CAREST
CARIBBEAN NETWORK OF RESEARCHERS ON SICKLE CELL DISEASE AND THALASSEMIA

GREX

5th CARIBBEAN CONFERENCE

Sickle cell disease and Thalassemia

Update in clinical care and research

French Guiana University, Cayenne
October 24-26, 2018

Université de Guyane

CLUB DU GLOBULE ROUGE ET DU FER

ars Agence Régionale de Santé Guyane
A.G.D.P.M

Ville de Cayenne
L'évolution d'une tradition

ars Agence Régionale de Santé Guadeloupe

centre de référence maladies rares

CHOG Centre Hospitalier de l'Ouest Guyanais

CHC Centre Hospitalier de Cayenne

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French Guiana University, Cayenne October 24-26, 2018 - Building A, Amphitheater

Scientific Committee

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N. Elenga, French Guiana
M. Etienne-Julan, Guadeloupe
G. Carles, French Guiana
M. Nacher, French Guiana
M. Romana, Guadeloupe
G. Loko, Martinique
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R. Villaescusa, Cuba
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Organizing Committee

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Secretariat

Stella Ilise, Guadeloupe
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Contact for information and registration :

carestcom@gmail.com
http://www.carest-network.org/

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Mercredi 24/10/2018

15h – 17h : **Réunion d'information, débat**
(public : élèves de terminale, étudiants de l'Université de Guyane) :
Qu'est-ce que le CAREST ?
Les métiers de la recherche
Echanges internationaux et recherche

Participants : représentant de l'Inserm, des universités de Paris Diderot, Paris Descartes, West Indies, São Paulo, la Havana, Santo-Domingo, de l'université fédérale de Rio de Janeiro, Imperial College of London, université de Guyane et du Groupement d'Intérêt Scientifique de Guyane

19h00– 20h00 : **Cérémonie d'ouverture**

Salle des délibérations de la Mairie de Cayenne

Maire de Cayenne, Président de l'Université de Guyane, Président de la Collectivité territoriale, Directrice du Centre Hospitalier Andrée Rosemon, Directeur Centre Hospitalier de l'Ouest Guyanais, Directeur Général ARS, Directeur Centre drépanocytose Guyane, Présidente de CAREST, Coordinateur du Laboratoire d'excellence, GR-Ex

Sickle cell disease and Thalassemia

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French Guiana University, Cayenne October 24-26, 2018 - Building A, Amphitheater

Wednesday 24/10/2018

PM

3:00 – 5:00 : **Information/debate meeting**
(public: senior high-school and university students of French Guiana university):
What is CAREST?
Careers in research
International exchanges and research

Participants : representative of Inserm, universities of Paris Diderot, Paris Descartes, West Indies, São Paulo, la Havana, Santo-Domingo, Federal University of Rio de Janeiro, Imperial College of London, university of French Guiana and the Group of Scientific Interest of French Guiana

7:00 – 8:00 : **Opening ceremony**

Deliberations room of the Town Hall of Cayenne

Mayor of Cayenne, President of the French Guiana University, President of the Territorial Collectivity, Director of Andree Rosemon Hospital Center, Director of West Guiana Hospital Center, Director of the Regional Health Agency in French Guiana, Director of French Guiana Sickle Cell Center, President of CAREST, Coordinator of the Laboratory of Excellence, GR-Ex.

Sickle cell disease and Thalassemia

Update in clinical care and research

French Guiana University, Cayenne October 24-26, 2018 - Building A, Amphitheater

Jeudi 25/10/2018

7h00 - 8h30 : **Inscription**

> Epidémiologie des maladies du globule rouge
Modérateurs : Jacques Elion & Narcisse Elenga

8h30 - 8h50 : Epidémiologie mondiale des hémoglobinopathies :
Frédéric Piel (Londres, UK)

8h50 - 9h05 : Focus sur les Caraïbes : Marc Romana (Pointe-à-Pitre, Guadeloupe, France)

9h05 - 9h25 : Déficit en G6PD, update : Frédéric Galactéros (Créteil, France)

9h25 - 9h45 : Transition épidémiologique de la drépanocytose en Afrique de l'Ouest et Centrale : évolution de la morbi-mortalité dans les zones Urbaines :
Brigitte Ranque (GR-Ex - Paris, France)

9h45 - 10h00 : Discussion

10h00 - 10h20 : Présentations orales sélectionnées

"Sickle Cell Disease in Venezuela is Currently in Crisis (Venezuela)":
Adriana Bello (Caracas, Venezuela)

"Cuban Program for Prevention of Sickle Cell Disease. Thirty-five years results (Cuba)": Beatriz Marcheco-Teruel (La Habana, Cuba)

10h20 - 10h35 : Discussion

10h35 - 11h00 : Pause

> Prise en charge globale : les recommandations
Modérateurs : Mariane de Montalembert & Ketty Lee

11h00 - 11h20 : Indications de splénectomie dans les pathologies de la membrane du globule rouge : Loïc Garçon (Amiens, France)

11h20 - 11h40 : Nouvelles thérapeutiques pour les thalassémies :
Olivier Hermine (GR-Ex - Paris, France)

Sickle cell disease and Thalassemia

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Thursday 25/10/2018

7:00 - 8:30 : **Registration**

> Epidemiology of red blood cell disorders
Chairmen : Jacques Elion & Narcisse Elenga

8:30 - 8:50 : Global epidemiology of haemoglobinopaties: Frédéric Piel (London, UK)

8:50 - 9:05 : Focus on the Caribbean: Marc Romana (Pointe-à-Pitre, Guadeloupe, France)

9:05 - 9:25 : G6PD deficiency, an update: Frédéric Galactéros (Créteil, France)

9:25 - 9:45 : Epidemiological transition of Sickle Cell Disease in Western and Central Africa: evolution of the morbi-mortality in urban areas: Brigitte Ranque (GR-Ex - Paris, France)

9:45 - 10:00 : Discussion

10:00 - 10:20 : Selected oral presentations

"Sickle Cell Disease in Venezuela is Currently in Crisis (Venezuela)": Adriana Bello (Caracas, Venezuela)

