Clinico-epidemiologic characteristics of spinal muscular atrophy among Egyptians

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Abstract  Spinal muscular atrophy (SMA) is characterized by progressive hypotonia and muscular weakness because of progressive degeneration of alpha motor neuron from anterior horn cells in the spinal cord. It is inherited by an autosomal recessive pattern. The precise frequency of SMA in Egypt has not been determined. We tried to estimate the frequency, clinical and molecular characteristics of SMA in Egypt. The study included all patients with SMA attended the Pediatric Hospital, Ain-Shams University during the period (year 1966–2009). The study included 117 patients with SMA out of 660,280 patients attending the Pediatric Hospital. Patients selection was based on clinical examination, CPK, EMG, nerve conduction velocity, histopathology and molecular diagnosis. Frequency of SMA was 17.7/100,000, which is considered high. Type I was the commonest type (60.6%), followed by type II (26.7%), and type III (8.8%). Consanguinity was reported in 45.5 and family history in 47.8% of patients. Molecular study was done and 54.5% of patients (types I and II) have homozygous deletion of exon 7, 36.3% of whom had also homozygous deletion of exon 8 of SMN1 gene which is considered lower than that reported in other countries. SMA is more prevalent in Egypt than in many other countries. Forty-five percent of patients were chromosome 5-unlinked. We should continue to search for other mutation in Egypt to facilitate detection of carriers and prenatal diagnosis.

1. Introduction

Spinal muscular atrophy (SMA) is an autosomal recessive disease characterized by progressive hypotonia and muscular weakness. The muscle weakness occurs because of progressive degeneration of the alpha motor neuron from anterior horn cells in the spinal cord leading to proximal and symmetrical weakness and atrophy of limbs and trunk. In certain patients, the motor neurons of cranial nerves (especially the CN V–CN XII) are also involved. Sensations, which originates from the posterior horn cells of the spinal cord is spared, as is intelligence. Several muscles are also spared, including the diaphragm,
of the gastrointestinal system, the heart and sphincter [1–4].

According to age of onset and clinical severity, SMA is divided into three types I–III. Type I (Werdnig–Hoffman disease). This acute infantile SMA is the most severe form. It is usually identified from birth to 6 months. Affected children never acquire the ability to sit and they usually die before the second year from respiratory failure or aspiration pneumonia. Type II (chronic infantile SMA or intermediate form) occurs from 6 to 12 months of age and patients never stand. Survival depends on the degree of respiratory muscle involvement and death occurs after the second year. Type III (Kugelberg–Welander disease) is diagnosed in children 2–15 years. Patients learn to walk but suffer from proximal muscle weakness which results in scoliosis, wheelchair dependence and death in adulthood [5]. The SMA gene is located on the long arm of chromosome 5 (5q11.2-q13.3). The genes involved in SMA are the survival motor neuron (SMN), the neuronal apoptosis inhibitory protein (NAIP), the gene encoding p44 and the H4F5 gene. SMN gene is present in telomeric (SMN1) and centromeric (SMN2) copies, within the SMN region. SMN1 and SMN2 genes can be distinguished by two single nucleotide sequence variation in exons 7 and 8 [6].

More than 95% of patients with SMA have a homozygous disruption in the SMN1 gene, caused by mutation, deletion, or rearrangement. However all patients with SMA retain at least one copy of SMN2, which generates only 10% of the amount of full-length SMN protein versus SMN1. This genome organization provides a therapeutic pathway to promote SMN2, existing in all patients, so function like the missing SMN1 gene [7]. The incidence of SMA is about 1 in 10,000 live births with a carrier frequency of 1:50 [8,9]. Egypt enjoys a distinguished geographical location at the juncture of the ancient world continents of Africa, Asia and Europe. Egypt is about 1 million (m) km² and is located in the northern-eastern corner of Africa and Southwestern Asia. On its northern coasts lies the Mediterranean and on its eastern coasts lies the red sea. It is bounded on the south by Sudan and on the West by Libya [10].

Egypt is divided into 26 governorates: four urban (Cairo, Alexandria, Portsaid and Suez) with no rural populations. The other 22 have both urban and rural areas. Nine of the mixed governorates are in the Nile Delta (Lower Egypt) and eight in the Nile Valley (Upper Egypt), while the remaining five frontier governorates are the eastern and western boundaries of Egypt. Cairo, the most populous Arab country, is the glorious capital of Egypt, the cradle of civilization and the beacon of religion. Cairo's population rose to more than 18 millions (the highest population density in Egypt), although figures suggested large scale migration has ended. Egyptians are mainly descended from ancient Egyptian Society (94%). Ethnic minorities in Egypt include, Nubians, Berbers, Bedouin Arabs, Beja and Dome (4%) and others (2%) [10].

