The first registered type 0 spinal muscular atrophy patient in Latvia: call for change in prenatal diagnostic procedures, case report

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Research Article

Keywords: 5q SMA, type 0 SMA, case report

Posted Date: October 24th, 2022

DOI: https://doi.org/10.21203/rs.3.rs-2134554/v1

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Abstract

Background
currently, there are only a few published case reports detailing an increased nuchal translucency (NT) measurement in association with a diagnosis of SMA in the foetus. However, an increased NT measurement is a clinically relevant sign as it can be related to genetic syndromes, foetal malformations, disruptions and dysplasias. This case report highlights the prenatal signs and symptoms in relation to type 0 SMA.

Case presentation:
this case report presents the first registered patient in Latvia with type 0 spinal muscular atrophy (SMA). The index case was a Caucasian male infant from non-consanguineous parents. During the first-trimester ultrasonography of the unborn patient, an increased thickness of the nuchal fold was detected. The mother reported decreased foetal movements during the pregnancy. After the boy was born, his general condition was extremely severe. The clinical signs indicated a suspected neuromuscular disorder. A precise diagnosis – type 0 SMA – was determined 7 days after birth through a newborn pilot-screening for SMA. The condition of the infant deteriorated. He had severe respiratory distress followed by multiple events leading to death.

Conclusions
since there are no treatment options for infants with type 0 SMA at present, it is vital to be able to detect this disease prenatally in order to provide the best possible care for the patient and parents. Employment of extensive panel genetic testing using next-generation sequencing would be beneficial for prenatal diagnosis of type 0 SMA cases. Moreover, sequencing of foetal exomes covering single nucleotide variations and copy number variations (also \textit{SMN1}) offers a broader diagnostic capacity for pregnancies with unexpected foetal anomalies, thus improving both diagnostic timing and counselling for parents. Early recognition of the disease would give parents time to come to terms with the situation, as well as provide the option of pregnancy termination.

Background
Spinal muscular atrophy 5q (SMA5q) is a genetic disease characterised by degeneration of anterior horn cells in the spinal cord and motor nuclei in the lower brainstem. The most common cause is the deletion of exon 7 in the survival motor neuron 1 (\textit{SMN1}) gene. The severity of the disease correlates with the number of copies of the survival motor neuron 2 (\textit{SMN2}) gene. According to available data, the incidence of the disease in Latvia is 1/9,091. However, the incidence worldwide is about 1 in 10,000 live births. The carrier frequency worldwide is around 1 in 50.
The disease is classified into five types depending on the age of onset and the clinical course. The most severe type is SMA type 0 and the least severe SMA type 4 (Table 1). SMA type 0 manifests prenatally. Mothers of affected children can experience a decrease or even a loss of foetal movements during pregnancy. In addition, foetuses may present with intrauterine growth retardation, pulmonary hypoplasia and skeletal abnormalities. Newborns with SMA type 0 have a severe weakness and hypotonia at birth. They often present with areflexia, congenital heart defects and facial diplegia. Affected infants are not able to achieve any motor function milestones. Death arises from respiratory failure, most commonly by one month of age. Patients usually present with one copy of the *SMN2* gene.

### Table 1

<table>
<thead>
<tr>
<th>SMA type</th>
<th>SMN2 copies</th>
<th>Age of onset</th>
<th>Motor ability</th>
<th>Prognosis</th>
</tr>
</thead>
<tbody>
<tr>
<td>Type 0</td>
<td>1</td>
<td>Before birth</td>
<td>Severe hypotonia. The patient cannot reach any motor function milestones.</td>
<td>The child presents with respiratory insufficiency at birth. Death within a few weeks.</td>
</tr>
<tr>
<td>Type 1</td>
<td>2</td>
<td>&lt; 6 months</td>
<td>Severe hypotonia. The patient cannot sit or roll.</td>
<td>The symptoms progress rapidly. Most infants die before the age of 2 years.</td>
</tr>
<tr>
<td>Type 2</td>
<td>3</td>
<td>6–18 months</td>
<td>Proximal muscle weakness. The patient cannot walk independently.</td>
<td>Patients can have a shortened life expectancy. Frequently live into adulthood.</td>
</tr>
<tr>
<td>Type 3</td>
<td>3–4</td>
<td>&gt; 18 months</td>
<td>The patient can lose the ability to walk.</td>
<td>Usually life expectancy is not affected.</td>
</tr>
<tr>
<td>Type 4</td>
<td>4–8</td>
<td>Adulthood</td>
<td>The patient has a slight motor function impairment.</td>
<td>Life expectancy is not affected.</td>
</tr>
</tbody>
</table>

## Case Presentation

This case report presents the first registered patient in Latvia with type 0 SMA. The index case was a male infant from non-consanguineous parents. The mother was a 33-year-old Caucasian female. She did not smoke and had no health issues. The father was a 35-year-old Caucasian male with no chronic illnesses. There was no positive family history of SMA; however, both parents were carriers of a mutated *SMN1* gene. This was their second pregnancy and second labour. The previous pregnancy was uneventful and a healthy child was born, thus far with no SMA5q symptoms being reported.

