Clinical Profile of Genetically Confirmed Spinal Muscular Atrophy (SMA) Among Filipino Children Less Than 18 Years Old

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ABSTRACT

Spinal muscular atrophy (SMA) is the most common inherited lethal disease in children. Confirmatory diagnosis is based on molecular genetic testing of survival motor neuron (SMN) genes. We aimed to describe the phenotypic presentation of Filipino infants and children with SMA based on the copy number analysis of SMN genes. Medical records of 17 Filipino children were reviewed from January 2017 to December 2019. De-identified clinical data fulfilled the diagnostic criteria defined by the International SMA Consortium.

Among Filipino children, the predominant SMA type by copy number was type I having two copies of SMN2 gene. The clinical severity based on symptom onset and highest functional motor capacity attained correlated with SMN2 copy number congruent with existing data. A significant time lag between symptom onset to confirmation of genetic diagnosis was noted. Nine out of the 17 (52%) children did not have a family history of the disease, raising the possibility of mutation carriers in these families since the incidence of de novo mutations in literature is about 2%.

These data offered the first epidemiological pattern of genetically confirmed SMA among Filipino children; provided additional information for genetic counselling; and an avenue to consider pre-symptomatic newborn screening and carrier testing that would change proactive measures and opportunities for therapy. These measures unavoidably will decrease the incidence and prevalence of disease in the future.

Key words Clinical profile, spinal muscular atrophy, genetically-confirmed, Filipino children, survival motor neuron

INTRODUCTION

Spinal muscular atrophy (SMA) is a neuromuscular disorder causing progressive muscular weakness associated with the loss of anterior horn cells in the spinal cord, with onset in infancy and early death. This was first described in the early 1890s by Austrian clinician Guido Werdnig and German physician Johann Hoffmann.[1]
The current classification of SMA distinguishes five SMA types (type 0–IV) based on the combination of age at onset and acquired gross motor milestones. Distinction of additional subtypes based on differences in the age at onset, first for SMA type III (IIla and IIlb) and more recently for type I (Ia–Ic) has been proposed.[2] Type Ia and Ib will not achieve head control with its onset before and after the neonatal period, respectively while Ic will achieve head control after the neonatal period. In SMA type IIIa and IIIb onset of muscle weakness was before and after the age of 3, respectively. This may help to further clarify differences in prognosis within SMA types and balance baseline characteristics in clinical trials. There was an inverse dose-relationship between SMN2 copy number and disease severity. The majority of patients with severe type I form have one or two copies of SMN2; type II has three SMN2 copies; and type III has three or four SMN2 copies.[3]

An incidence of SMA has been estimated 1 in 6,000 to 11,000 live births and considered the most common lethal genetic disease of children.[1] The Philippine Pediatric Society Registry of Childhood Diseases reported 192 out of all 4 million cases of hospital discharges for the past 10 years (2010-2020). Local data could be lacking, most likely largely undiagnosed due to many factors from access to specialists to confirmatory testing.

The milestones of SMA from early description to actual approved current therapies noted an increasing interest. Historically, diagnosis was made through electromyography but with the advent of gene testing, this should be prioritized. The gold standard of SMA genetic testing is a quantitative analysis of both SMN1 and SMN2 using multiplex ligation dependent probe amplification (MLPA), quantitative polymerase chain reaction (qPCR) or next generation sequencing (NGS).[5] Genetic studies have found homozygous deletions or mutations involving the SMN gene. Human chromosome 5 has two copies of the SMN gene, designated SMN1 and SMN2 using multiplex ligation dependent probe amplification (MLPA), quantitative polymerase chain reaction (qPCR) or next generation sequencing (NGS).[5]

Genetic studies have found homozygous deletions or mutations involving the SMN gene. Human chromosome 5 has two copies of the SMN gene, designated SMN1 and SMN2, which form an inverted duplication at locus 5q13. The duplicated SMN2 gene is differentiated from SMN1 by five nucleotide changes that do not change amino acids. A single nucleotide change in SMN2 creates an exonic splicing suppressor in exon 7, leading to exclusion of exon 7 in most transcripts and thus diminished production of the functional SMN protein, which is responsible for motor function of an affected individual.[1]

With the advent of recently discovered disease-modifying treatments that are valuable when given early, this paper apart from contributing to local data and genetic counselling implications, will provide a landscape for future inclusion in therapies and early testing recommendation (like pre-symptomatic newborn screening and carrier testing).

