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

Lalaine B. Villaflor-Oida, MD,[1] Raymond L. Rosales, MD, PhD,[2] Ma. Antonia Aurora M. Valencia, MD,[1] Michelle G. Sy, MD,[1] Yuh-Jyh Jong, MD, DMSci[3]

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

✉ Lalaine B. Villaflor-Oida
ustchildneuro@gmail.com

1 Section of Child Neurology and Developmental Medicine, University of Santo Tomas Hospital, Manila

2 Research Center for Health Sciences, Faculty of Medicine and Surgery, University of Santo Tomas Hospital, Manila

3 Kaohsiung Medical University Hospital, Taiwan.

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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 (IIIa and IIIb) 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 notable 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,* 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

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

PATIENT NO. (n=7)	SMN COPY	SMA TYPE	AGE OF SYMPTOM ONSET (months)	AGE OF SMN TEST (months)	SEX	CLINICAL PRESENTATION	HIGHEST MOTOR FUNCTION ACHIEVED	FAMILY HISTORY
1	0:2	Ic	5	10	F	Hypotonia, respiratory distress	Flexion position, turns head side to side	2 siblings floppy at birth (died at 3 and 5 months) and 1 sibling abortus 5 months
2	0:2	Ic	4	12	F	No head control, hypotonia	Flexion position, turns head side to side	None
3	0:2	Ib	2	5	M	Hypotonia, respiratory distress, decreased fetal movement	Flexion position	None
4	0:2	Ic	3	8	F	Hypotonia, decreased fetal movement	Turns head side to side	None
5	0:2	Ib	At birth	15	F	Hypotonia, feeding difficulty	Flexion position	Paternal side, 4th gen
6	0:2	Ic	5	5	M	Hypotonia	Flexion position	None
7	0:2	Ic	6	24	F	Unable to walk	Sits alone	None

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 2. Clinical profile of Filipino children with three copies of *SMN2* gene

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

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.

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