

## **Neuromuscular Junction Alterations in Patients with AIDS**

**Luis G. Cuello<sup>1</sup>, Miguel E. Quiñones<sup>2</sup>, Héctor J. Finol<sup>1</sup>, Aaram Márquez<sup>3</sup>, Raúl Suárez Chacón<sup>4</sup> and Milagros Gómez<sup>4</sup>**

**1. Center of Electron Microscopy, Sciences Faculty, Central University of Venezuela,  
Fax: 58-2-963.06.69**

**2. Center of Molecular Biology, Sciences Faculty, Autonomic University of Madrid,**

**3. Institute of Experimental Medicine, Central University of Venezuela 4. Center of Cancer  
Chemotherapy and Hematology, Health Secretary of Venezuela.**

### **ABSTRACT**

Muscle biopsies from two AIDS patients (stage III-IV) with proximal muscular weakness and myalgias were studied by means of transmission electron microscopy. Intramuscular nerve twig, terminal axon and postsynaptic region alterations were found. They included axonolysis and demyelination, vacuolation and retraction of terminal axon and poor development of postsynaptic membrane. This study confirms the existence of neurogenic factors in AIDS myopathy.

### **INTRODUCTION**

A wide variety of neuromuscular disorders may accompany HIV infection [1-15], they occur in 30-50 % of patients presenting latent infection or AIDS [6]. Electrodiagnostic test alterations have been described in 5-70 % of AIDS patients [6] including those with no signs of peripheral neuropathy. These data suggest that subclinical neuromuscular involvement is common in patients with AIDS. Light and electron microscopic studies have been performed in nerve and muscle tissues from patients with AIDS [2, 3, 7, 8, 11, 12, 14]. Although AIDS patients with disorders of neuromuscular transmission have been reported [6, 16] and neurogenic atrophy has been observed [4, 8], the neuromuscular junction ultrastructure has not been investigated. This paper shows the first evidence of neuromuscular junction ultrastructural abnormalities in patients with AIDS.

### **MATERIALS AND METHODS**

Patients admitted to the study (n=2) were attending the AIDS clinics at the Center of Cancer Chemotherapy and Hematology. Positive serology was first detected on enzyme-linked immunosorbent assay and confirmed on Western blot analysis. The patients had stage 3-4 AIDS and were homosexual. The clinical status assessment was carried out according to the Center for Disease Control criteria [17]. Clinical manifestations of muscle disease included myalgias and mild proximal weakness. Biopsies

### **KEYWORDS**

Neuromuscular Junction, AIDS, endplate, alterations.

were obtained from gastrocnemius muscle. The specimens were fixed with 3% glutaraldehyde, postfixed in 2% osmium tetroxide in phosphate buffer (pH 7.4), dehydrated in ethanol and embedded in Epon. Ultrathin sections stained with uranyl acetate and lead citrate were examined in a Hitachi H-500 electron microscope.

## **RESULTS**

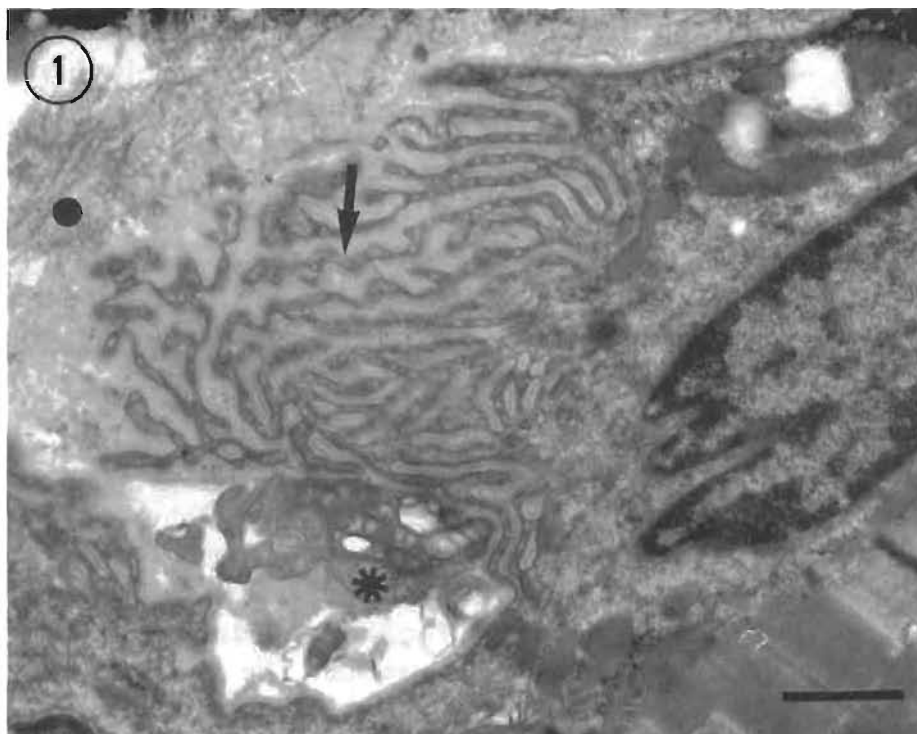
Axon terminals looked retracted and vacuolated (Fig.1) and eventually they may disappear (Fig.2). Secondary synaptic clefts were normal in some end-plates (Fig.1), in others the postsynaptic membrane looked poorly differentiated and almost smooth (Fig.2). The twigs looked degenerated with axon and myelin sheet disappearance (Fig.3). An increase of collagen fibrils was observed next to endplates (Fig.1) and intramuscular nerve twigs (Fig.3).