"Cuban Program for Prevention of Sickle Cell Disease. Thirty-five years results (Cuba)": Beatriz Marcheco-Teruel (La Habana, Cuba)

10:20 - 10:35 : Discussion

10:35 - 11:00 : Break

> Comprehensive medical management: recommendations
Chairmen : Mariane de Montalembert & Ketty Lee

11:00 - 11:20 : Indications of splenectomy in red cell membrane disorders: Loïc Garçon (Amiens, France)

11:20 - 11:40 : Novel therapeutic approaches for thalassemia :
Olivier Hermine (GR-Ex - Paris, France)

Sickle cell disease and Thalassemia

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11h40 - 12h00 :	Drépanocytose – couverture vaccinale : Narcisse Elenga (Cayenne, Guyane Française)
12h00 - 12h15 :	Discussion
12h15 - 13h35 :	Repas
	> Diagnostic et Organisation du DNN *Modérateurs : Marvin Reid & Marie-Dominique Hardy-Dessources*
13h35 - 13h50 :	Synthèse de l'expérience pour la Caraïbe non francophone : Monica Asnani (Kingston, Jamaïque)
13h50 - 14h05 :	Synthèse de l'expérience francophone et des collaborations avec Tobago et Grenade : Ketty Lee (Pointe-à-Pitre, Guadeloupe, France)
14h05 - 14h25 :	Nouvelles stratégies de dépistage : des tests rapides aux plate formes de très haut débit : Jacques Elion (GR-Ex - Paris, France)
14h25 - 14h45 :	Présentations orales sélectionnées
	"Newborn screening in Cap Haitian, Haiti: present and future": Ofelia Alvarez (Miami, USA)
	"Presence of non-african haplotypes in sickle cell patients in Colombia probably due to admixture among amerindian, european, and african populations": Cristian Fong (Cali, Colombia)
14h45 - 15h00 :	Discussion
15h00 - 15h20 :	Pause
	> Thématiques spécifiques Modérateurs : Bérengère Koehl & Gisèle Elana
15h20 - 15h40 :	Prise en charge des grossesses chez les femmes drépanocytaires en Guyane : aspects historiques, adaptation de la prise en charge : Gabriel Carles (Saint Laurent du Maroni, Guyane Française)

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11:40 - 12:00 :	Sickle cell disease – vaccination coverage: Narcisse Elenga (Cayenne, French Guiana)
12:00 - 12:15 :	Discussion
12:15 - 1:35 :	Lunch
	> Diagnostic and organization of newborn screening *Chairmen : Marvin Reid & Marie-Dominique Hardy-Dessources*
1:35 - 1:50 :	Review of the experience of the non-French speaking Caribbean: Monika Asnani (Kingston, Jamaica)
1:50 - 2:05 :	Review of the French Caribbean experience and its collaborations with Tobago and Grenada: Ketty Lee (Pointe-à-Pitre, Guadeloupe, France)
2:05 - 2:25 :	New screening strategies: from rapid tests to high-throughput screening platforms: Jacques Elion (GR-Ex-Paris, France)
2:25 - 2:45 :	Selected oral presentations
	"Newborn screening in Cap Haitian, Haiti: present and future": Ofelia Alvarez (Miami, USA)
	"Presence of non-african haplotypes in sickle cell patients in Colombia probably due to admixture among amerindian, european, and african populations": Cristian Fong (Cali, Colombia)
2:45 - 3:00 :	Discussion
3:00 - 3:20 :	Break
	> Specific Topics *Chairmen: Bérengère Koehl & Gisèle Elana*
3:20 - 3:40 :	Management of sickle cell women 's pregnancies in French Guiana : historical aspects, evolution: Gabriel Carles (Saint Laurent du Maroni, French Guiana).

Sickle cell disease and Thalassemia

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15h40 - 15h55 :	Nouvelles approches du traitement de la douleur : Maryse Etienne-Julan (Pointe-à-Pitre, Guadeloupe, France)
15h55 - 16h10 :	Cinétique des antibiotiques chez les patients drépanocytaires : Bérengère Koehl (Paris, France)
16h10- 16h25 :	Echo Doppler Transcranien : analyse à distance, expérience de la République Dominicaine : Rosa Nieves (Santo-Domingo, République Dominicaine)
16h25 - 16h40 :	Répercussions scolaires de la drépanocytose : Corinne Pondarré (Créteil, France)
16h40 - 16h50 :	Présentations orales sélectionnées "Implications of a paediatrician-psychologist tandem for sickle cell disease care and impact on cognitive functioning": Adrienne Lerner (Paris, France)
16h50 - 17h05 :	Discussion
17h05 - 17h20 :	Pause
17h20 - 18h00 :	**> Table Ronde :** Education thérapeutique Anne Jolivet, Chantal Placide (CHOG - Guyane Française), Gylna Loko (EVAD - Lamentin, Martinique, France), Alizée Sterlin (ROFSED - Paris, France), Gisèle Elana (Pédiatrie, Martinique, France), Lydia Di vialle-Doumdo (UTD - Guadeloupe, France)
18h00 - 19h00 :	**> Communications visée grand public** *Modérateurs : Edda Hadeed & Gylna Loko* Impliquer les patients en tant qu'experts pour la conception d'outils de santé mobile destinés à soutenir l'auto-gestion de la drépanocytose : David Issom (Genève, Suisse) Greffe de cellules souches hématopoïétiques : Jean-Hugues Dalle (Paris, France) Thérapie génique : Emmanuel Payen (GR-Ex - Fontenay-aux-Roses, France)

