SPINAL MUSCULAR ATROPHY: A CLINICAL SURVEY

*** Melda Bozluolcay, ** Zerrin Pelin, * Veysi Demirbilek, * Gökhan Erkol, *** Özlem Çokar,**

SPİNAL MUSKÜLER ATROFİ: BİR KLİNİK GÖZDEN GEÇİRME

ÖZET

Dünyada çocuk ölümüne yol açan genetik nedenler arasında en sık rastlanılanlardan biri, otozomal resesif geçişli bir hastalık olan spinal musküler atrofiDİR (SMA). SMA belirgin hipotoni, ağır güçsüzlük ve sıklıkla ölümle sonuçlanabilen restriktif akciğer hastalığı ile seyretmektedir.

Klinik olarak SMA, erişkin yaşlara kadar ambulatuar halde kalabilen tip 3 varyantından; erken bebeklikte yerleşip, yüksek mortalitesi olan tip 1 varyantına kadar değişen bir spektrum gösterir. Akut; SMA Tip 1, olarak adlandırılan Werdnig Hoffmann Hastalığı, ara; SMA Tip2 ve jüvenil; SMA Tip 3 Kugelberg Welander olmak üzere üç formu bulunmaktadır. Akut formunda hızlı progresyon izlenmektedir. Bu formda vakaların çoğu 3 yaş civarında solunum enfeksiyonu nedeni ile kaybedilmektedir. Tip 2 SMA 'da gelişim ilk 6 ayda normal olup, 18 ay civarında motor yeteneklerde duraksama gözlenmektedir. Tip 3 SMA ise diğer formlara göre daha hafif seyretmekte, erişkin yaşlara kadar yaşam mümkün olabilmektedir. Klinik tabloda kas hareketlerindeki azalma belirgindir. Kas güçsüzlüğü simetrik olup, ekstremitelerin proksimal kısımlarındadır. Gövde, boyun ve toraks kasları da bu güçsüzlükten etkilenmektedir. Etkilenen kaslar atrofiye uğramakla birlikte, diafragma, kalp kası ve düz kaslar hastalığın son evresine kadar korunmaktadır. Hastalığın kesin tanısı genetik inceleme ile yapılabilmektedir. SMA'nın 3 formu da beşinci kromozomun uzun kolunda yer alan, SMN ("Survival of Motor Neuron") adı verilen bir gene lokalizedir. Hastalık için ileri sürülen ikinci gen ise NAIP (Neuronal Apoptosis Inhibiting Protein) adı verilen nöronal apoptozu engelleme proteinine âit bir gendir. Klinik olarak değişik formların bulunması birden fazla genin varolduğunu düşündürmektedir.

Bu yazıda, genetik olarak tanısı doğrulanmış 13 SMA hastasının, klinik belirtileri, hastalarda gözlenen komplikasyonlar ve tanıya yaklaşımda karşılaşılan zorluklar irdelenmiştir

Anahtar Kelimeler: spinal musküler atrofi, SMN, EMG, NAIP

ABSTRACT

Spinal muscular atrophy (SMA) is an autosomal recessive disease and is also one of the most common genetic causes of death in childhood. SMA causes profound hypotonia, severe weakness, and often fatal restrictive pulmonary disease. Patients with SMA present a spectrum of the disease from the most severe infantile-onset type associated with a high mortality rate to a late-onset mild form (type 3), where the patients remain independently ambulatory throughout adult life. In the present report, various clinical presentations, complications and some difficulties in diagnostic approach were documented in 13 genetically defined cases with SMA.