Hence, we aimed to describe the phenotypic presentation of Filipino infants and children with SMA based on the copy number analysis of SMN genes. Specifically, to determine the most common genotypic classification, correlate the severity of SMA with SMN copy number, determine timelines from symptom onset to genotypic diagnosis and compare the frequency of SMA with and without a family history for the disease.

PATIENTS AND METHODS

The medical records of Filipino children with genetically confirmed SMA using MLPA assay from the USTH Neuroscience Institute were reviewed from January 2017 to December 2019. All 17 Filipino children fulfilled the diagnostic criteria defined by the International SMA Consortium. De-identified clinical data were recorded and analyzed.

RESULT

The clinical diagnosis of SMA was genetically confirmed in 17 children. SMN2 copy number varied from 2 to 3 and overlapped between SMA types. Age of motor onset defined the SMA type. SMN2 copy number correlated inversely with SMA type. Clinical characteristics based on SMN2 copy number were summarized as given below.

There were a total of 7 children with two copies of SMN2 gene, 5/7 (71%) of which were female. Two out of seven (28.5%) children were categorized as SMA type Ib while the rest belonged to type Ic. The age of onset symptom was from birth to 6 months old. Six children presented with hypotonia, two of which presented with decreased fetal movement. Their highest motor function was flexion position with minimal head movement. For the family history, two children had relatives with clinically similar presentation while five of them did not have any family history of disease. Of note, patient number 7
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who initially presented with motor weakness at 6 months with no family history of disease had better motor function than the rest.

There were 10/17 (59%) children identified with 3 copies of SMN2 gene with equal gender distribution. Sixty percent (7/10) were classified as SMA type II, 20% (2/10) type IIIa and 10% (1/10) type Ic. Onset of symptoms were noted at 4-24 months presenting as hypotonia, inability to crawl and walk; and 1 child with decreased intrauterine fetal movement. The highest motor function achieved were ability to sit in 4/10 (40%) and walk with support in 6/10 (60%). Predominantly, 7/10 (70%) had family history or sibling with SMA while 3/10 (30%) did not have family history or a relative with clinically similar disease. We noted one subject whose symptoms were noted at 4-6 months and can ambulate with assist.

DISCUSSION

In this study, we described the phenotypic presentation of Filipino infants and children with SMA based on the copy number analysis of SMN genes. The results of the study showed that the most common genotype is 3 copies of SMN2 gene 10/17 (59%) as against 41% who had 2 copies. The SMN2 copy numbers among sitters and walkers (59%) were higher than those who had minimal head movement (41%). The result of this study is congruent with universal knowledge that the more copy numbers of SMN2 gene, later is the onset of motor weakness and less severe motor dysfunction. However, we observed a discrepancy on the age of onset and motor milestone in two patients. One patient with 2 copies of SMN2 gene had onset of symptom at 6 months, was able to sit alone, and another patient with 3 copies of SMN2 gene who presented at 4-6 months was able to walk assisted. This is an uncommon finding since patients with type I (non-sitters) will have its onset at 3-6 months, type II (sitters) at 6-18 months, while type III (walkers) at more than 18 months. In a study of Wadman, et al. (2017) discrepancies between age at onset and acquired motor milestones occurred in 20%.