Sickle cell disease and Thalassemia

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3:40 - 3:55 :	New approaches of pain management: Maryse Etienne-Julan (Pointe-à-Pitre, Guadeloupe, France)
3:55 - 4:10 :	Kinetics of antibiotics in sickle cell patients: Bérengère Koehl (Paris, France)
4:10 - 4:25 :	Transcranial Doppler screening: analysis at distance, experience developed by Dominican Republic: Rosa Nieves (Santo Domingo, Dominican Republic)
4:25 - 4:40 :	School impacts of SCD: Corinne Pondarré (Créteil, France)
4:40 - 4:50 :	Selected oral presentations
	"Implications of a paediatrician-psychologist tandem for sickle cell disease care and impact on cognitive functioning": Adrienne Lerner (Paris, France)
4:50 - 5:05 :	Discussions
5:05 - 5:20 :	Break
5:20 - 6:00 :	**> Round Table:** Therapeutic education Anne Jolivet, Chantal Placide (CHOG - French Guiana), Gylna Loko (EVAD - Lamentin, Martinique, France), Alizée Sterlin (ROFSED - Paris, France), Gisèle Elana (Pédiatrie, Martinique, France), Lydia Divialle-Doumdo (UTD - Guadeloupe, France)
6:00 - 7:00 :	**> Curative treatments: Communications for general public** *Chairmen: Edda Hadeed & Gylna Loko* Coping with: contribution of new technologies (Living with Sickle Cell Disease in the Age of Medicine 2.0): David Issom (Geneva, Switzerland) Hematopoietic stem cell transplantation: Jean-Hugues Dalle (Paris, France) Gene therapy: Emmanuel Payen (GR-Ex - Fontenay-aux-Roses, France)

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Vendredi 26/10/2018

> Thérapeutiques :

Hydroxycarbamide
Modérateurs : Caroline Le Van Kim & Monika Asnani

8h00 - 8h20 : Expérience Américaine : Dose maximale tolérée : Russell Ware (Cincinnati, USA)

8h20 - 8h40 : Expérience de l'Inde : faible dose fixe : Dipty Jain (Nagpur, India)

8h40 - 8h55 : Hydroxycarbamide et AVC - Jamaïque : Marvin Reid (Kingston, Jamaïque)

8h55 - 9h15 : Exploitation des données HU-ESCORT pour les DFA :
Enfants : Narcisse Elenga (Cayenne, Guyane Française)
Adultes : Maryse Etienne-Julan (Pointe-à-Pitre, Guadeloupe, France)

9h15 - 9h30 : Discussion

9h30 - 9h50 : Applications thérapeutiques de l'hepcidine :
Sophie Vaulont (GR-Ex - Paris, France)

9h50 - 10h20 : Présentations orales sélectionnées

"Fetal hemoglobin in sickle cell disease: new insights into the expression, cellular distribution and the effect of hydroxycarbamide on the cellular level": Sara El Hoss (CGRF-Paris, France)

"Identification of components of the mechanistic target of rapamycin complex 1 (mtorc1) pathway as potential regulators of fetal globin": Danitza M. Nébor (Bar Harbor, ME, USA)

"Hydroxyurea treatment in sickle cell anemia induces changes in microparticles characteristics and their impact on endothelial cell phenotype": Yohann Garnier (Pointe-à-Pitre, Guadeloupe, France)

10h20 - 10h35 : Discussions

10h35 - 10h50 : Pause

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Friday 26/10/2018

> Therapeutic aspects:

Hydroxycarbamide
Chairmen: Caroline Le Van Kim & Monika Asnani

8:00 - 8:20 : USA experience: Maximal Tolerated Dose: Russell Ware (Cincinnati, USA)

8:20 - 8:40 : Indian experience: fixed low dose: Dipty Jain (Nagpur, India)

8:40 - 8:55 : Hydroxycarbamide and stroke – Jamaica experience: Marvin Reid (Kingston, Jamaica)

8:55 - 9:15 : Exploitation of HU-ESCORT data (French Caribbean)
Children: Narcisse Elenga (Cayenne, French Guiana)
Adults: Maryse Etienne-Julan (Pointe-à-Pitre, Guadeloupe, France)

9:15 - 9:30 : Discussion

9:30 - 9:50 : Therapeutic applications of hepcidin: Sophie Vaulont (GR-Ex - Paris, France)

9:50 - 10:20 : Selected oral presentations

"Fetal hemoglobin in sickle cell disease: new insights into the expression, cellular distribution and the effect of hydroxycarbamide on the cellular level": Sara El Hoss (CGRF-Paris, France)

"Identification of components of the mechanistic target of rapamycin complex 1 (mtorc1) pathway as potential regulators of fetal globin": Danitza M. Nébor (Bar Harbor, ME, USA)

"Hydroxyurea treatment in sickle cell anemia induces changes in microparticles characteristics and their impact on endothelial cell phenotype": Yohann Garnier (Pointe-à-Pitre, Guadeloupe, France)

10:20 - 10:35 : Discussion

10:35 - 10:50 : Break

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La Transfusion
Modérateurs : Yves Colin Aronovicz & Rinaldo Villaescusa

10h50 - 11h10 : Risque infectieux et transfusion :
Expérience du Brésil : Luiz Amorim (Rio de Janeiro, Brésil)

11h10 - 11h25 : Lésions de stockage : faut-il transfuser des concentrés globulaires jeunes ?
Caroline Le Van Kim (GR-Ex – Paris, France)

11h25 - 11h45 : Adaptation entre les donneurs, les dons, les circuits et les patients :
un défi pour la Guyane française : Olivier Garraud (Paris, France)

11h45 - 12h00 : Discussion

12h00 - 12h40 : **Table ronde :** Le don du sang en Guyane française
La place de la transfusion dans la prise en charge des patients drépanocytaires : Lydia Divialle (Pointe-à-Pitre, Guadeloupe, France)
Don du sang en Guyane française : Point de vue de l'EFS Antilles-Guyane :
Françoise Maire (Cayenne, Guyane, France)
Don du sang en Guyane française : Point de vue de l'INTS :
Olivier Garraud (Paris, France)

12h40 - 14h00 : Repas

Traitements curatifs
Modérateurs : Russell Ware & Maryse Etienne-Julan

14h00 - 14h20 : **Greffe de Cellules Souches Hématopoïétiques :**
Expérience globale : Jean-Hugues Dalle (Paris, France)