## **DISCUSSION**

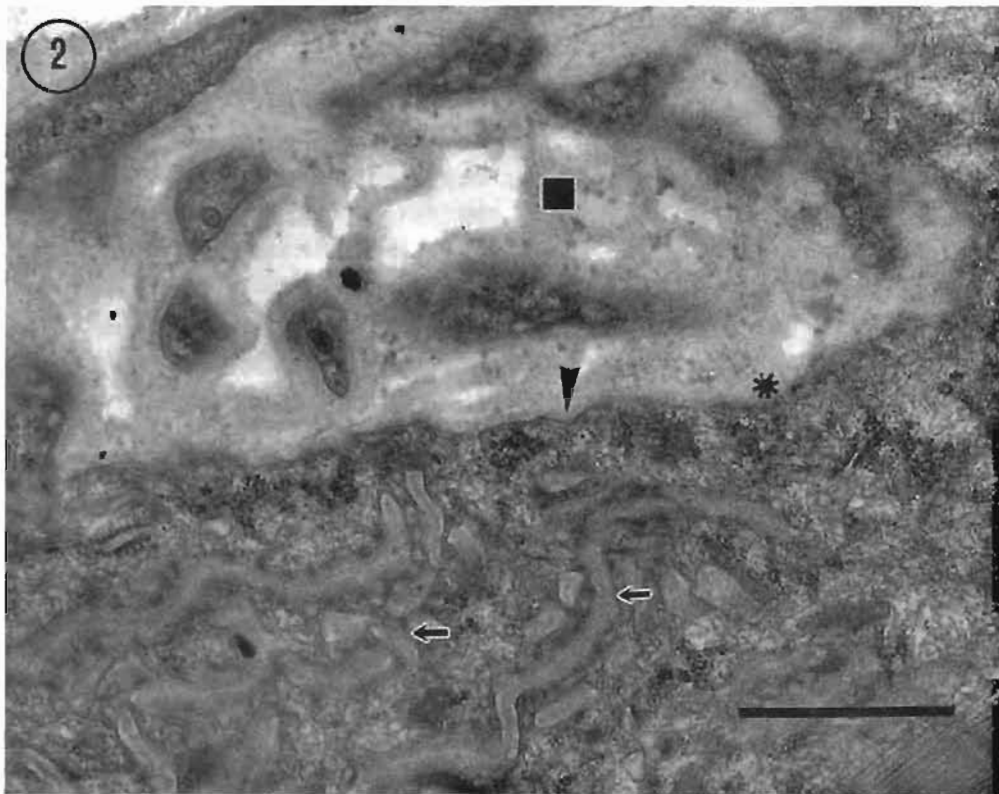
Our results provide additional ultrastructural information supporting the view

that neurogenic atrophy is a component of the muscular disorders associated with AIDS. In previous works nerve examination has shown axonal degeneration and loss of myelinated fibers [6, 7] and electrophysiological studies have demonstrated slow nerve conduction velocities and muscle denervation [6, 18]. Neurogenic damage of muscle has also been described [4, 10, 13, 15]. Although alterations of neuromuscular transmission have been reported [6,16] no previous study of neuromuscular junction alterations had been performed. The motor end-plate abnormalities we observed are similar to those found in patients with myasthenia gravis [19]. Usually, primary myopathic changes coexist with signs of denervation atrophy, and a complex ethiopathogenic mechanism seems to exist.