We conducted a study to determine the frequency, clinical and molecular characteristics of spinal muscular atrophy (SMA) in the Genetics Clinic, Pediatric Hospital, Faculty of Medicine, Ain-Shams University, as it is one of the main referral centers in Egypt. This hospital is located in the northeast section of Cairo [11]. It has a good reputation and high standard of health care so nearly all patients in this area attend this hospital for consultation. Also patients come nearly from all governorates to take good health care in this hospital. So the frequency and characteristics of SMA will represent the frequency and characteristics of this disease in the general population to a great extent.

2. Subjects and methods

This study was conducted from January 1966 to December 2009. The sources from which cases were ascertained came from retrospective surveys of medical records in the Genetics Unit, Pediatric Hospital during this period, as well as various studies published in national and international journals.

We intended to identify all patients with spinal muscle atrophy attended the hospital during the period of the study (117 patients among 28,689 patients attended the Genetics Clinic and 660,280 patients attended the Pediatric Hospital). Patients selection was based on history, pedigree analysis, clinical examination and investigations including CPK, EMG, nerve conduction velocity, histopathology and molecular diagnosis (available in last 10 years only) using single strand confirmation polymorphism analysis [12]. The age of studied patients ranged from 1.5 months to 7 years and 6 of them were adults aged 30–36 years. Forty-eight patients were males and sixty-seven patients were females (0.7–1). The sample was divided into three groups according to the age of onset and rate of progression of the disease:

Group I – acute infantile SMA: age of onset before 6 months and rapidly progressive. This group included 79 patients.

Group II – chronic childhood SMA: onset after the age of 6 months and slowly progressive. This group included 32 patients.

Group III – adult type: Onset in the third decade of life and showing slow progression. This group included 6 patients.

3. Results

One hundred and seventeen patients with spinal muscle atrophy attended the Genetics Clinic out of 627 patients with neuromuscular disorders and 660,280 patients attended the Pediatric Hospital during the period of the study. Spinal muscle atrophy thus constituted 18.66% of neuromuscular disorders and 17.7/100,000 of patients attending the Pediatric Hospital. Sluggish fetal movements and kicking in utero were reported by the mothers of all type I patients. Other details of prenatal, natal and postnatal history were found to be irrelevant. A family history was reported in 56 families (47.8% of patients). Consanguinity was reported in 54 families (46% of patients).

The most common complain were recurrent chest infection, hypotonia and weakness in all type I patients (67.5%) secondary inability to walk in all type II patients (27.3%), and weakness and difficulty in walking in all type III patients (5.2%). All type I patients presented with profound weakness and hypotonia, but wasting was not marked because of early death. Deep reflexes were absent, sensations were intact and mentality was normal. Tongue fasciculations were prominent and hand tremors were present in the second and third groups of patients. CPK was normal or slightly elevated in all patients. EMG showed neurogenic pattern and nerve conduction velocity...
was normal. Muscle biopsy revealed large group atrophy in severe SMA, but the atrophic group of both fiber types appeared to be smaller in the chronic form of the disease.

Molecular study was done for 33 patients and showed 18 patients (55%) to have homozygous deletion of exon 7, 12 of whom (36%), also had homozygous deletion of exon 8. All of these patients had SMA types I or II. Another 12 patients (36%), had either a homozygous deletion of both exons 7 and 8, or both exons were normal. These patients also belonged to SMA types I and II. The three patients with the adult type SMA (9%) were either heterozygous or normal for exon 7 and heterozygous for an abnormally sized atypical exon 8 [13].

4. Discussion

SMA constituted 18.66% of neuromuscular disorders and 0.02% of all patients attending the Pediatric Hospital (17.7/100,000). This frequency is higher than that reported/100,000 in USA (5–7)[14], in Germany (9)[15], in Italy (7–8)[14], in Poland (5)[14], in England (4)[14], in Saudi Arabia (4.5)[16] and in Libya (0.3)[17]. This may be due to high consanguinity rate reported in this study (47.8%) compared to that reported among the general population in Egypt (38.9%)[18]. These data reveal the importance of lowering the consanguinity rate and the value of genetic counseling and prenatal diagnosis in preventing SMA. Also considerable variations in prevalences and incidence in different countries may be due to genetic differences.