14h20 - 15h00 : **Table ronde :**
Expérience des DFA (G. Elana, Martinique), de la France hexagonale (J-H Dalle, Paris), de Trinidad pour les patients thalassémiques (Waveney Charles, Trinidad et Tobago)

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Transfusion
Chairmen: Yves Colin Aronovicz & Rinaldo Villaescusa

10:50 - 11:10 :	Infectious risk and transfusion: Brazil experience: Luiz Amorim (Rio de Janeiro, Brazil)
11:10 - 11:25 :	Storage lesions: Caroline Le Van Kim (GR-Ex - Paris, France)
11:25 - 11:45 :	Adaptation between donors, donations, tours and patients: a challenge for French Guiana: Olivier Garraud (Paris, France)
11:45 - 12:00 :	Discussion
12:00 - 12:40 :	**Round table:** Blood donation in French Guiana Role of transfusion in the management of SCD patients: Lydia Divialle (Pointe-à-Pitre, Guadeloupe, France) Blood donation in French Guiana: French West Indies EFS point of view: Françoise Maire (Cayenne, French Guiana) Blood donation in French Guiana: INTS point of view: Olivier Garraud (Paris, France)
12:40 - 2:00 :	Lunch

Curative treatments
Chairmen: Russell Ware & Maryse Etienne-Julan

2:00 - 2:20 :	**Hematopoietic stem cell transplantation:** Global experience: Jean-Hugues Dalle (Paris, France)
2:20 - 3:00 :	**Round Table** HSCT experience in the French Caribbean (Gisèle Elana, Martinique), in mainland France (Jean-Hugues Dalle, Paris), in Trinidad in thalassaemia patients (Waveney Charles, Trinidad and Tobago)

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15h00 - 15h20 : Présentations orales sélectionnées

"BID cleavage pattern dependent on erythropoietin-induced casein kinase-1a determines the fate of erythroid precursors": Geneviève Courtois (Paris, France)

"Cell-derived microparticles in sickle cell disease chronic vasculo pathy in sub-saharan africa": Abdoul Karim DEMBELE (CGRF-Paris, France)

15h20 - 15h30 : Discussion

15h30 - 15h45 : Pause

Architecture génétique et thérapie génique des hémoglobinopathies
Modérateurs : Olivier Hermine & Marc Romana

15H45 - 16h05 : Thérapie génique des hémoglobinopathies : Emmanuel Payen (GR-Ex - Fontenay-aux-Roses, France)

16h05 - 16h25 : Génétique, génomique et drépanocytose : Laurent Gouya (GR-Ex, Paris, France)

16h25 - 16h35 : Discussions

16h35 - 17h30 : **Débat :** Guérir la drépanocytose versus Améliorer la prise en charge

16h35 - 16h55 : Priorité : guérir la drépanocytose : Marianne de Montalembert (Paris, France)

16h55 - 17h15 : Priorité : améliorer la prise en charge : Russell Ware (Cincinnati, USA)

17h15 - 17h30 : Discussion

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3:00 - 3:20 : Selected oral presentations

"BID cleavage pattern dependent on erythropoietin-induced casein kinase-1a determines the fate of erythroid precursors": Geneviève Courtois (Paris, France)

Cell-derived microparticles in sickle cell disease chronic vasculopathy in sub-saharan africa": Abdoul Karim DEMBELE (CGRF-Paris, France)

3:20 - 3:30 : Discussion

3:30 - 3:45 : Break

Genetic architecture and Gene therapy of hemoglobinopathies
Chairmen: Olivier Hermine & Marc Romana

3:45 - 4:05 : Gene therapy of the hemoglobinopathies: Emmanuel Payen (GR-Ex - Fontenay-aux-Roses, France)

4:05 - 4:25 : Genetics, Genomics and Sickle Cell Disease: Laurent Gouya (GR-Ex – Paris, France)

4:25 - 4:35 : Discussion

4:35 - 5:30 : **Debate: Point /Counter Point:** Priority: Curative treatment of sickle cell disease versus improving care

4:35 - 4:55 : Priority: Curative treatment: Mariane de Montalembert (Paris, France)

4:55 - 5:15 : Priority: Improving care: Russell Ware (Cincinnati, USA)

5:15 - 5:30 : Discussion

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French Guiana University, Cayenne October 24-26, 2018 - Building F, Board room

Vendredi 26/10/2018

> Session simultanée dédiée aux associations
Modérateur : Vincent Vantilcke

8h00 - 9h35 :	Présentation de chaque association : objectifs, activités,
9h35 - 10h35 :	Simulation d'une séance d'éducation thérapeutique du patient animée par le ROFSED : Alizée Sterlin (Paris, France)
10h35 - 10h50 :	Pause
10h50 - 11h25 :	"Intensification thérapeutique" dans la drépanocytose : faut-il le faire avant ou après l'apparition des complications ? : Mariane de Montalembert (Paris, France)
11h25 - 12h15 :	Echanges sur la drépanocytose et inégalités de santé, animé par des psychologues, assistantes sociales et un responsable de la MDPH (maison départementale des personnes handicapées) : Constance Leconte, Joelle Chandey, Josette Ponceau, Yolène Lutin Montina (Cayenne, Guyane Française)

Sickle cell disease and Thalassemia

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Friday 26/10/2018

> Simultaneous session dedicated to associations
Chairmen: Vincent Vantilcke

AM

8:00 - 9:35 : Presentation of each association: objectives, activities

9:35 - 10:35 : Simulation of a therapeutic patient education session led by ROFSED: Alizee Sterlin (Paris, France)

10:55 - 10:50 : Break

10:50 - 11:25 : Therapeutic intensification in sickle cell disease: should it be done before or after the onset of complications?:
Mariane de Montalembert (Paris, France)

11:25 - 12:15 : Exchanges on sickle cell disease and health inequalities, led by a psychologist, a social worker and a person in charge of the departmental house of the disabled: Constance Leconte, Joelle Chandey, Josette Ponceau, Yolène Lutin Montina (Cayenne, French Guiana)

