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Original article

Clinical characteristics of three subtypes of spinal muscular atrophy in children

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Abstract

Background: The severity of spinal muscular atrophy (SMA) is highly variable and children with heterogeneous clinical features can be classified into three phenotypes (type I–III) on the basis of age of onset and maximum motor function achieved. The aim of this study was to compare the clinical characteristics of three phenotypes in children with SMA. *Methods:* One hundred and thirty-two SMA patients were classified as type I, II or III according to the SMA classification criteria. The clinical features, deletion of survival motor neuron 1 (SMN1) gene and electrophysiology were analyzed and compared. The survival and functional status were obtained through telephone follow up. *Results:* In our study, 90.6% of the patients lacked both copies of SMNl. No difference in the deletion frequency among the 3 groups was observed. Although most of the neurophysiological parameters showed no differences among the groups, the amplitudes of compound muscle action potential (CMAP) was lower in type III SMA. Absent sensory nerve action potential (SNAP) amplitude of the sural nerve was observed in 26 (25.4%) of the patients. The survival pattern and functional status of 66 cases were obtained. Two type II SMA patients could walk unaided during follow-up. The functional ability of lower extremities improved in 4 patients with type III SMA. *Conclusions:* In this study, we confirm that EMG examination and homozygous deletion of SMN1 do not correlate with the subtypes. Motor function of patients with SMA type II and III can improve. A period of follow-up is necessary before rendering accurate classification and prognosis.

Keywords: Spinal muscular atrophy; Electrophysiology; SMN1 deletion

1. Introduction

Spinal muscular atrophy (SMA) is one of the most common fatal autosomal recessive disorders with an estimated incidence of 1 in 11,000 live births [1]. The major pathological characteristic is selective degeneration of alpha motor neurons in the ventral horn of the spinal cord, resulting in progressive muscle denervation, skeletal muscular atrophy and eventual paralysis. It is caused by homozygous deletion or mutation of the survival motor neuron 1 (SMN1) gene, and the absence of exon 7 and/or exon 8 in SMN1 is responsible for 95% of SMA [1]. Based on the age of onset and motor function achieved, SMA is classified into three clinical forms or phenotypes, i.e. Type I, II and III [2]. The increased attention to early diagnosis and management has stimulated the development of clinical guidelines and standards of care for SMA, which have affected the survival and natural history of patients [3,4]. Accurate classification is of great significance for different

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management, evaluation of prognosis and genetic counseling. The aim of this study was to compare the clinical feature, electrophysiological changes, SMN1 genotypes, functional status and survival pattern of SMA patients with different phenotypes.

2. Patients and methods

One hundred and thirty two cases of SMA hospitalized in Children's Hospital of Chongqing Medical University from January 2000 to March 2013 were studied. The study was approved by the ethical committee of the institution. All patients were diagnosed and classified according to the criteria established by the International SMA Consortium [2]. In SMA type 1, onset is before 6 months of age, and patients never achieve the ability to sit. SMA type 2 is defined by onset between 6 and 18 months, with patients not reaching the motor milestone of standing. Patients with SMA type 3 have disease onset after 18 months and gain the ability to walk. Eighty boys and fifty two girls were recruited for the study. The patients were diagnosed with SMA and classified into three groups based on the criteria established by the International SMA Consortium (Table 1). All medical records were reviewed for age of first visit, age of onset, gender, family history, muscle strength, muscle tone, disease progression, motor milestones, involvement of respiratory or bulbar muscles and deformities (joint contracture and scoliosis, see Table 2). The onset was defined as the age at which the first abnormalities were obvious from the descriptions of the parents about the first signs of weakness, e.g. age of delayed motor milestones or loss of functions. The medium age of 52 eligible cases with SMA type I was 1.2 months. The earliest onset was at birth. There were 9 children in the most severe forms presenting with severe weakness and joint contractures at birth with decreased intrauterine movements. Interestingly, the onset of one patient with SMA type II was also at birth because the parent described the baby with "soft limbs" and delayed motor milestones of sit at 12 months but could never learn to walk unassisted.

Electromyogram (EMG) was performed in 120 patients, in that spontaneous activity, duration of motor unit potential (MUP) and amplitude of MUP of muscles in four limbs were recorded. Nerve conduction velocity (NCV) was measured in 106 cases, including motor nerve conduction (MCV) of nerves in limbs (ulnar, radial, sural and tibial nerve), compound muscle action potential (CMAP) and sensory nerve action potential (SNAP) in these nerves. A total of 96 patients in our cohort of 132 patients had their diagnosis confirmed with molecular analyses. A polymerase chain reaction and restriction fragment length polymorphism (PCR–RFLP) assay was used to detect the homozygous deletion of exon 7 and/or exon 8 in SMNl. The survival pattern, whether the patient is alive with or without ventilator, and functional status including the motor milestone reached and other gross motor functions of 66 cases were obtained through telephone follow-ups.

The statistics analysis was done by SPSS17.0 software for Windows. Chi-square test or Fisher's exact test was used to compare the difference between 3 phenotypes in detection ratios of electrophysiological results and gene deletion frequency. Difference was considered statistically significant at $p < 0.05$.

Table 1
General information of patients with different phenotypes of SMA.

Type	Case number (% of total)	Gender (m:f)	Age of first visit (mo, median ± SD)	Age of onset (mo)		
				Median	Min	Max
SMA I	52 (39.4)	29:23	7.8 ± 5.7	1.2	0	6.0
SMA II	46 (34.8)	26:20	36.2 ± 23.0	12.0	0	18.0
SMA III	34 (25.8)	16:18	110.3 ± 63.2	23.5	18	156

Table 2
Clinical manifestation in different phenotypes of SMA [*n* (%)].

	SMA I	SMA II	SMA III	Total
Case	52	46	34	132
Weakness: only legs	0	18 (39.1)	18 (52.9)	36 (27.3)
Arms and legs	52 (100)	31 (67.4)	19 (55.8)	102 (77.3)
Muscle atrophy	20 (38.4)	25 (54.3)	15 (44.1)	60 (45.5)
Muscle trembling: tongue	8 (15.4)	28 (60.9)	10 (29.4)	46 (34.8)
Distal upper limb	2 (3.8)	25 (54.3)	16 (47.1)	43 (32.6)
Bulbar paralysis	32 (61.5)	3 (6.5)	2 (5.9)	37 (28.0)
Paradoxical breath	17 (32.6)	0	0	17 (12.9)
Pneumonia	30 (57.6)	9 (19.6)	5 (14.7)	44 (33.3)
Deformity	12 (23.1)	17 (37.0)	15 (44.1)	44 (33.3)
Decreased fetal movement	9 (17.3)	0	0	9 (6.8)