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Abnormal Newborn SCID Screening Secondary to In-Utero Exposure to Azathioprine: Pharmacogenetics Revealed Nonfunctional Allele of the TMPT or NUDT15 Gene

Frauke Forger[1,2*], Patricia Buhr[2], Astrid Zbinden[2], Carlo R. Largiader[3]

[1]Department of Rheumatology, HOCH Cantonal Hospital St. Gallen, St. Gallen, Switzerland

[2]Department of Rheumatology and Immunology, Bern University Hospital, Inselspital, Bern, Switzerland

[3]Department of Clinical Chemistry, Bern University Hospital, Inselspital, University of Bern, Switzerland

***Corresponding Author:** Frauke Forger, Department of Rheumatology, HOCH Cantonal Hospital St. Gallen, St. Gallen, Switzerland

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Abstract

Based on the evidence and international recommendations, azathioprine is among the immunosuppressive drugs that can be used in pregnancy to control maternal disease. We describe two mothers treated with azathioprine throughout their pregnancies whose term-born neonates presented abnormal screening tests for severe combined immunodeficiency (SCID) at day 3 postpartum. Both SCID tests showed reduced levels of kappa-deleting recombination excision circles (KREC), indicating B-cell lymphopenia. KREC values normalized within 2 to 4 weeks. Pharmacogenetic testing of the infants' dried blood spots revealed one loss-of function allele of the TPMT gene in one case and of NUDT15 in the other. Thus, in the rare case of a TPMT or NUDT15 deficiency, in-utero exposure to azathioprine can lead to lymphopenia at birth, resulting in transiently abnormal SCID newborn screening tests. This potential finding may cause anxiety and uncertainty for parents; therefore, the information should be included in the preconception counselling.

Keywords: Pregnancy, SCID test, Azathioprine, TPMT, NUDT15

Introduction

In pregnancy, uncontrolled chronic inflammatory diseases are often associated with unfavourable pregnancy outcomes, yet these risks can be reduced by effective treatment during pregnancy [1]. Azathioprine is an immunosuppressive drug for which the current body of evidence on 5619 exposures has not shown an increased rate of congenital malformations or miscarriages and which is therefore considered to be compatible throughout pregnancy [1, 2]. As a prodrug azathioprine is metabolized by multiple enzymes into active 6-thioguanine nucleotides, whereas the catabolizing enzymes thiopurine methyltransferase (TPMT) and nudix (nucleoside diphosphate linked moiety X)-type motif 15 (NUDT15) convert thiopurines into inactive metabolites [3]. During pregnancy, 6-TGN partly cross the placental barrier, with a median of 40 percent of the maternal drug levels being detectable in the umbilical cord blood [4].

In Switzerland, the newborn screening (NBS) program includes testing for severe combined immunodeficiencies (SCID) to detect severe primary T-cell and B-cell disorders. For this purpose, the dried blood spots of the neonates are analysed for the quantity of T cell receptor excision circles (TRECs) and kappa-deleting

recombination excision circles (KREC) that correlate with number of freshly generated naïve T- and B-cells [5, 6].

Our two cases demonstrate that there is a need to inform about possible SCID screening results in infants with in-utero exposure to maternal azathioprine.

Case Presentation

Case 1 is a 31-year-old woman diagnosed with ulcerative colitis in 2018 and treated with azathioprine and oral glucocorticoids. One year later, her colitis flared and adalimumab was added. Her disease was stable and inactive when she got pregnant in 2021. She continued her combination therapy with azathioprine (150 mg/day) and adalimumab (40 mg/2 weeks) throughout pregnancy without drug-related adverse effects. Her ulcerative colitis remained inactive and the pregnancy course was uneventful with delivery of a healthy boy at term in November 2021. The infant's NBS test that was performed at day 3 was abnormal with undetectable KREC copies, indicating B-cell depression. At the follow-up measurement 25 days later, the KREC copy number was within the normal range and the neonate remained without infectious symptoms. The transient neonatal B-cell lymphopenia following in-utero azathioprine exposure was the reason for performing a pharmacogenetic test in the child using its dried blood spot. The result showed that the infant carried one normal and one non-function allele of the TPMT (genotype: *1/*3A) gene, explaining a reduced enzyme capacity to metabolize 6-TGN (Table 1).

Case 2 is a 29-year-old woman who was diagnosed with bilateral non-infectious uveitis with retinal vasculitis in 2020, yet no definite chronic inflammatory systemic disease. Since her uveitis was insufficiently controlled with topical and oral glucocorticoids alone, azathioprine (75 mg/day) was added in 2021 (Table 1) that was well tolerated without cytopenia in the differential blood count. In 2022, the patient got pregnant and continued azathioprine throughout pregnancy alongside 5 mg daily prednisolone in the first and second trimester. After an uncomplicated pregnancy the patient delivered a healthy girl at term in May 2022. On day 3 postpartum, the NBS test revealed a decreased number of KREC copies, indicating low peripheral B-lymphocytes. On follow-up testing at day 15 after birth, the KREC value normalized. The neonate was asymptomatic. Pharmacogenetic analysis of thiopurine-catalysing enzymes was performed in the mother and the infant (reusing the infant's dried blood spot). Genotyping for TPMT showed normal function alleles (wildtype genotype *1/*1) in both the mother and her child. Further investigations revealed that the infant was heterozygous for a non-function allele of the NUDT15 gene (genotype: *1/*2 or *3), which leads to impaired activity of the NUDT15 enzyme in the breakdown of active 6-TGN metabolites (Table 1).