Sickle cell disease and Thalassemia

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SELECTED POSTERS

Echanges Transfusionnels au Centre Hospitalier de Cayenne : les problèmes techniques d'accès vasculaires : Etude prospective sur 553 échanges pédiatriques (depuis 2012) et 364 chez l'adulte (depuis 2014). M. Parisot, A. Brune lin, E. Cuadro, E. Martin, Y.Mrsic, AC. Dzierzek, F. Nkontcho, N. Elenga, T. Basset (French Guiana)

Air Drep – A retrospective study evaluating the influence of weather conditions and the impact of viral epidemics on vaso-occlusive crisis in patients with sickle cell disease living in French Guiana. Marie-Claire Parriault, Claire Cropet, Aniza Fahrasmane, Michaël Parisot, Mathieu Nacher, Narcisse Elenga (French Guiana)

Hope for Children with Sickle Cell Disease in Haiti: A Pilot Project using Hydroxyurea at Saint Damien Hospital. Emmeline Lerebours, Nicholas McGregor, Nora Saint-Victor, Prasad Bodas (Haiti)

Alpha thalassemia diagnosis of the -SEA deletion in a Costa Rican family with Chinese ancestry. Wálter E. Rodríguez- Romero1, Mariela Solano Vargas1, David H. K. Chui (Costa-Rica, USA)

Patient's Perspective: Hydroxyurea Therapy for Sickle Cell Disease. Dr Kenneth James, Dr Monika Parshad-Asnani, Kellyn George (Jamaica)

"My sibling has sickle cell disease". Psychological experiences of Cameroonian children with a diagnosed sibling. Hassan Njifon Nsangou (Paris, France)

Teaching self-hypnosis to sickle cell disease adults in order to manage pain and anxiety: a clinical study. Marion Richard, Antoine Bioy (Paris, France)

Evaluation of a Point-of-Care Testing Device (HemoTypeSCTM) for screening of Sickle Cell Disease. Gisele Elana, Mireille Capro-Placide, Magali Flechelles, Lisiane Keclard, Marie-Dominique Hardy Dessources (Martinique, Guadeloupe, CAREST)

Rare Hemoglobin Presbyterian found in a Nicaraguan Family. Pernudy Allan, Salinas-Molina Jaslyn, Requenez Yaneris, Ortiz-López Marianela, Puller Ann-Christin, Rodríguez-Estrada Anaishelle, Rodríguez-Romero Walter, Mejía-Baltodano Gerardo, Hong-Yuang Lou, Chui David (Nicaragua, USA)

Subclinical evidence of inflammatory biomarkers in sickle cell trait. Rinaldo Villaescusa Blanco, Ada Amalia Arce Hernández, Carlos Hernández Padrón, CAREST Study Group (Cuba, CAREST)

Anti-neutrophil cytoplasmic antibodies (ANCA): anti-MPO and anti-PR 3 in sickle cell disease
Ada Amalia Arce Hernández, Rinaldo Villaescusa Blanco, Ana María Guerreiro Hernández, Carlos Hernández Padrón, CAREST Study Group (Cuba, CAREST)

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ABSTRACTS

Thursday 25/10/2018

GLOBAL EPIDEMIOLOGY OF HAEMOGLOBINOPATHIES

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The global distribution of haemoglobinopathies is still largely driven by the extent of malarious areas. The vast majority of individuals with sickle cell anaemia are born in sub-Saharan Africa, while severe forms of alpha- and beta-thalassaemia are mostly prevalent in Southeast Asia. Following human diasporas and recent globalisation fluxes and migrations, these disorders are now common across most parts of the global, including in North America and Western Europe. For example, haemoglobin H disease is now common in California. In some European countries such as Germany, the number of patients with sickle cell disease has recently increased, particularly in large cities. In others, including France and England, the national distribution of patients is also changing with a tendency for patients to move out of capital cities. This raises important questions in terms of access to care and of support to commissioners and providers of services for people with SCD.

Quantitative epidemiological information is essential to guide control and prevention public health policies. Although an up-to-date assessment of the global health and economic burden of haemoglobinopathies is currently lacking, various reports and studies have suggested that the number of individuals affected by these disorders is increasing. In high-income countries, this is due to better survivals leading to improve life expectancy and an overall ageing of the patients. This has substantial implications in terms of costs and in terms of the range and complexity of complications seen in older patients. In low- and middle-income countries, where the vast majority of individuals affected are born, high fertility rates combined with improvements in the overall survival of infants and young children also leads to increasing number of individuals affected. For example, the global number of annual births with sickle cell anaemia is expected to increase from about 300,000 newborns in 2010 to more than 400,000 by 2050. Estimating the number of patients with haemoglobinopathies is very challenging, even in high-income countries which have well implemented universal newborn screening programmes and well-developed healthcare systems, such as the United States or the United Kingdom. Data on prevalence, incidence and survival are very sparse for most low- and middle-income countries, and estimations of these epidemiological measurements is made particularly difficult due to remarkable heterogeneities observed over short distances.

FOCUS ON THE CARIBBEAN

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The Caribbean is defined as the geographical region including the Caribbean Sea, more than 700 islands and the surrounding coasts. The region is located southeast of the Gulf of Mexico and the North American, east of Central America and north of South America. A wider definition includes Belize, the Caribbean region of Columbia, the Yucatán peninsula (Mexico), the Guyanas (Guyana, Suriname, French Guiana, the Guayana region of Venezuela and the state of Amapà in Brazil) because of their political and cultural ties with the region. The Caribbean islands are organized in 13 sovereign states and 17 overseas territories/departments and dependencies, with 43 million of inhabitants and more than 6 official spoken languages.
All the Caribbean islands share some common historical features. Indeed, less than two centuries after the arrival of Christopher Columbus in the New World, all these territories were under the rules of the European colonial powers (France, United Kingdom - UK, Spain, Portugal, The Netherlands, Denmark). The introduction of new cultures such as tobacco, cotton or sugarcanes, which need intensive work, led to the development of the Atlantic salve trade and the triangular trade. More than 12 million of unfortunate Africans were deported to the New World (1). After Brazil, the Caribbean was the second area of deportation of African slaves. One of the consequences of these massive deportation was the introduction of sickle cell disease (SCD) in the New World.