Keywords: spinal muscular atrophy, SMN, EMG, NAIP

INTRODUCTION

In children, the most common entity affecting the motor neuron in the brainstem and spinal cord is the spinal muscular atrophy (SMA) (Minks 1995). SMAs are a group of relatively common diseases occurring in infancy or early childhood transmitted by an autosomal gene (Melki 1994). Three forms of SMA have been recognized: Acute form (SMA type 1 or Werdnig-Hoffmann disease); intermediate form (SMA type 2); and the juvenile form (SMA type 3 or Kugelberg-Welander syndrome) (Minks 1995). In the acute form, progression is rapid. Infants who are hypotonic at birth rarely survive the first year whereas those whose weaknesses appear postnatally deteriorate more slowly. In most cases the disease is fatal by the age of 3 and the cause is usually a respiratory infection. Children with SMA2 develop normally for the first 6 months. On the 18th month, an arrest of motor abilities can be observed; tremor of the upper extremities can frequently be detected. SMA 3 is a milder form with survival into adult life. Muscle weakness develops after the 18th month and in some patients does not manifest itself until adult life (Minks 1995).

The three forms are determined by a gene localized to the long arm of chromosome 5 (5ql2-ql3.3) (Melki 1994) which is known as the Survival of Motor Neuron (SMN). Deletion on the 7th and 8th exons has been found. The second gene supposed to be determined for the disease is Neuronal Apoptosis Inhibiting Protein (NAIP) (Somerville et al. 1997). Having various clinical manifestations may be linked to the fact that more than one alleorphic gene could be in the same locus. The multiplicity of this allele combination is being used to explain the variety of clinical manifestations, age of onset, survival time and the anatomic dispersity of the affected motor neurons (Somerville et al. 1997). The clinical picture is marked by reduction of muscle mo-

* Istanbul University, Cerrahpaşa Medical School, Department of Neurology / Correspondence address: Melda Bozluolcay, Istanbul University, Cerrahpaşa Medical School, Department of Neurology, Cerrahpaşa, Istanbul, Turkey. Telephone: 90 212 4143000/21835, E-mail: melda56@tnn.net
** Pendik State Hospital, Department of Neurology
*** Haseki State Hospital, Department of Neurology

vement. Muscle weakness is symmetric and is in the proximal part of the limbs. Muscles of the trunk, neck, and thorax are affected equally. The affected muscles undergo atrophy. Diaphragm, cardiac and smooth muscles are spared until the late stages of the disease. With progression, involvement of bulbar musculature becomes more prominent and atrophy and fasciculations of the tongue are noted. Deep tendon reflexes are frequently reduced or absent. There is no sensory loss, no intellectual retardation and no sphincter disturbance (Minks 1995).

In this report, we aimed to document our genetically (with SMN analysis) confirmed SMA cases with their histories, the clinical manifestations and physical examination findings.

METHOD

In this report, the clinical features of 13 children with SMA were reviewed and classified into 3 stages. Designation of the patients who administered to the Child Neurology Unit of Cerrahpaşa Medical School between the years 1996-1999 was based on history, physical examination, electromyography (EMG) and the SMN gene analysis. The history was taken from the parents, the EMG was performed in anterior tibialis and biceps muscles with a needle electrode (Nihon Kohden Neurocompact 2). The genetic analysis was done in the molecular genetic laboratories of Istanbul University Experimental Medical Research Institute.

FINDINGS

All the patients were the children of Turkish parents. There were 6 boys and 7 girls. The range of their ages was from 45 days to 13 years with a mean age of 34 months. 3 were in the SMA type 1 group, 6 were in type 2 and the other 4 cases were in type 3. 2 out of 3 patients with SMA type 1 presented with reduced fetal movements, severe weakness at birth and severe respiratory insufficiency.

There was consanguinity in 5 parents. 4 couples were cousins (children of brothers or sisters) and 1 couple was cousins of the second degree. Concerning the 5 consanguine parents, there were total of 3 deaths at the ages of 3 months, 8 months and 2.5 years with weakness of the muscles and respiratory infection. In the non-consanguine group 2 women had 3 abortuses in the first trimester of their pregnancies.10 women had spontaneous and vaginal deliveries following uncomplicated pregnancies while 3 had cesarean sections because of their pelvic problems. 2 women experienced reduced fetal movements.

10 infants appeared normal at birth whereas 3 children had difficulties in sucking and had generalized hypotonia; no movement against gravity was observed. They could not keep their heads up and the trunk muscles were weak. Their diaphragmatic movements were slow, they cried weakly and they had respiratory problems.

