



A new ankyrin mutation (ANK1 EXON E9X) causing severe hereditary spherocytosis in the neonatal period

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Dear Mr. Ganser,

I revised the manuscript as required in the following points:

1. 2nd paragraph, line 4: I added "increased" prior to MCHC.
2. 2nd paragraph, line 8: Molecular genetic (2 words) instead of molecular genetic
3. 2 paragraph, line 9: On the protein level (codon 9) the guanine/thymine substitution leads to an...
Please find the revision in the attached file.

We would be very grateful if you consider the work for publication.

Yours sincerely

Florian Gundel, MD

A new ankyrin mutation (ANK1 EXON E9X) causing severe hereditary spherocytosis in the neonatal period

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Key words:

- Severe hereditary spherocytosis in newborn
- dominant de novo ankyrin mutation with origin in germ cell lineage

1 Dear editor,
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4 Although hereditary spherocytosis (HS) is a common disorder of the red cell
5 membrane, it is diagnosed in only one third of affected infants during the first year of
6 life [1] and rarely in the newborn period. The degree of hemolysis varies widely from
7 patient to patient, even though the molecular defect appears to be similar [1]. In
8 approximately two thirds of HS patients, inheritance is autosomal dominant. In this
9 group of "typical" HS patients, nonsense and frameshift mutations of ankyrin are the
10 most common cause [2], followed by mutations in band 3 and β spectrin [3]. Cases
11 with autosomal recessive inheritance are due to defects in either alpha-spectrin or
12 protein 4.2. Ankyrin is the principal binding site for spectrin on the red cell membrane;
13 as a result, ankyrin deficiency leads to decreased incorporation of spectrin on the
14 membrane. In approximately one-third of patients with ankyrin deficiency, one ankyrin
15 mRNA allele is virtually missing due to deletion, frameshift, or nonsense mutations
16 that alter transcription, processing, or stability of ankyrin mRNA [1,4,5]. Other ankyrin
17 mutations in dominant hereditary spherocytosis include truncated variants and one
18 nonexpressed isoform [6,7]. Up to now, 55 distinct ankyrin mutations have been
19 reported in human hereditary spherocytosis [8].
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35 We report on a male neonate who was admitted to our hospital because of pallor and
36 tachypnoea at the age of 4 weeks. On admission blood counts revealed low
37 hemoglobin [5.1g/dl], red blood cells [1.9/pl], mean corpuscular volume (MCV)
38 [75,8fl], increased MCHC [36,0 g/dl] and elevated reticulocytes [134‰].
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42 The peripheral blood smear showed spherocytes. Further laboratory investigations as
43 test with hypotonic NaCl dilutions and acidified glycerol lysis test showed the typical
44 decreased osmotic resistance of red cells compatible with a spherocytosis.
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47 Molecular genetic analyses of the patient and the parents were performed. A
48 heterozygous de novo mutation E9X (p.Glu9Term, c.25G>T, GAA>TAA) in exon 1 of
49 the ANK1-gene was detected in the patient. On the protein level (codon 9) the
50 guanine/thymine substitution leads to an aminoacid-break (GAA codes for glutamic
51 acid, TAA is a termination code). As the truncated amino acid chain is highly
52 unstable, no anomalous ankyrin protein should be present in peripheral blood.
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1 This case reports on a new de novo nonsense mutation in the ankyrin protein. In
2 contrast to most affected infants this mutation leads to a severe hemolysis already in
3 the newborn period [9].
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5 Because the mutation was not present in the patient's parents, we emanate from a
6 dominant de novo mutation surfaced during the differentiation of one of the parents'
7 germ cell line precursors, probably late in development. This is consistent to genetic
8 studies in which in most sporadic cases a large number of de novo mutations arises
9 in the maternal germ line [4].
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11 As often the requirement for transfusion was transient [6,9]. The patient reached
12 sustained transfusion independence at an age of 6 months.
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