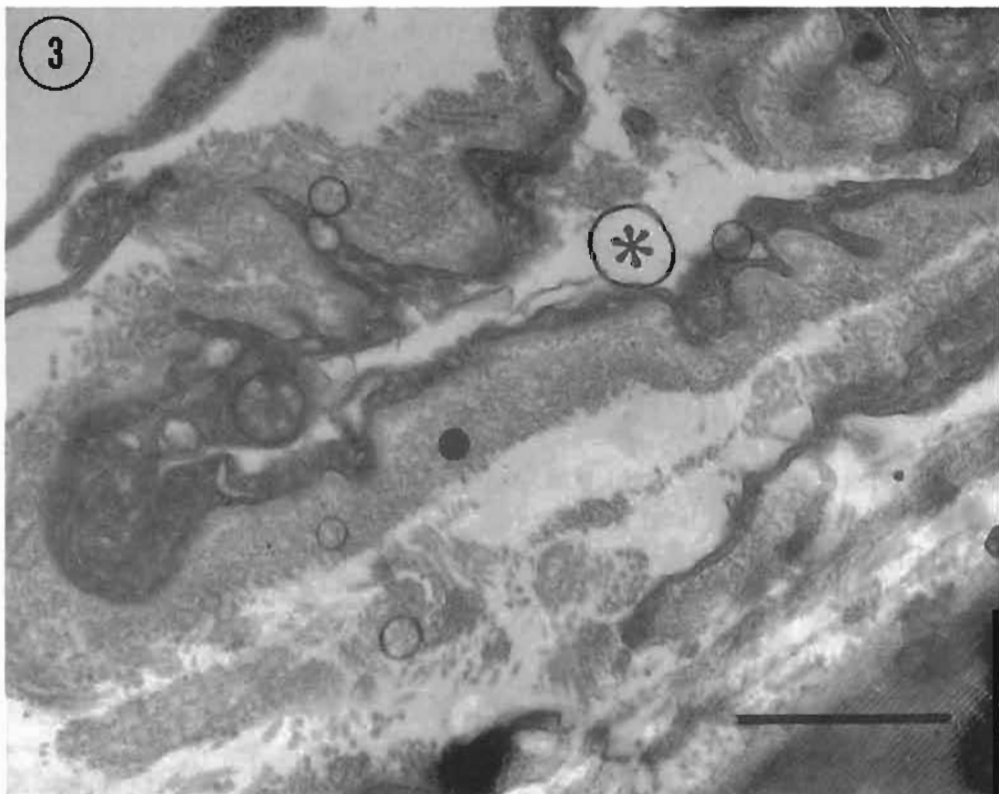
Alterations of muscle capillaries have been found [7], as similar abnormalities have been repeatedly observed in autoimmune myopathies [20, 23] and it has been suggested that the pathogenesis of the myopathy associated with AIDS might be autoimmune [2]. It is necessary to realize a systematic study of muscular



**Fig. 1.** A retracted axon terminal (asterisk) in small portion of the postsynaptic region. Swollen mitochondria are evident. Secondary synaptic clefts are numerous and elongated (arrow). Note abundant collagen fibrils (circle). In this and all figures Bar = 1 $\mu$ m.



**Fig. 2.** The axon terminal is absent (square). Postsynaptic membrane is almost smooth (arrowhead) and secondary clefts are scarce and disorganized (arrows). Some areas are devoid of clefts (asterisk).



**Fig. 3.** A degenerated nerve twig. (asterisk). Collagen fibrils are abundant (circle).

microvasculature in patients with AIDS.

### **ACKNOWLEDGEMENTS**

This work was supported by the CDCH of UCV (No. 03.10.2709.92).

### **RESUMEN**

Biopsias musculares obtenidas en dos pacientes con SIDA (estados II-IV) que presentaban debilidad muscular proximal y mialgias, fueron estudiadas al microscopio electrónico de transmisión. Se encontraron alteraciones, en las ramificaciones nerviosas intramusculares, los terminales axónicos y las regiones post-sinápticas. Ellas incluyeron axonolisis y demielinización; vacuolización y retracción de los terminales axónicos y la existencia de un pobre desarrollo de la membrana post-sináptica. Este estudio confirma la existencia de factores neurogénicos en la miopatía asociada al SIDA.

