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# Spinal Muscular Atrophy: A Time for Screening in Saudi Arabia

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Spinal muscular atrophy (SMA), an autosomal-recessive neuromuscular condition, is a major cause of infant mortality worldwide. There is a high incidence of SMA in the Saudi Arabian population due to the prevalence of cousin marriages and the high rate of consanguinity (57.7%) in this culture. Despite the high incidence of SMA, however, Saudi Arabia lacks a standardized newborn screening program for this disorder. Therefore, the purpose of this review was to examine the current SMA screening and detection landscape in Saudi Arabia. The primary reasons necessitating the addition of SMA to the current Saudi newborn screening program include 1) the inability of current screening methods to accurately predict disease severity; 2) the introduction of polymerase chain reaction (PCR) analysis for SMA diagnosis, and 3) recent data suggesting that available therapies (onasemnogene abeparvovec-xioi and nusinersen) are more effective when administered to SMA patients earlier on during the disease course. Collectively, SMA screening is essential because it facilitates early disease detection and subsequent rapid access to treatment strategies. The parents of affected infants may also opt for genetic counseling.

**Keywords: spinal muscular atrophy, consanguineous marriage, newborn screening, *SMN1*, *SMN2***

## INTRODUCTION

Spinal muscular atrophy (SMA) is an autosomal-recessive condition that occurs in one per 10,000 live births worldwide and is the second-most common neuromuscular condition in children (Czeizel and Hamula 1989). This disorder is primarily caused by homozygous deletions in exon 7 of *SMN1* (5q13.11) and resulting in deficiencies in the levels of survival of motor neuron 2 (SMN2) protein. Clinically, SMA is characterized by spinal alpha motor neuron damage and leads to progressive muscle weakness (e.g., trunk and proximal limb) and paralysis in affected individuals. Patients with severe SMA may experience symptoms such as the inability to control their head movements, difficulties sitting and walking without support, and challenges with bodily functions such as swallowing and breathing.

Different types of SMA are characterized by varying levels of disease severity. For example, children are predominantly affected by SMA type 1 (Werdnig–Hoffmann disease) and usually present with motor skill deficits, difficulties sitting, and nutritional deficiencies, the latter of which can be overcome with gastric tube feeding. Patients with SMA type 1 also experience respiratory deficits due to orthopedic issues such as scoliosis (Kostova, Williams et al. 2007, Ross and Clarke 2017), and children with this SMA type often die of respiratory failure. Health-care professionals may employ tracheostomy and invasive ventilation for such children to prevent mortality; however, patients cannot speak during this intervention, encouraging the use of non-invasive methods of respiratory support to enhance the quality of life.

The second most prevalent form of SMA is SMA type 2 (Dubowitz disease), which affects 20% of all SMA patients and usually presents at six to 18 months of age. Affected children can sit without support but cannot walk and typically die in young adulthood (Kostova, Williams et al. 2007, Ross and Clarke 2017). SMA type 3 (Kugelberg–Welander disease) and type 4 present after 18 months of age and in adulthood, respectively. These two types of SMA differ from types 1 and 2 in that patients with types 3 and 4 experience a normal life expectancy.

Nevertheless, SMA types 3 and 4 may still impact locomotion and quality of life by causing fatigue. The introduction of novel gene therapies, such as onasemnogene, abeparvovec-xioi (Zolgensma; AveXis, Bannockburn, IL, USA), nusinersen (Spinraza; Biogen, Cambridge, MA, USA), has revolutionized SMA treatment. These treatments introduce the *SMN1* and *SMN2* genes into the bodies of affected individuals, leading to the expression of the proteins that regulate muscle movement (Haché, Swoboda et al. 2016, Farrar, Teoh et al. 2018) and significantly enhance motor skills and survival (Rao, Kapp et al. 2018).

The incorporation of SMA screening into newborn screening (NBS) protocols facilitates early detection of this condition, thus preventing affected individuals from undergoing painful and costly testing later on in life. Also, screening can enhance patients' quality of life and prolong their life expectancy (Rao, Kapp et al. 2018); indeed, children affected by SMA exhibit significant delays in disease progression if intervention is started in the pre-symptomatic period. For example, the neurologic degeneration that presents in infants affected by SMA type 1 can lead to nutritional deficiencies that, in turn, can accelerate SMA progression. Therefore, early detection of SMA allows for timely and practical management of this condition through nutritional intervention. It has also been observed that earlier use of non-invasive respiratory interventions, such as mechanically supported coughing instruments, facilitates airway clearance of secretions, thus reducing respiratory difficulties and prolonging life expectancy. Taken together, early treatment initiation in patients with SMA may enhance motor function, waive the need for permanent ventilation, and improve survival.