If SCD cases have been detected in a large number of Caribbean countries and territories, the prevalence of SCD and the frequency of the βS allele (responsible for this genetic disorder) through new born screening (NBS) program have been determined in a limited number of them. Jamaica was the first country to implement NBS program for SCD on 100,000 new born in 1973 (2). Now-a-day, universal NBS programs are performed in the French Antilles (Guadeloupe and Martinique), French Guiana, Tobago, Jamaica and Brazil (3-7). In Cuba, prenatal diagnosis in couples at risk was chosen since 1982 as a screening procedure of SCD cases in a policy aimed at limiting the number of births of affected children (8). Pilot NBS programs have also been performed in several of the other Caribbean countries (Table) (9-11).

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Table: SCD birth prevalence in the Caribbean countries and territories

Country	Screening method	Carrier prevalence (Hb S and Hb C trait)	Gene frequencies	SCD prevalence
Jamaica	Universal	15	βs: 0.055-βC: 0.019	1/188
Guadeloupe	Universal	10.5	βs: 0.042-βC: 0.013	1/304
Martinique	Universal	10	βs: 0.040-βC: 0.012	1/300
French Guiana	Universal	10	βs: 0.039-βC: 0.012	1/235
Tobago	Universal	12.9	βs: 0.098-βC: 0.036	1/238
Cuba	Prenatal diagnosis	3.1	βs: 0.011-βC: 0.0036 a βs: 0.053-βC: 0.006 b	1/5,000
Grenada	Pilot NBS	12.85	βs: 0.054-βC: 0.018	1/160
Haiti	Pilot NBS	13.46	βs: 0.059-βC: 0.013	1/173
St Vincent & Grenadines	Pilot NBS	15.27	βs: 0.065-βC: 0.016	1/382

NA: not available; a: Western Cuba; b: Eastern Cuba

Various factors may explain the variations of SCD prevalence observed such as the selective introduction of cultures needing large number of slaves, the settlement policy of the colonial powers: France and United Kingdom imported few of their own population compared to Spain for example, as well as the persistence of migrations after the end of slavery.
Because of the scattered nature of the historical records, the details of the African origins of the slaves and thus of their descendants, has long remained unresolved. The analysis of the genetic polymorphisms surrounding the βS gene (βS-haplotypes), in the nowadays Caribbean populations has provided useful information. Indeed, four geographically-specific βS haplotypes have been described in Africa: Senegal, Benin, Bantu, and Cameroon **(12)**. In Guadeloupe, Martinique (colonized by France), and Jamaica (colonized by the UK), the Benin haplotype accounts for more than 70% of the cases **(13-14)**. In contrast, the Bantu haplotype (Central Africa) is detected at higher or equal frequency than the Benin haplotype in territories under the rule of Spain or Portugal **(15)**. At last, an intermediate situation exists in Trinidad and Tobago that were first colonized by Spain, then by the UK **(16)**. The Senegal and Cameroon haplotypes were also detected in all Caribbean countries/territories studied so far but at a much lower frequency. These data are in agreement with historical records reporting that France and the UK imported slaves mainly from West Africa (Senegal, Mali, Guinea-Bissau, Sierra Leone, Ivory Coast, Ghana, Benin) and Spain and Portugal mainly from Central Africa (Angola, the Republics of Congo) **(1)**.
In summary, SCD is by all odds the first genetic disorder in the Caribbean area. However, only few Caribbean countries and territories have implemented SCD NBS programs and comprehensive sickle cell centers so far which are urgently needed to improve the clinical management of SCD patients in the Caribbean area.

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G6PD DEFICIENCY: HEMATOLOGICAL AND NON-HEMATOLOGICAL CONSEQUENCES

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G6PD deficiency has a worldwide distribution and is probably one of the more common genetic defects in humans. It probably affects not less than 500 million individuals. The highest prevalence in newborns are found in holoendemic malaria regions. G6PD is an enzyme which furnishes the reduced form of NADP+; the sugar moiety of nucleic acids and for other purposes. Complete deficiency induces embryonic lethality. WHO has classified G6PD deficiencies according to their consequences on red blood cells (RBC). G6PD protein and the corresponding enzyme activity are one of the less stable within the RBC. Even in normal individuals the about 10% oldest RBC are deficient. The severity gradient of deficiency is roughly genotype dependent and is reflected by the proportion of RBC having no residual G6PD activity and hence having the main hemolytic role when the RBC are challenged by an oxidative stress. However, the G6PD genotype is only one, may be principal, factor of the severity of the hemolytic crisis: the type and intensity of the oxidative stress are also determinant. Some mutations may lead to prenatal consequences and prevention of hemolytic crisis must involve pregnancy and breast feeding on the mother side. However, one of the most dangerous events is neonatal hyperbilirubinemia which comprises the risk of kernicterus and even death. Neonatal screening and professional awareness are keys to prevention of such issues. Probably some genes by their peculiar functional polymorphisms may contribute to the severity of neonatal icterus.

Around 30% of clinically significant neonatal icterus are linked to G6PD deficiency. Hemolytic crisis is most often triggered by a number of chemical substances which in the physiologic conditions, have an oxido-reduction strength which make them able to oxidize biological substance and in particular Hb. Glutathione which have a very high concentration within the RBC is buffering such oxidative stress and G6PD deficiency by reducing the RBC capacity to regenerate the reduced form of glutathione let the oxidative process to reach an irreversible state at which red cells lyse. Red cell lysis may be massive and acute, leading to a major endothelial stress and possibly multivisceral failure. A list of substances found in a limited number of drugs and foods is regularly updated in France, Italy, Greece, UK, US... and health practioners as well as at-risk individuals must be aware of prevention ways. However, the drugs in use in

different countries often differ. Like for neonatal icterus, heath education plays a central preventive role. Some very commonly used drugs like ascorbic acid, acetaminophen, salicylates, can be used in G6PD deficient individuals if the administrated dose is less than drug specific limit. During the last 10 years a small number of new at-risk exposures have been described. G6PD gene being located on Xp28, exerts its function or dysfunction in a dominant manner in males. In females it behaves more or less like a recessive disorder. In fact, heterozygous individuals may have variable lowered enzyme activity according to the X inactivation respective degree of normal and abnormal G6PD genes. Our capacity to detect heterozygosity is linked to the inactivation rate of the normal G6PD gene. It also drives the hemolytic crisis risk and severity. The factors governing X inactivation are both intrinsic and extrinsic to G6PD genes; inactivation can also change with ageing.