In this study type I was the commonest type (67.6%), followed by type II (27.3%) and type III (5.1%). The same was also previously reported in Egypt (13) [19] as well as in many other Arab and European countries [20–24]. 47.8% of Egyptian SMA families had a positive family history of similarly affected members. A report from Hungary gave a rate of 32% [25]. In the Egyptian familial cases, the age of onset was very similar and all affected family members belonged to the same type of SMA. However another study by Rudnik-Schoneborn et al. suggested that other SMA types such as I and III can frequently be observed among the siblings of patients with SMA type II, another argument in favour of a continuous spectrum in childhood SMA [26].

Males are more commonly affected than females (2:1) and the clinical course is more severe in males [27], although in this study as well as in another Egyptian study females were more commonly affected than males 0.7:1 [13]. Zerres and Rudnik-Schoneborn, suggested that there may be a female sparing factor, responsible for the marked decrease in number of affected girls in late onset group [28]. However no significant effect of sex was established by Rudnik-Schoneborn et al. [26].

Molecular study of SMA Egyptian patients [13] revealed that the frequency of homozygous deletion of exons 7 and 8 or exon 7 alone of SMN1 gene was present in 54.5% irrespective of clinical severity [13]. In another Egyptian study, 80% of studied patients have either homozygous absence of SMN1 exons 7 and 8 or exon 7 alone [19]. A larger molecular study in Egypt could resolve this controversy. Another interesting finding in an Egyptian study is that all patients with absence of exon 8 had also absence of SMN1 exon 7. Independent of clinical severity, homozygous deletion of SMN1 gene has been demonstrated in up to 98% of patients with SMA many ethnic groups [29–33]. Vander Steege et al. [34] have reported homozygous deletion of SMN1 gene in 98.6% of Dutch patients with SMN and Shafeghati et al. [35] detected homozygous deletion in 95% in Iranian population. Also 96.4% of SMA German patients display homozygous absence of SMN exons 7 and 8 or exon 7 only, where as 3.6% present compound heterozygosity with a subtle mutation on one chromosome and a deletion/gene conversion on the other chromosome. Among the 23 different subtle mutations described, the Y27 C missense mutation is the most frequent one, at 20%. The number of SMN2 copies modulated SMA phenotype. Nevertheless, it should not be used for prediction of severity of the SMA [36]. Nighty four percent of SMA Saudi [37] and 100% of Kuwaiti [38] patients demonstrated deletion of SMN1 gene. Exon 5 of NAIP was homozygously absent in all type I Kuwaiti patients, but was retained in type II cases [38].

In terms of genotype-phenotype correlation there is a higher incidence of homozygous absence of both exons 7 and 8 of SMN1 gene in Egyptian patients with the severe type I (42.9%) compared to type II patients (33.3%) [13]. However in another Egyptian study the frequency of homozygous absence of SMN1 exons 7 and 8 or exon 7 alone was higher (100%) in patients with mildest form of disease compared to those with the severest (80%) and the intermediate forms (67%). These results are similar to that reported by other studies [39–41]. Also in South African blacks SMA patients, the frequency of homozygous absence of exons 7 and 8 was higher in types II/III than in type I [42]. A higher incidence of homologous deletions of exons 7 and 8 of SMN1 gene and exon 5 of NAIP gene were detected in all Kuwaiti type II patients and exon 5 of NAIP gene in one type II patient. This latter patient had associated Pierre Robin syndrome [43]. Another interesting finding in an Egyptian study is that all patients with absence of exon 8 had also absence of SMN1 exon [19]. The same result was also reported by several studies [44–49]. The deletion of NAIP gene was found in 45% of Egyptian SMA patients [19]. The frequency of the deletion was more frequent in type I patients (80%) as compared to type II (22%) and type III (50%). In Kuwaiti [38] and Saudi Arabian patients [45], the incidence was even higher (100%). Thus higher frequencies of NAIP gene deletions were found in Arab populations compared to populations of other ethnic groups [50]. Relatively lower incidence (66–68%) was reported for Spanish [44], Finnish [51], Turkish [49] and Chinese [52]. Japanese patients showed even lower incidence (17–40%) [39].