Several effective methods for SMA screening are currently in use. For example, one vital SMA screening technique used in newborns is polymerase chain reaction (PCR) analysis. This technique is performed using DNA obtained from one 3-mm dried blood spot on filter paper (Takeuchi, Tode et al. 2019). Two recent pilot studies reported that SMA could be detected via PCR testing of dried blood specimens. This test can identify the relevant genetic deletion with 95% accuracy and a 0% false-negative rate. As such, DNA obtained from newborn blood spots can be used for a precise diagnosis of SMA (Kato, Sa'Adah et al. 2015, Rochmah, Harahap et al. 2017).

In Saudi Arabia, the rate of consanguineous marriages—particularly first-cousin marriages—is high, thereby elevating the incidence of SMA in this population compared to other ethnic groups (Salahshourifar, Shafeghati et al. 2007). Indeed, in one study of 25 SMA type I cases, Al-Rajeh et al. reported that 64% of patients had consanguineous parents (Al-Rajeh, Bademosi et al. 1992). Hence, this review aims to argue for the need to include SMA in the existing national NBS program panel as a step toward rapid diagnosis and treatment of all affected infants. Incorporation of SMA screening into existing NBS protocols will also facilitate the identification of parents at high risk of transmitting SMA, and it is recommended that genetic counselling and carrier testing be conducted on the basis of NBS outcomes for the prevention of additional SMA cases.

**SMA and consanguineous marriages**

Bittles et al. (2010) contended that nearly 10.4% of the global population is either the offspring of a consanguineous union or married to a biological family member (Bittles and Black 2010). Western Europe, North America, and Australia have persistently witnessed low consanguineous marriage rates of nearly below 1%. In comparison, intermediate levels of consanguinity (1–20%) are observed in South America, the Iberian Peninsula, and Japan (Bittles 2012). In contrast, several Middle Eastern countries widely practice this tradition, with first-cousin marriages being particularly prevalent. For instance, rates of consanguineous marriages are reportedly 60% in Pakistan (Hakim 1994), 51.3% in Jordan (Khoury and Massad 1992), 54.0% in Qatar (Bener and Alali 2006), 50.5% in the United Arab Emirates (Al-Gazali, Bener et al. 1997), 40% in Yemen (Jurdi and Saxena 2003), and 29% in Egypt (Hafez, El-Tahan et al. 1983). Moreover, according to El-Hazmi et al. a consanguinity frequency of 57.7% with frequent first-cousin marriages was reported among Saudis (El-hazmi, Al-Suwailem et al. 1995).

As an autosomal-recessive disease, SMA is associated with a high degree of consanguinity in Muslim populations, with reported SMA prevalence rates of 65% in Iran (Salahshourifar, Shafeghati et al. 2007), 60 % in Pakistan (Kouser Karim and Munim 2020) (Ibrahim, Moatter et al. 2012), 46% in Egypt (Shawky and El-Sayed 2011) and 49% in Oman (Koul, Al-Futaisi et al. 2006). However, consanguinity among Saudis with offspring who suffer from SMA generally is similar to that within the general Saudi population, although rates of the first-degree consanguinity linked to SMA type I cases are higher than those in the general Saudi population (56% vs. 35%) (Al Rajeh, Majumdar et al. 1998, Al-Jumah, Majumdar et al. 2003).

**SMA control programme**

The incidence of SMA can be reduced by identifying SMA carriers and genetic counseling to prevent further disease transmission. Specifically, carrier-detection efforts should be made for families with SMA-affected members. SMA carriers can safely have unaffected children if they undergo genetic screening of the embryos before implantation. Many individuals may be unable to afford this costly procedure; however, government subsidization of all or part of the cost may mitigate this obstacle. For patients currently living with SMA, the counseling of patients and their families, together with the arrangement of support groups, is an important step for tackling the care issues involved in handling SMA. Additional measures to control the number of SMA cases may be implemented more broadly throughout the community. Key measures may include SMA education and awareness campaigns deployed both in public at large and by medical professionals. Specifically, the dissemination of meaningful information on SMA to both couples and schoolchildren could be achieved by extensive media coverage, classroom instruction, workshops, symposia, and/or conferences.

Furthermore, the public may have limited knowledge concerning the likely consequences of consanguineous marriage. Therefore, the development of awareness programs by the relevant authorities at the local and national levels could provide information about the risks associated with this practice. Ultimately, Saudi Arabian health experts should curtail the number of consanguineous marriages—particularly those between first cousins—to reduce the likelihood that children will be affected by autosomal-recessive disorders such as SMA.