### **REFERENCES**

1. Dalakas, M.C., Pezeshkpour, G.H., Gravell, M. and Sever, J.L. (1986) Polymyositis associated with AIDS retrovirus. *JAMA*, **256**:2381-2383.
2. Simpson, D.M. and Wolfe, D.E. (1991) Neuromuscular complications of HIV infection and its treatment. *AIDS*, **5**:917-926.
3. Simpson, D.M. and Bender, A.N. (1988) Human immunodeficiency virus-associated myopathy: Analysis of 11 patients. *Ann. Neurol.*, **24**:79-84.
4. Wrzolek, M.A., Sher, J.H., Kozlowski, P.B. and Chandrakant, R. (1990). Skeletal muscle pathology in AIDS: An autopsy study. *Muscle & Nerve.*, **13**: 508-515.
5. Stern, R., Gold, J. and Dicarlo, E. (1987) Myopathy complicating the acquired immune deficiency syndrome. *Muscle & Nerve.*, **10**:318-322.
6. Lange, D.J. (1994) AAEM minimonograph

- #41: Neuromuscular diseases associated with HIV-1 infection. *Muscle & Nerve.*, **17**:16-30.
7. Mezin, P., Brion, J.P, Vermont, J., Micoud, M. and Stoebner, P. (1991) Ultrastructural changes associated with peripheral neuropathy in HIV/AIDS. *Ultrastruct. Pathol.* , **15**: 593-602
8. Hantai, D., Foernier, J.G., Vaseux, R., Collin, H., Baudrimont, M. and Fardeau, M. (1991) Skeletal muscle involvement in human immunodeficiency virus infection. *Acta Neuropathol.*, **81**: 496-502.
9. Buskila, D. and Gladman, D. (1990) Muscle skeletal manifestation of infection with human immunodeficiency virus. *Rev. Infect. Dis.*, **12**: 223-235.
10. Gabbai, A.A., Schmidt, B., Castelo, A., Oliveira, A. and Lima J. (1990). Muscle biopsy in AIDS and ARC: Analysis of 50 patients. *Muscle Nerve.*, **13**: 541-544.
11. Nordstrom, D.M., Petropolis, A.A., Giorno, R., Gates, R.H. and Reddy, V.B. (1989). Inflammatory myopathy and acquired immunodeficiency syndrome. *Arthritis Rheum.*, **32**: 475-479.
12. Panegyres, P.K., Papadimitriou, J.M., Hollingsworth, P.N., Armstrong, J.A. and Kakulas BA. (1990). Vesicular changes in the myopathies of AIDS. Ultrastructural observations and their relationship to zidovudine treatment. *J. Neurol. Neurosurg. Psychiatry.*, **53**: 649-655.
13. Willey, C.A. (1989). Neuromuscular diseases of AIDS. *FASEB J.*, **3**: 2503-2511.
14. Simpson, D.M., Citak, K.A., Godfrey, E., Godbold, J., Wolfe, D.E. (1993). Myopathies associated with human immunodeficiency virus and zidovudine: Can their effects be distinguished?. *Neurology.*, **43**:971-976
15. Verma, R.K., Ziegler, D.K. and Kepes, J.J. (1990). HIV-related neuromuscular syndrome simulating motor neuron disease. *Neurology.*

40:544-546.

16. Nath, A., Kerman, R.H., Novak, I.S. and Wolinsky, J.S. (1990). Immune studies in human immunodeficiency virus infection with myasthenia gravis: A case report. *Neurology.*, **40**: 581-583.

17. Centers for Disease Control., (1991). Review of draft for revision of HIV infection classification and expansion of AIDS surveillance case definition. *MMWR.*, **40**:787.

18. Snider, W.D., Simpson, D.M., Nielsen, S., Gold, J.W., Metroka, C.E. and Posner, J.B.. (1983). Neurological complications of acquired immune deficiency syndrome: Analysis of 50 patients. *Ann. Neurol.*, **14**: 403-418.

19. Bergman, R.A. and Johns, R.J. (1971). Ultrastructural alterations in muscle from patients with myasthenia gravis and Eaton-Lambert syndrome. *Ann. N.Y. Acad. Sci.*, (VOL 183) 88-122.

20. Finol, H.J., Müller, B., Torres, S.H., Dominguez, J.J., Perdomo, P. and Montes de Oca I. (1986). Ultrastructural abnormalities in muscular vessels of hyperthyroid patients. *Acta Neuropathol.*, **71**: 64-69.

21. Finol, H.J., Montagnani, S., Márques, A., Montes de Oca, Y. and Müller, B. (1990). Ultrastructural pathology of skeletal muscle in systemic lupus erithematosus. *J. Rheumatol.* **17**:210-219.

22. Finol, H.J., Márquez, A., Rodriguez, I., Montes de Oca, I., Tonino, P. and Müller B. (1993). Neuromuscular pathology in the paraneoplastic phenomenon associated with cervix carcinoma. *J. Exp. Clin. Cancer. Res.*, **12**: 53-58.

23. Finol, H.J., Márquez, A., Rivera, H., Montes de Oca, Y. and Müller, B. (1994). Ultrastructure of systemic sclerosis inflammatory myopathy. *J. Submicrosc. Cytol. Pathol.* **26**: 245-253