There was a significant delay from symptom onset to genotypic diagnosis. Lin, et al. (2015) noted that the delays in diagnosis of SMA resulted from patient visits to multiple health care professionals to rule out the possibility of other illnesses before genetic testing was performed. Other factors included challenges with access to specialists, cost of care, physical

Table 1. Clinical profile of Filipino children with two copies of SMN2 gene.

<table>
<thead>
<tr>
<th>PATIENT NO. (n=7)</th>
<th>SMN COPY</th>
<th>SMA TYPE</th>
<th>AGE OF SYMPTOM ONSET (months)</th>
<th>AGE OF SMN TEST (months)</th>
<th>SEX</th>
<th>CLINICAL PRESENTATION</th>
<th>HIGHEST MOTOR FUNCTION ACHIEVED</th>
<th>FAMILY HISTORY</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 0:2</td>
<td>lc</td>
<td>Ic</td>
<td>5</td>
<td>10</td>
<td>F</td>
<td>Hypotonia, respiratory distress</td>
<td>Flexion position, turns head side to side</td>
<td>2 siblings floppy at birth (died at 3 and 5 months) and 1 sibling abortus 5 months</td>
</tr>
<tr>
<td>2 0:2</td>
<td>lc</td>
<td>Ic</td>
<td>4</td>
<td>12</td>
<td>F</td>
<td>No head control, hypotonia</td>
<td>Flexion position, turns head side to side</td>
<td>None</td>
</tr>
<tr>
<td>3 0:2</td>
<td>lb</td>
<td>Ib</td>
<td>2</td>
<td>5</td>
<td>M</td>
<td>Hypotonia, respiratory distress, decreased fetal movement</td>
<td>Flexion position</td>
<td>None</td>
</tr>
<tr>
<td>4 0:2</td>
<td>lc</td>
<td>Ic</td>
<td>3</td>
<td>8</td>
<td>F</td>
<td>Hypotonia, decreased fetal movement</td>
<td>Turns head side to side</td>
<td>None</td>
</tr>
<tr>
<td>5 0:2</td>
<td>lb</td>
<td>Ib</td>
<td>At birth</td>
<td>15</td>
<td>F</td>
<td>Hypotonia, feeding difficulty</td>
<td>Flexion position, Paternal side, 4th gen</td>
<td>None</td>
</tr>
<tr>
<td>6 0:2</td>
<td>lc</td>
<td>Ic</td>
<td>5</td>
<td>5</td>
<td>M</td>
<td>Hypotonia</td>
<td>Flexion position</td>
<td>None</td>
</tr>
<tr>
<td>7 0:2</td>
<td>lc</td>
<td>Ic</td>
<td>6</td>
<td>24</td>
<td>F</td>
<td>Unable to walk</td>
<td>Sits alone</td>
<td>None</td>
</tr>
</tbody>
</table>
Table 2. Clinical profile of Filipino children with three copies of SMN2 gene