**NBS and SMA disease in Saudi Arabia**

Heritable and congenital disorders can be identified and prevented via the implementation of a public health program. Accordingly, identifying affected babies before the onset of clinical symptoms is the primary aim of the Saudi NBS program (SNSP). Great economic and social demands have been placed on the Kingdom of Saudi Arabia as a result of physical and mental disabilities, alongside other health complications. The Saudi government is greatly concerned by the augmented mortality rate among individuals with disabilities and by other critical issues regarding the well-being of these individuals. These syndromes can trigger intellectual challenges, physical ailments, and even death if they are not treated in their early stages. Thus, early diagnosis can help prevent some of the consequences of these disorders.

The following phases are included in the comprehensive SNSP: education, testing, diagnosis, follow-up, management, treatment, and assessment. From August 2005 to 31 December 2012, Saudi Arabia conducted an NBS pilot program for 16 endocrine and metabolic disorders, wherein a total of 775,000 newborns were assessed at 139 hospitals across the Kingdom. For biochemical and immunoassay testing, all newborns underwent a heel-prick dry blood sample collection (Alfadhel, Al Othaim et al. 2017). Initial positive results were acquired through recall screening testing and were substantiated by the relevant biochemical assays. The assessment discovered 743 cases of these disorders, with an overall incidence rate of one in 1,043 infants. Countrywide, congenital hypothyroidism, and congenital adrenal hyperplasia, with incidence rates of one in 7,175 infants and one in 7,908 infants, respectively, were among the most frequently detected disorders (Alfadhel, Al Othaim et al. 2017). In contrast, propionic acidaemia, a metabolic condition with a rate of one in 14,000 infants, was relatively uncommon among those surveyed (Alfadhel, Al Othaim et al. 2017).

The quality of life of many children with various disorders has improved since the launch of the SNSP in 2005. Newborns must be screened so that those with congenital disorders can be identified. Disease incidence, ease of access to treatment, and the accessibility of confirmatory testing are parameters for inclusion in the SNSP. Currently, screening for the following conditions is generally conducted: argininosuccinate lyase deficiency;

aminoacidopathies including phenylketonuria; organic acid disorders including propionic acidaemia, maple syrup urine disease, and citrullinemia; glutaric acidaemia type-I; methylmalonic acidaemia; fatty acid oxidation defects such as medium-chain acyl-coenzyme A (CoA) dehydrogenase deficiency, isovaleric acidaemia, and 3-methylcrotonyl-CoA carboxylase deficiency; ketogenesis and ketolysis defects including beta-ketothiolase deficiency and 3-hydroxy-3-methylglutaryl-CoA lyase deficiency; carbohydrate disorders including galactosemia; endocrine disorders such as congenital adrenal hyperplasia and congenital hypothyroidism; and vitamin metabolism disorders including biotinidase deficiency (Alfadhel, Al Othaim et al. 2017).

In contrast, SMA is not currently included in the SNSP, and the treatment of affected individuals is initiated upon clinical symptoms presentation. However, successful pre-symptomatic screening and early therapeutic intervention for infants with SMA have been achieved through NBS programs enacted in the United States and Australia (Kemper, Lam et al. 2018, Kariyawasam, Russell et al. 2020). Therefore, given that Saudi Arabia has access to pre-existing NBS methodologies and SMA therapies, health authorities have proposed incorporating SMA into the SNSP panel to attain increased detection rates and facilitate early therapeutic intervention (Alfadhel, Al Othaim et al. 2017).

## CONCLUSION

SMA is a relatively prevalent autosomal-recessive disorder in Saudi Arabia. There is a critical need to detect adult carriers in SMA-affected families and prevent further genetic transmission of the disease. Together with government-sponsored genetic counseling services, the employment of competent laboratory technicians through the existing Saudi newborn screening program will facilitate the rapid incorporation of SMA into the NBS program and ensure timely health care delivery. Furthermore, many studies have illustrated a significant correlation between consanguineous marriages and SMA incidence; high consanguinity rates likely underlie the prevalence of and high mortality rates from SMA in Saudi Arabia. Thus, the Saudi people must be advised of consanguineous marriage risks concerning the transmission of genetic diseases.

## CONFLICT OF INTEREST

The author declared that present study was performed in absence of any conflict of interest.

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## AUTHOR CONTRIBUTIONS

SAA, designed, wrote, reviewed the manuscript and approved the final version.



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