Along with hematology aspects of G6PD deficiency other domains of research have been developed. G6PD having a key role in cellular growing and division, a focus has appeared taking G6PD as a target for onco-therapeutics. G6PD and G6PD deficiency interfere by many aspects with diabetes. And diabetes can also trigger hemolytic crisis.
Most of the above considerations will be exemplified by clinical reports.

EPIDEMIOLOGICAL TRANSITION IN SICKLE CELL DISEASE: EVOLUTION OF THE DISEASE-RELATED MORBI-MORTALITY AND ITS CONSEQUENCES IN SUB-SAHARAN AFRICA

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At least 240,000 children are born each year with sickle cell disease (SCD) in Africa. Historically, in the absence of newborn screening and appropriate treatment, the majority of such children use to die undiagnosed in early childhood. Nowadays, like many other low-income countries, sub-Saharan African countries are undergoing an economic and epidemiological transition, with an increase in child survival and life expectancy.

The reduction in childhood mortality is thought to be predominantly the result of improvements in hygiene, nutrition, and public health interventions, which has led to a decrease in mortality caused by infectious diseases. This global reduction of child mortality also relates to children with SCD, since infectious diseases (and especially malaria) are the leading cause of mortality in SCD children as well. Moreover, with increased awareness of the disease, many specialized centers for SCD have emerged in Africa, thus further improving the survival of the patients. Several studies have indeed reported a low rate of mortality in children with SCD who are monitored in African reference centers and data from the CADRE study show that the median age of patients with SCD is now around 18 years in such centers in West and Central Africa.

Thus, many adult patients are currently living with SCD in Africa. Furthermore, mathematical modelling using available demographic information estimates that more than 11 million newborns affected by SCD will be born between 2010 and 2050 in Sub Saharan Africa. Together with the high natality rates, the improved survival will lead to a tremendous increase in the prevalence of both children and adult patients living with SCD in Africa.

Unfortunately, these patients still face very serious health, economic and sociological issues. Many new born screening programs have already been implemented in several African regions in order to improve the earliness of care, but never at a country-wide level. Moreover,

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although neonatal screening has very much improved the survival and quality of life in patients with SCD living in high-income countries, it is not demonstrated that its effect will be similar in Africa, given the evident lack of medical and social services to take care of the early diagnosed patients. There is therefore an urgent need for integrative health programs dedicated to SCD in Africa, which cannot be implemented without a strong support of the local governments.

In addition, whereas the pathogenesis, prognosis factors and treatment of SCD have been greatly deciphered in North America and Europe for the past decades, very few data have been gathered in sub-Saharan Africa. Consequently, it would be a mistake to believe that high income countries' clinical guidelines can apply to affected subjects living in Africa, who face very specific economic, social, health and environmental (including infectious) challenges. Epidemiological studies have found that the prevalence and risk factors of SCD-related complications may be different in Africa. However, there is no reliable data about the incidence of SCD-related organ damages and the cause of mortality in adult patients with SCD in this continent. Similarly, very few data are available regarding the consequences of high infectious burden and malnutrition in the disease's course. Thus, organ-targeted screening programs and treatment priorities are very hard to establish in this population. Moreover, in such countries with very limited health resources, choosing the best therapeutic option (as defined in the USA or Europe) for the most severe patients may prevent other patients from receiving simple but life-saving treatments.

Overall, only a greater investment in basic, clinical, epidemiological and medico-economic research in the African context, and an increased sensitization of African ministries of health regarding the importance of this condition, could further improve the survival and quality of life of millions of people living with SCD on the continent and their families.

SICKLE CELL DISEASE IN VENEZUELA IS CURRENTLY IN CRISIS

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Sickle cell disease (SCD) is prevalent in Venezuela, because as a country from the Caribbean coast, which arose from European colonization in the 15th century, who brought slaves, settled and developed crossbred inheritance with natives from this land.
Population studies have been performed by A. Arends et al, finding a high prevalence, up to 9% of SCD, in different regions of Venezuela, which is highest in the coast.
Diagnosis has been performed, mainly by clinical suspicion, or less frequently, through neonatal screening programs. Methods mostly used have been hemoglobin electrophoresis -acetate and citrate- as well as HPLC (high pressure liquid chromatography) and capillary electrophoresis.
Neonatal screening has been performed by isoelectric focusing, with good results, in governmental sponsored programs across the country.
The care of people affected by sickle cell anemia (SCA) has been carried out in Venezuela, mainly by hematologists, in referral centers that have access to blood transfusions and multidisciplinary approach. Universal recommendations have been undertaken by most specialists, and patients have been carefully managed, or sometimes referred to bigger cities for optimal care.
Despite the effort of health providers and patients, there has currently been a sharp decline in the general care of patients, due to socio-political reasons. Some aspects that have been particularly afflicted are transportation to health care centers, availability of immunizations, safe blood products, and medical care.
Disease modifying treatments are very difficult to provide, nowadays, given the inconsistent availability of Hydroxycarbamide and deterioration of blood banks throughout the country.
Also, hospitals are becoming very precarious in regards to quality of service, from basic laboratory tests to drug availability, such as antibiotics, intravenous solutions and analgesics.
There has been a shortage of vaccines and resurgence of once eradicated communicable diseases, such as diphtheria, measles and tuberculosis.
The incidence of malaria has also risen in Venezuela, and places near the Bolivar State, where mining is carried out, have been especially afflicted.
In conclusion, sickle cell disease in Venezuela is prevalent. Current management of sickle cell anemia is very challenging. There is an increasing need for resources and dedication towards this especially vulnerable population.