A notable result obtained in Egypt is the higher frequency of E5 deletion in type III (50%), than in type II (22%) SMA patients [19]. Similar results have also been reported by two other studies in Spanish [44] and Finnish [51] patients, respectively. The correlation of the deletion and clinical severity is obvious thus justifying the use of this information for prognosis and genetic counseling [19].

SMA1 gene has been linked to pre-mRNA splicing, spliceosome biogenesis, and the nuclear protein fibrillin. The absence or dysfunction of SMN is reflected by an enhanced neuronal death. A heterozygous deletion leads to an asymptomatic carrier state [38]. The SMN2 gene is not interrupted in 95% normal and SMA chromosomes. The other candidate gene (NAIP), shows homozygous deletions in 45–67% of type I and 20–42% of type II and type III patients. Deletions of NAIP5 and SMN1 exon 7 have been associated with a 5-fold increased risk of type I SMA. NAIP gene mutation can lead to extensive neuronal cell death at the onset of the disease thus
modifying the clinical presentation of SMA into the severe form. Furthermore in type I patients lacking NAIP gene the deterioration in respiratory function was more rapid than in type I patients retaining NAIP gene [39].

A commonly used polymerase chain reaction/restriction fragment length polymorphism (PCR–RFLP) assay can be used to detect a homozygous absence of SMN 1 exon 7. SMN gene dosage analysis, which can determine the copy numbers of SMN1 and SMN2 (an SMN1 homolog and a modifier for SMA), have been developed for SMA carrier testing. Linkage analysis remains an important component of SMA genetic testing in certain circumstances. Haplotype analysis also may be widely used [53,54].

There is no effective cure or treatment for SMA and the recurrence risk is 25% for high risk families. Thus, the availability of prenatal testing is important. Savas et al. using direct digestion analysis of SMN1 gene by restriction digestion demonstrated that a careful molecular analysis of the SMN gene is very useful in predicting the phenotype of the fetus in families at risk [55].

Forty-five percent in this study and 20% in another study of Egyptian SMA patients did not show homozygosity for a deletion in SMN1 gene exon 7. These patients have been diagnosed based on international consortium criteria [56]. Also in Germany 4% of SMA patients are unlinked to chromosome 5q13 [36]. SMA patients who did not show deletions of SMN exons 7 and 8 or 7 only were clinically indistinguishable from deleted patients [42]. Also homozygous deletions of SMN gene exons 7 and 8 was found in one unaffected mother of type II SMA patient, as well as in six further unaffected individuals, all sibs of types II and III. So these families were regarded as chromosome 5 unlinked. This suggests that other genes or mechanisms may be necessary to produce SMA phenotype [42]. Also Novelli et al. [57] observed 2 sibs affected by the severe neonatal form of SMA with diaphragmatic paralysis that were discordant for the haplotypes determined by DNA markers flanking the SMA locus. This supports non-linkage of SMA to chromosome 5 in this family and indicated that the uncommon SMA type I variant associated with early onset respiratory failure maps outside the 5q11.2-q13.3. Alsamam and Tomoum [58] present the first genetically proven case of infantile spinal muscular atrophy with respiratory distress type I from Saudi Arabia. It is an unusual variant of spinal muscular atrophy type I that is characterized by early respiratory failure due to diaphragmatic paralysis. The defective gene is the immunoglobulin μ-binding protein 2 (IGH MBP2 gene) which is located on chromosome 11q13 and encodes μ-binding protein 2.

SMA has a carrier frequency of 1:33–1:60 in most populations. Carrier screening was carried out among residents of an isolated Israeli Arab Village with a high frequency of SMA to identify carriers of SMA type I and SMA with respiratory distress I (SMARDI). However, 13.1% were found to be carriers of SMA and 9.9% for SMARDI [59]. In Saudi Arabia carrier frequency was 1:20 was also reported which is considered very high [60].

To conclude the frequency of SMA among Egyptians is high and carrier frequency should be considered in Egypt in a population-based screening program as it is expected to be high. As there is no cure for this disease, genetic counseling becomes very important in disease management. We should continue to search for other mutations in Egypt to facilitate detection of carriers and presymptomatic cases especially those unlinked to chromosome 5. SMN gene dosage analysis, and linkage analysis, combined with appropriate genetic risk assessment and genetic counseling, offers the most important complete evaluation of SMA patients and their families [53].

5. Conflict of interest

The authors declare no conflict of interest.

References

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