among the neurological disorders looked for in the family members, dementia among family members of cases was more often reported and had an elevated OR and significant coefficient value. Armon et al [27] in a case control study of ALS observed that greater proportion of patients than controls had atleast one affected relative with neurodegenerative disorder. A number of factors such as economic status, literacy, life habits, (tobacco, alcohol intake, consuming raw milk), exposure to environmental toxins like lead, pesticides, industrial pollutants, unpotable water, and general medical disorders (diabetes, hypertension, tuberculosis, hepatitis) were not found to be frequent in cases as compared to controls. Exposure to heavy metals including lead has been considered to be a significant factor in MND by some workers [10], [27], [28] while it has not been substantiated by others [29].

It is clear from the foregoing discussion that there are certain common risk factors such as heavy physical activity and exposure to animals, both in the classical MND and MMA. While both are chronic anterior horn cell disorders, the distinctive features of MND such as worldwide distribution, older age at onset, upper and lower motor neurone signs and rapid progression with fatal outcome are in sharp contrast to the characteristic features of regional distribution (chiefly confined to Asia), young age to onset, lower motor neurone signs restricted to a single limb and slow progression with a benign course in MMA. The obvious differences between these two diseases could probably be due to an interaction of unidentified influences with the recognised factors and interrelation to some host factors determining the site of lesions in the neuraxis, severity of the disease process, course of illness and the ultimate outcome.

Case-control studies are considered to be suitable for determining the risk factors in rare disorders affecting nervous system. The choice of controls is critical in evaluating the results. Studies have been repaired in MND using hospital controls with neurological disorders [23] or other diseases [11] while others had selected controls from the population [30] the latter method being more representative of the population from which cases originate [31]. In the present study controls were chosen from the family and neighbourhood eliminating the bias originating from the use of hospital controls. Recall bias in case-control studies is difficult to overcome and is an inherent problem. All attempts were made to obtain reliable and accurate information by cross verification with family members and available medical records. MMA being a rare neurological disease, the number of patients seen in a particular centre would be limited. However, in view of the unique geographic distribution to Asia particularly Japan and India, the relevance of the present study despite its limitation, is in focussing attention to the identification of possible risk factors in the causation of single limb atrophy. Heavy physical work, varicella in childhood, exposure to animals and dementia in relatives have emerged as the significant risk factors. To what extent singly or in combination they determine the evolution of the disease needs to be explored. Furthermore, there may be other factors which may affect the disease process. Focussed studies to clearly delineate the role of identified risk factors in the causation of the disease need to be undertaken.

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