Immuno-hematological findings in Delayed Hemolytic Transfusion Reaction (DHTR)

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Transfusion is still a key therapeutic tool in SCD patient management

**Features of blood transfusion in children with sickle cell disease**

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- General population in 2016 => 0,78 % (Annual report hemovigilance 2016 - ANSM)
- 150 SCD children (0,1-18 y/o) : 53 % were transfused at least once

- Another cohort of 245 children : 71 % were transfused at least once

Chronic exposure to blood transfusion => 2 main complications :
- Iron overload
- Risk of allo-immunization
Discrepancies between recipients and donors

Risk of allo-immunization => Phenotype discrepancies between recipients (African descendants) and donors (mostly Europeans)

"Typical SCD recipient phenotype":
RH: 1, -2, -3, 4, 5; KEL: -1; FY: -1, -2; JK: 1, -2; MNS: -3, 4

Geographic distribution of the $R^0$ haplotype
Geographic distribution of the $GYPB^*03$ allele
Geographic distribution of the $FY^*02N.01$ allele
Geographic distribution of the $JK^*02$ allele
Discrepancies between recipients and donors

Diagram showing the distribution of ABO phenotypes in six selected populations

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Group B

Geographic distribution of KEL *02.06 (encoding Jsα or KEL6)

Les groupes sanguins érythrocytaires, Première édition. P. Bailly et al.

Prevalence => up to 20% - Not really a low frequency antigen!
Discrepancies between recipients and donors

France - RH genotyping 403 patients

⇒ 34/403 with partial-D phenotype: 8.4%
⇒ 21/101 with partial-C phenotype: 20.8%
⇒ 14/400 with partial-e phenotype: 3.5%

Alloimmunization rate 6/34: 17.6%
Alloimmunization rate 3/21: 14.3%
Alloimmunization rate 1/14: 7.1%
Anti-e seems to be mostly autoantibody

USA - RH genotyping 226 patients (Bead chip / BioArray and Sequencing)

⇒ RHD variant alleles in 36% of individuals
⇒ RHCE*ce variant alleles in 72% of individuals

Nb: these alleles may be compensated => number of individuals is lower
Main features of the alloimmunization risk in SCD patients

• Much higher risk of immunization in SCD patients
  3.9% (general population)
  7% to 58% (depending on unit selection policy)
  23.4% (pediatric cohort - 152 patients)
  4% to 16% will experience a DTHR

• Once immunized 61% higher chance of developing a new Ab

• Presence of auto-Ab is risk factor for alloimmunization

• Evanescent Ab => up to 30%

• Anti-RH2, anti-RH5, anti-RH1, anti-RH3, anti-FY1, anti-JK2, anti-MNS3
  and anti-MNS1, anti-KEL3, anti-CO2 are the most common antibodies
  found
Which specificities do we focus on?

- Anti-H1I1
- Anti-RH1 (Anti-D) / anti-RH2 (Anti-C) / anti-RH5 (Anti-e)
- Anti-JK2 or Anti-JK1 (Anti-JkB or Anti-JKa)
- Anti-MNS3 (Anti-S)
- Anti-LFA => Anti-KEL6 (Anti-Jsa) / Anti-RH10/20 (anti-V, anti-VS) / anti-RH23 (Anti-Dw)
- Anti-HFA => Anti-MNS5 (Anti-U) / Anti-MNS30 / anti-FY3 (Anti-Fy3) / Anti-DO4 (Anti-Hy) / Anti-DO5 (Anti-Joa) / anti-RH
- Ruling out every antibody of common specificity

RH1(D), RH2(C), RH3(E), RH4(C), RH5(e), RH8(Cw), KEL1(K), KEL2(k), KEL3(KpA), KEL4(KpB), FY1(FyA), FY2(FyB), JK1(JKa), JK2(JkB), MNS1(M), MNS2(N), MNS3(S), MNS4(s), LE1(Lea), LE2(Leb), P1PK1(P1), LU1(Lua), LU2(Lub), DO1(Doa), DO2(DoB), LU1(Lua), LU2(Lub), CO1(Coa), CO2(Cob), YT1(Yta), YT2(Ytb), XG1(Xga)
What molecular workup do we perform?

- Never conclude autoantibody in the RH system without performing molecular workup
  - If patient C+ (RH:2) => tested for (C)ceS and RN
  - If anti-D => genomics
  - If anti-e => testing for:
    - c.254C>G => RHCE*ceAG
    - c.340C>T => RHCE*ceJAL
    - c.667G>T => RHCE*ceMO
    - c.712A>G => RHCE*ceAR / RHCE*ceEK / RHCE*ceBI / RHCE*ceSM
    - c.1006G>T => RHCE*ceS
    - c.1025C>T => RHCE*ceT1

- Perform an extended genotype to deduce the phenotype
  - DO1/DO2 (Do\textsuperscript{a} / Do\textsuperscript{b})
  - RH10/RH20 (V/VS)
  - KEL6/KEL7 (Anti-\textit{Js}\textsuperscript{a} / Anti-\textit{Js}\textsuperscript{b})
Different situations encountered when a DHTR was reported
Case report n°1