The mother’s pregnancy with the proband was considered high risk due to her age. Consequently, several ultrasonographic parameters (thickness of foetal nuchal translucency (NT), nasal bone length, tricuspid valve and ductus venosus dopplerometry, foetal heart rate) were assessed, as were maternal serum biochemical parameters. Due to the increased risk of aneuploidy, chorionic villus sampling was performed.
During the first-trimester ultrasonography, an increased thickness of the nuchal fold (7.9 mm; < 2.5 mm or < 95th percentile – places the pregnancy at a low risk, ≥ 6.5 mm – places the pregnancy at a high risk) was detected as well as a cystic hygroma. No heart defects were detected. Chorionic villus sampling excluded common chromosomal aneuploidies by quantitative fluorescent PCR. Furthermore, chromosomal microarray analysis did not show any pathological variations. The mother reported reduced foetal movements throughout the pregnancy, especially during the third trimester. Despite a normal chromosomal microarray analysis result, suspicion of a genetic pathology persisted for the duration of the prenatal period. However, extensive panel genetic testing using next-generation sequencing or exome sequencing was not performed as it is not a routine prenatal test in Latvia.

The patient was born at 36+1 weeks of gestational age. Due to pelvic presentation, followed by an external cephalic version and bradycardia, an acute caesarean section was performed. The weight of the neonate was 2,950 grams (17th percentile) and the height was 50 cm (52nd percentile). The head circumference was 35 cm (66th percentile).

After the birth, the general condition of the infant was extremely severe. Primary resuscitation was initiated, comprising tactile stimulation, upper airway suctioning and ventilation. The patient had severe respiratory distress, no active movements, atonia and areflexia, and his skin was cyanotic. The Apgar scores were 1/1/2/3. To provide ventilatory support, intubation was required in the first minute after birth; however, the patient’s condition deteriorated and so mechanical ventilation was implemented.

To identify the cause of the infant’s severe condition, TORCH infections were checked for and excluded, head MRI was performed and a geneticist was consulted. The head MRI results reported multiple ischaemic foci in the frontal and parietal lobes and in the basal ganglia. Based on the patient’s clinical signs and symptoms, the geneticist suspected SMA. The parents consented to newborn screening for SMA5q and 7 days after birth a homozygous deletion of exon 7 in the \(SMN1\) gene was reported. Further genetic analysis as part of the Latvian newborn screening protocol detected 0 copies of the \(SMN1\) gene and 1 copy of the \(SMN2\) gene. A diagnosis of type 0 SMA was confirmed.

Ten days after their son's birth, a multidisciplinary team informed the parents about his type 0 SMA diagnosis. They were also informed about the limited treatment options and pessimistic outcome expectancy. Following a full discussion, the parents decided that their son’s aggressive support therapy (mechanical pulmonary ventilation) should be withdrawn and the infant was extubated. Rapid desaturation, bradycardia and cardiac arrest followed and the patient died.

The concluding diagnoses of the neonate were as follows: type 0 SMA, severe asphyxia during labour, femur fracture, atrial septal defect and newborn hypoglycaemia.

**Discussion**

We report here the case of a newborn with type 0 SMA. At the first-trimester ultrasonography, an increased NT thickness was detected. After birth, the patient had severe respiratory distress followed by multiple
events leading to a fatal outcome.

Currently, the identification of SMA-affected infants prior to the presentation of clinical symptoms is accomplished by newborn screening. However, the severity of this disorder highlights the importance of early prenatal detection.

NT thickness evaluation is associated with multiple foetal malformations, genetic syndromes, intrauterine death risk, congenital heart defects and high risk of miscarriage. Most of the structural anomalies are undetectable prior to childbirth. There are only a few published case reports of an increased NT measurement in association with a diagnosis of SMA in the foetus.