	Case 1			**Case 2**	
Maternal diagnosis	Ulcerative colitis (pancolitis)			Anterior/intermediate uveitis	
Maternal age at delivery	31			29	
Medication during pregnancy	Azathioprine 150 mg/d Adalimumab 40 mg / 2 weeks			Prednisolone 5 mg/d (1T +2T) Azathioprine 75 mg/d	
Infant					
Weeks gestation at birth	37+4			39+0	
Gender	Male			Female	
Birth weight [g] (birth percentile)	4420 (>97)			3060 (25)	
Newborn SCID-screening (day postpartum)	day 3	day 11	day 28	day 3	day 15
TREC (copies/punch of DBS, [ref ≥6])	98	171	101	196	468
KREC (copies/punch of DBS, [ref ≥4])	**0**	**1**	79	**1**	10
Pharmacogenetics					
TPMT genotype mother	unknown			2 normal function alleles	
TPMT genotype infant	**1 no function allele (*1/*3A)**			2 normal function alleles	
NUDT15 genotype infant	2 normal function alleles			**1 no function allele (*1/*2 or *3)**	

DBS: dried blood spot; **TMPT**: Thiopurine Methyltransferase, **NUDT15**: Nudix-Type Motif 15; TMPT genotype determined by genotyping rs1800460 and rs1142345; **NUDT15** genotype determined by genotyping rs116855232.

Table 1: Mother-infant characteristics, newborn SCID screenings and pharmacogenetic findings**.**

Discussion

In summary, we report on two full-term infants exposed to azathioprine in utero who showed B-cell depression in the newborn SCID screening after birth. In both cases, the B-cell depression was temporary, unrelated to SCID, and attributable to a heterozygous non-functional allele of the catabolizing enzymes TPMT or NUDT15, which led to a reduced degradation of cytotoxic azathioprine metabolites. Based on their genotype, both newborns were classified as intermediate azathioprine metabolizers, but despite temporary B-cell cytopenia they remained clinically asymptomatic.

The SCID results caused great concern among the parents, as they weren't expecting such a possible finding in their infants. The scale of the frequency of abnormal SCID screenings in the general population is very low; as shown in a Swedish cohort of 58'834 newborns of whom only 64 (0.1%) had abnormal test results [7]. The majority of these abnormal SCID tests were due to non-SCID conditions such as prematurity or maternal treatment with thiopurine drugs during pregnancy (azathioprine (n=9), mercaptopurine (n=1), azathioprine and tacrolimus (n=3)) [7]. Similar to our cases, all 13 infants with in-utero drug exposure had selectively low KREC levels at birth that recovered spontaneously within a few weeks, suggesting that B cell generation is more sensitive to cytotoxic azathioprine metabolites than T cell generation [7, 8]. However, transiently low TREC levels in SCID screenings were also found in a small case series of four infants after in-utero exposure to maternal immunosuppressives, two of whom were exposed to azathioprine [9].

The current evidence of azathioprine in pregnancy that was recently reviewed by EULAR does not raise safety concerns [2]. No increased rate of serious infections was found in two large cohorts of 102 and 3392 infants born to mothers with inflammatory bowel disease who were treated with azathioprine during pregnancy and breastfeeding [10, 11]. Cord blood on 4 infants exposed to azathioprine in-utero showed normal TREC level at delivery, and normal B-cell and T-cell levels, immunoglobulin levels and a normal concentration of protecting antibody levels to Tetanus, Diphtheria, Hemophilus influenza-B and hepatitis B at 12 months [12].

Adverse events of azathioprine depend on the dosing and, less commonly, on genetic polymorphisms that result in low activity of azathioprine-catabolizing enzymes. In Caucasians, the frequency of intermediate metabolizers, i.e. heterozygous carriers of a loss-of-function allele, is 0.083 for TMPT and 0.007 for NUDT15; in such cases lymphopenia may occur at normal doses of azathioprine [3]. Accordingly, in a report of four newborns whose mothers used azathioprine throughout their pregnancies, abnormal SCID tests and lymphopenia could be attributed to TPMT loss-of-function variants in three infants and to a relatively high dose of maternal azathioprine (200 mg/day) in one case [13].

Conclusions

Our two cases highlight that in-utero exposure to azathioprine may results in a transient abnormal SCID screening in the neonate. Pharmacogenetic testing could clarify that the reduced B-lymphopenia in both newborns was due to heterozygous nonfunctional gene variant of the azathioprine catabolizing enzymes, TPMT in one case and NUDT15 in the other. Our report and other studies showed that lymphopenia was clinically irrelevant and normalized within a few weeks [7, 9, 13]. On the other hand, there is extensive evidence supporting the safety of azathioprine in pregnant women at doses up to 2 mg/kg, most notably without serious adverse events in exposed infants [1, 2]. A well-tolerated azathioprine medication should therefore be continued during pregnancy to ensure stable, inactive disease in the mother, which in turn is crucial for a favourable birth outcome. However, abnormal newborn SCID tests secondary to maternal immunosuppressives can cause concern and anxiety in parents who are not informed about this possible finding. Our two cases should raise awareness and encourage to include this information in the pre-pregnancy counselling.

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