<table>
<thead>
<tr>
<th>PATIENT NO.</th>
<th>SMN COPY</th>
<th>SMA TYPE</th>
<th>AGE OF SYMPTOM ONSET (months)</th>
<th>AGE OF SMN TEST (years)</th>
<th>SEX</th>
<th>CLINICAL PRESENTATION</th>
<th>HIGHEST MOTOR FUNCTION ACHIEVED</th>
<th>FAMILY HISTORY</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>0:3</td>
<td>Illa</td>
<td>24</td>
<td>5</td>
<td>M</td>
<td>Hypotonia</td>
<td>Sits alone</td>
<td>Paternal cousin-motor delay, died at 7 years old</td>
</tr>
<tr>
<td>2</td>
<td>0:3</td>
<td>II</td>
<td>12</td>
<td>8</td>
<td>F</td>
<td>Walking difficulty</td>
<td>Walks with support</td>
<td>Paternal sibling-delay in motor skills</td>
</tr>
<tr>
<td>3</td>
<td>0:3</td>
<td>II</td>
<td>12</td>
<td>4 11/12</td>
<td>M</td>
<td>Hypotonia, walking difficulty</td>
<td>Sits alone</td>
<td>Older brother-SMA (0:3)</td>
</tr>
<tr>
<td>4</td>
<td>0:3</td>
<td>II</td>
<td>10</td>
<td>13 8/12</td>
<td>M</td>
<td>Unable to walk</td>
<td>Sits alone</td>
<td>Youngest brother SMA (0:3)</td>
</tr>
<tr>
<td>5</td>
<td>0:3</td>
<td>Ic</td>
<td>4-6</td>
<td>2 4/12</td>
<td>M</td>
<td>Hypotonia</td>
<td>Walks with support</td>
<td>Eldest sister clinically diagnosed with SMA, died 10 years old</td>
</tr>
<tr>
<td>6</td>
<td>0:3</td>
<td>II</td>
<td>9</td>
<td>2 11/12</td>
<td>F</td>
<td>Hypotonia, decreased fetal movement</td>
<td>Sits alone</td>
<td>None</td>
</tr>
<tr>
<td>7</td>
<td>0:3</td>
<td>Illa</td>
<td>24</td>
<td>7 3/12</td>
<td>F</td>
<td>Unable to walk alone</td>
<td>Walks with support</td>
<td>None</td>
</tr>
<tr>
<td>8</td>
<td>0:3</td>
<td>II</td>
<td>12</td>
<td>2 9/12</td>
<td>M</td>
<td>Unable to walk</td>
<td>Walks with support</td>
<td>None</td>
</tr>
<tr>
<td>9</td>
<td>0:3</td>
<td>II</td>
<td>6</td>
<td>12 7/12</td>
<td>F</td>
<td>Unable to crawl</td>
<td>Walks with support</td>
<td>Younger sister with SMA [SMN 0:3]</td>
</tr>
<tr>
<td>10</td>
<td>0:3</td>
<td>II</td>
<td>9</td>
<td>10 4/12</td>
<td>F</td>
<td>Unable to crawl</td>
<td>Walks with support</td>
<td>Older sister with SMA [SMN 0:3]</td>
</tr>
</tbody>
</table>

and mental burden for patients and caregivers and
lastly, the availability of genetic testing not only for
SMA but also for other rare genetic diseases, which
are especially true in developing countries. A later
diagnosis may result in a missed opportunity for
optimal early intervention, thus tools for improving
early detection of SMA like pre-symptomatic
newborn screening may be essential in view of the
possibility of easier access to treatment in the future.

In this study, 53% did not have family history of
disease, raising the possibility of mutation carriers
in these families since the incidence of de novo
mutations in literature is about 2%. No family history
can be seen among carriers in 1 out of 50 people.
In a study of Hendrickson, et al. (2009) SMA is a
pan-ethnic disease. Studies have shown that SMN1
mutation and carrier frequencies varied among
ethnic groups. Population studies have indicated
variations in the carrier frequency of SMN1 deletions,
with Asians having the highest carrier frequency at 2.4%.[6] This may have future applications for
recommendations of widespread carrier screening
that will aid in identifying couples at risk of having
an SMA offspring.

CONCLUSION

This series showed that although in general the
SMN2 copy number is correlated with disease
severity for some patients, SMN2 copies are not
functionally equivalent with the SMA type. The
predominant SMA type by copy number was type
2-3 having 3 copies of SMN2 gene. The clinical
severity based on symptom onset and highest
functional motor capacity attained correlated with
SMN2 copy number congruent with existing data.
A significant time lag between symptom onset to confirmation of genetic diagnosis was documented. Those children who had no family history of SMA (or clinically similar motor weakness), most likely have parents who are carriers of the affected gene and need to be tested. These data offered the first epidemiological pattern of genetically confirmed SMA among Filipino children; provided additional information for genetic counselling; and an avenue to consider pre-symptomatic newborn screening and carrier testing that would change proactive measures and opportunities for therapy. These measures unavoidably will decrease the incidence and prevalence of disease in future.
REFERENCES