It is well established that an increased NT thickness is a predictive value for an adverse pregnancy outcome, even if conventional karyotyping is normal. The risk of foetal malformations is proportional to the NT thickness. Specifically, if the enlargement is between 3.5 and 4.4 mm, the risk of a foetal chromosome abnormality is 21%, rising to 33% if it is 5 mm, 50% if it is 6 mm, and 65% if it is greater than 6.5 mm. However, multiple studies have shown no association between an increased NT thickness and the diagnosis of SMA, suggesting that SMA-affected foetuses have normal NT thickness values. For instance, a study by Zadeh et al. investigated 12 SMA-affected infants with confirmed NT thickness results during pregnancy. All the foetuses had normal NT thickness values ranging from 0.7 to 2.4 mm, implying SMA is not associated with an enlarged NT. Barone and Bianca examining 29 women proposed that foetal genetic testing of the $SMN1$ gene on the basis of increased NT thickness is not indicated in couples with no previous history of SMA. Nevertheless, the findings of Parra et al. support the idea that $SMN2$ gene copy number in SMA foetuses is relevant for the development of congenital heart defects and increased NT thickness values.

A broad range of options is needed to help diagnose SMA prenatally. The gold standard for SMA diagnosis is multiplex ligation probe analysis, a targeted test. However, as an increased NT thickness is not currently considered a sign of SMA, this would not have been employed in the case described here. If the signs are not clear, then prenatally the best next-generation sequencing method is exome sequencing; however, it requires specific bioinformatic analysis, as $SMN1$ and $SMN2$ are genes with high homology. If a neuromuscular disorder is suspected, then targeted neuromuscular disease panels can be used, as described by Zhao et al. and Tan et al. In the case described here, more comprehensive diagnostic procedures should have been performed to try and identify the cause of the abnormal NT result prenatally. This information would have given the parents the option of terminating the pregnancy. However, a major consideration in this case was the financial support provided by the parents’ health insurance, which did not allow for extensive diagnostic procedures.

Innovative treatments have been developed for patients with SMA. However, there are currently no treatment options available for patients with type 0 SMA. These patients require respiratory and feeding support, which typically is not enough to keep the patients alive. A recent case report from Matesanz et al. described the clinical course of a patient with type 0 SMA who was treated with nusinersen and
onasemogene abeparvovec. Although the infant had modest motor improvements, she also had continued systemic complications from her SMA, thus highlighting the challenges of treating patients with more severe phenotypes of SMA. Tiberi et al.’s case report presented the case of a type 0 SMA patient with 1 copy of the SMN2 gene. At the age of 13 days, the infant received treatment with nusinersen. Although he showed mild motor improvement, he required a tracheostomy at the age of 4 months. An increasing cardiac and autonomic dysfunction followed and he died at the age of 5 months. Therefore, the available data suggest that despite the development of innovative treatments for SMA, they are unlikely to produce a significant positive effect in type 0 patients.

Although the outcome expectancy of patients with type 0 SMA is pessimistic and the disease leads to early mortality, newborn screening for SMA5q can significantly improve the life expectancy and quality of patients with the other types of SMA. There is evidence that pre-symptomatic treatment initiated as a result of newborn screening improves the outcome of children with genetically proven SMA. Therefore, it is vital to include SMA in the state-funded newborn screening in Latvia in order to initiate treatment pre-symptomatically and obtain the best outcome for patients.

**Conclusion**

Since there are no treatment options for infants with type 0 SMA at present, it is vital to be able to detect this disease prenatally in order to provide the best possible care for the patient and parents. An increased NT thickness is a clinically relevant sign that can be related to multiple foetal malformations, genetic syndromes, intrauterine death risk, congenital heart defects and high risk of miscarriage. However, at present, there are only limited data supporting an association between NT enlargement and SMA.

Employment of extensive panel genetic testing using next-generation sequencing would be beneficial for prenatal diagnosis of type 0 SMA cases. Moreover, sequencing of foetal exomes covering single nucleotide variations and copy number variations (also SMN1) offers a broader diagnostic capacity for pregnancies with unexpected foetal anomalies, thus improving both diagnostic timing and counselling for parents. Early recognition of the disease would give parents time to come to terms with the situation, as well as provide the option of pregnancy termination.

**Declarations**

Ethics approval and consent to participate

Ethical approval was obtained from Ethics Committee for Research at University of Latvia, Faculty of medicine (ATZINUMS Nr. 19-25/152).

Consent for publication
Written informed consent was obtained from the patient for publication of this case report and any accompanying images. A copy of the written consent is available for review by the Editor-in-Chief of this journal.

Availability of data and materials

The datasets generated during and/or analysed during the current study are available from the corresponding author on reasonable request.

Competing interests

The authors declare that they have no competing interests.

Funding

This research received no specific grant from any funding agency in the public, commercial, or not-for-profit sectors.

Authors' contributions

M. Auzenbaha and T.Cupane conceived of the presented idea. T.Cupane wrote the manuscript with support from M.Auzenbaha, M.Diriks, G.Taurina, L.Kornejeva and L.Gailite. M.Auzenbaha supervised the research. All authors read and approved the final manuscript.

Acknowledgements

Not applicable.

References


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