10 had head control by 4 months and sat at 8 months. 10 children by the age of 12 months experienced walking and standing problems. Before administering to the Child Neurology Unit, 2 children were treated by orthopedists. Physical examinations of the children over 12 months revealed no abnormal findings. Hypotonia and weakness affecting the neck, proximal limbs and the trunk were present. 5 children were unable to stand on their feet with or without help; 2 needed support while sitting. 7 children could not stand up without any support. Gower's sign was (+). Deep tendon reflexes were absent in 12 and one child had hyperactive deep tendon reflexes. Babinsky sign was positive in 2 children who were over the age of 2. Fasciculation in the tongue was evident in one child. Tremor of the limbs was prominent in 2 children. Facial muscle strength was normal in 11 and was weak in 2 children. Cranial nerves seemed intact in all 13. 4 of these children had received treatment of multiple vitamin combinations.

Needle EMG findings were consistent with the diagnosis of motor neuron disease and chronic neurogenic involvement of muscles.

DISCUSSION

We have classified our children with SMA as type 1, type 2 and type 3 according to their histories, EMG, neurological examinations and gene (SMN) analysis. It is important to consider SMA in the differential diagnosis of reduced fetal movements (Mac Leod et al. 1999). Also the classical form of severe SMA type 1 has very consistent clinical manifestations that are well recognized by pediatricians but these children could sometimes be misdiagnosed as having tracheoesophageal reflux because of their hypersalivations, dysphagia, vomiting as a result of musculature weakness of the gastrointestinal tract (Innaccone 1998). Children with SMA type 2 and type 3 are diagnosed on the course of the illness as well as electrodiagnostic studies EMG and gene analysis (Minks 1995). The therapies available to these children are only supportive and consist of preventing and treating the complications of severe weakness (Dubowitz 1999) such as restrictive lung disease (Mellins 1974), poor nutrition, orthopedic deformities, immobility and psychosocial problems (Innaccone 1998, Strober and Tennekoon 1999). Again, researchers eagerly look for improved quality of life and extended life span (Innaccone 1998, Strober and Tennekoon 1999). However, SMA sometimes may be underestimated and these children keep on attending the orthopedists for walking and sitting difficulties as in our 2 cases. Also for the nutritional problems they are prescribed multivitamins as in our 4 cases.

CONCLUSION

More recently our understanding of the genetics of this disorder has provided a noninvasive approach to diagnosis. In our country where there is consanguinity and a great number of multipare women with more than 3 children, genetic analysis and counseling becomes outstandingly important for further generations.

REFERENCES

Dubowitz V (1999) Very severe spinal muscular atrophy (SMA Type 0): an expanding clinical phenotype (comment). Europ J Paediatr Neurol; 3: 49-51.

Iannaccone ST (1998) Spinal muscular atrophy. Semin Neurol; 18: 19-26.

MacLeod MJ, Taylor JE, Lunt PW, Mathew CG, Robb SA (1999) Prenatal onset spinal muscular atrophy. Europ J Paediatr Neurol; 3: 65-72.

Melki J (1994) De novo and inherited deletions of the 5ql3 region in spinal muscular atrophies. Science; 264: 1474-1477.

Mellins RB (1974) Respiratory distress as the initial manifestation of Werdnig-Hoffinann disease. Pediatrics; 53: 33-40.

Minks JH (1995) Textbook of Child Neurology Press, 5th edition. Baltimore, Maryland: Williams and Willkins, 815-882.

Somerville MJ, Hunter AG, Aubry HL, Korneluk RG, MacKenzie AE, Surh LC (1997) Clinical application of the molecular diagnosis of spinal muscular atrophy: deletions of neuronal apoptosis inhibitor protein and survival motor neuron genes. Am J Med Genet; 69: 159-165.

Strober JB, Tennekoon GI (1999) Progressive spinal muscular atrophies. J Child Neurol; 14: 691-695.