- Patient O RH:-2,-3; KEL:-1; FY:-1,-2; JK:-2; MNS:-1,-3
- Immunized with Anti-RH2, Anti-MNS3, Autoantibodies
- In 2016 => Transfused accidentally with 1 unit MNS:3 unit (pre-T Ab screen negative)
- 10 days post-transfusion => DHTR diagnosis Hb = 3g/dL
- Ab identification (+11 days) => Anti-RH2 + anti-MNS3 + anti-MNS1 + anti-FY3
- 1 year after => Ab screen negative
In 2018 hip surgery: Transfusion of 1 unit (fully matched) with premedication => DTHR 8 days after

In the CNRGS Ab screen was confirmed to be negative

New transfusion needed (Hb= 3g/dL) at day 10 (signs of cardiac failure) => made with eculizumab
Case report n°2

- Patient B RH:-2,-3; KEL:-1,-3; FY:-1,-2; JK:-2; MNS:-3
- Immunized : Anti-RH5 (auto), Anti-KEL3, Anti-JK1 (auto), Anti-JK2 and Anti-MNS3, Anti-FY3
- Since 2012, the antibody screen was negative (about 5 transfusion episodes)
- Sept 2017 VOC => 2 units (09/09) / 2 units (14/09) and a new prescription of 2 units (21/09) => no fresh units available
- Local blood bank’s demand => frozen units to treat resistant VOC
- Stop II => High suspicion of a DHTR Hb= 5,9 g/dL
- Ab screen showed an « autoantibody anti-HFA » and anti-RH10 / anti-RH20
- [Hb] nadir = 4,6 g/dL
Case report n°2

- Investigation of the imputability of anti-RH10/RH20
- Haemovigilance services called back the 4 donors of the 4 units transfused in September 2017
  - Phenotyped / genotyped
  - Cross match
- Interestingly, in the local blood bank => Xmatches were positive for some units (auto ? or a new alloantibody ?)
- Follow-up at 4 months: Autoantibody + anti-RH5 + anti-RH20 + anti-KEL3 + anti-MNS3
- Follow-up at 6 months: same specificities / same intensities
- New episode of DHTR 1 year after => Stand by of the bone marrow transplant
Case report n°3

- Patient O RH:-3, P4; KEL:-1  (RHCE*ceBl at heterozygous state)
- Genotyping => FY*O/FY*O; JK*1/JK*2; MNS*4/MNS*4; DO*2/DO*2; MNS*1/MNS*2; KEL*6/KEL*7
- Immunized: Anti-RH3, Anti-RH8, Anti-FY1, Anti-MNS3 and Anti-LE1
- 25-07 => Exchange transfusion (5 units)
  - RH:-3,-4; KEL:-1; FY:-1; JK:-2; MNS:-3.
- 03-08 => Cholecystectomy
- 04-08 => Suspicion of DHTR [Hb] nadir = 3.2 g/dL
- Ab screen in the local blood bank => pan agglutination
CNRGS identification of anti-FY3
Follow-up at 1 month: anti-FY3, anti-DO1, anti-KEL3, anti-RH3, anti-RH8 + « autoantibodies »
Other situations

- Patient with a complex mixture of auto and alloantibodies:
  - Anti-RH3, anti-RH4, anti-RH5, anti-FY1, anti-MNS1, anti-MNS3 and anti-KEL6 (pre-transfusion Ab screen was negative)
  - Anti-RH1 (auto), Anti-RH5(auto), Anti-RH7, Anti-KEL1, Anti-KEL3, anti-FY1, anti-FY3, anti-JK1, anti-DO1, anti-MNS2 (Ab still detectable)
    - GYPB sequencing to make sure that anti-MNS2 can be considered as an autoantobody => MNS:2 unit is safe to use.

- Sometimes what looks like an auto anti-U is an anti-MNS30 (alloantibody) => patient MNS:1,-2,-3,4 with a MNS*4 variant allele
Anti-HI can cause a severe delayed hemolytic transfusion reaction with hyperhemolysis in sickle cell disease patients

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Take-home messages

- DTHR Must be diagnosed as early as possible: Additional Transfusion worsens hemolysis => monitoring HbA is key
- Flag your patients with a history of DHTR
- Even a weak Ab / undetectable Ab can be dangerous
- Every specificity can be dangerous (including natural antibodies)
- Investigate partial antigen (mandatory for RH / should be considered for other systems)
- Think about «Low Frequency Antigens» => crossmatch every unit
- Not detecting antibodies does not rule out the diagnosis of DHTR (30%)
- Providing units with the matching phenotype is a must but is only one part of the solution
- Extended phenotype units: Implementing a phenotyping / genotyping policy / running a rare donor program
- Discuss a treatment of DHTR if transfusion is really needed (life-threatening situations)