CUBAN PROGRAM FOR PREVENTION OF SICKLE CELL DISEASE. THIRTY-FIVE YEARS RESULTS

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Sickle Cell Disease is the most frequent hereditary disease in Cuba. The average carrier frequency at the population is 3.5% and it ranges from 2% in the western to 6% in the most eastern provinces. In 1982 the National Health System initiated a nationwide program aimed to prevent the disease based on a prenatal screening. The program includes: screening of all pregnant woman at the first trimester, identification of carriers and couples at risk, genetic counseling, prenatal molecular diagnosis and choice of termination of pregnancy.

Up to the end of 2016, more than four millions pregnant women had been screened. 161 131 women (3.5%) carried a sickle cell allele. The average frequencies of the sickle cell traits, out of the total woman screened, were 3.2% for AS, 0.6% for AC and 0.02% for SS and SC respectively. Since 1982, 7 659 couples at risk were identified and 6 035 (78.8%) requested molecular prenatal diagnosis. 1 219 fetuses (20.2%) were identified as affected by the disease and 76.5% of the couples decided to terminate pregnancy after non-directive genetic counseling.

The National Health System has also developed a national program for comprehensive care of patients, at the country level, which includes: hematological follow up since the first months of life, prophylactic administration of penicillin in the first five years of age and folic acid supplementation. As result of the Cuban strategy, life expectancy for sickle cell patients have increased 15 years as average for both sexes in the period 1987-2016 and the disease frequency has decreased from 1 in 1 600 at the beginning of the program to 1 in 5 000 at present.

TOTAL AND SUBTOTAL SPLENECTOMY IN RED CELL MEMBRANE DISORDERS

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Deformability is one of the main properties of erythocytes, allowing them to survive during 120 days in the blood flow. During this lifetime, red cells will pass 14000 times through very narrow interstices between endothelial cells in the cords of the red pulp of the spleen. Any defect in this deformability increases the retention time in spleen cords and will lead to hemolysis. Several factors are involved in red cell deformability: a high surface/volume (S/V) ratio, an adequate internal viscosity, a sufficient energy production, and the intrinsic mechanical property of the membrane. In red cells, lipid bilayer is connected to a protein skeleton constituted by a network of spectrin tetramers parallel to the inner layer and linked to it through Ankyrin complexes. Red cell membrane disorders, including hereditary spherocytosis, elliptocytosis and stomatocytosis are mostly dominant chronic hemolytic diseases leading to anemia of various severity and splenomegaly. Since hemolysis occurs mainly in the spleen, total or subtotal splenectomy may be an option in severe cases. However, its efficiency and safety are heterogeneous according to the membrane defect. This review aims to clarify indications and contraindications of splenectomy in these disorders.

The most frequent red cell membrane disorder, hereditary spherocytosis (HS) is related to a weakness in the « vertical » interactions between spectrin network and the lipid bilayer, leading to membrane instability, microvesiculation and progressive decrease in the S/V ratio. As a consequence, spherocytes are selectively trapped in spleen cords. Therefore, in HS, hemolysis occurs most essentially in the spleen: total splenectomy abrogates hemolysis and should be performed in symptomatic/severe cases, after the age of 6. Subtotal splenectomy (STS) that consists in removing around 90% of the enlarged spleen has been proposed in order to decrease the hemolytic rate while preserving the immune function of the spleen. In children under 6 with transfusion-dependent HS, STS is an option, since it alleviates the transfusion rate and increases the hemoglobin to a level compatible with normal growth. However, persistence of functional spleen tissue may lead to remnant growth, gallstones, hematological relapse and subsequent total splenectomy.

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Hereditary elliptocytosis (HE) is due to a loss of membrane elasticity secondary to weakness in the horizontal interactions within the spectrin network. Most cases are a- or pauci-symptomatic, but in rare cases, called hereditary pyropoikilocytosis (HPP), membrane interactions are so weak that they break at physiological shear stress, leading to severe hemolytic anemia with particular polymorphic red cell morphology on peripheral blood smear and splenomegaly. In a recent study of 9 patients from 6 families that underwent splenectomy, STS was safe but inconstantly efficient, in contrast with TS that improved hemoglobin level and alleviated the transfusion rate in all cases. However, in contrast with HS, this hematological improvement was partial, highlighting the fact that clearance of the red cell fragments in HPP occurs mainly, but not exclusively, in the spleen.

Hereditary xerocytosis (HX) is the most frequent red cell hydration disorder. It is a dominant disorder linked to an activating mutation in the mechanotransductor PIEZO1 in most cases, or in KCNN4, encoding the Gardos channel in the remaining ones. Its pathophysiology involves primary or secondary activation of Gardos, a Ca2+-dependent channel that exports K+ from red cells, leading to water loss, erythrocyte dehydration, decreased red cell deformability at physiological osmolality and hemolysis. Most patients present a compensated hemolysis with splenomegaly. Even if hemolysis occurs at least partially in the spleen, TS is not or poorly efficient and should be contraindicated. Indeed, it is associated with a very high risk of venous and arterial thrombotic events in most cases. In a monocentric series of 126 patients with HX, 8 PIEZO1-mutated patients were splenectomised, all of them presented thrombotic events including cerebral strokes, deep venous thrombosis, pulmonary embolism with some cases of pulmonary hypertension, and a high rate of portal thrombosis. This highlights the absolute requirement of eliminating this diagnosis using familial history, red cell indices and morphology, osmotic gradient ektacytometry and genetic testing in any undiagnosed hemolytic disease when splenectomy is planned.

NOVEL THERAPEUTIC APPROACHES FOR THALASSEMIA

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SICKLE CELL DISEASE-IMMUNIZATION COVERAGE

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People living with Sickle Cell Disease (SCD) are at increased risk of infection. They present with an enlarged spleen during the first decade of life, which progressively atrophies due to repeated vaso-occlusion and infarction, resulting in "auto-splenectomy". This auto-splenectomy often occurs around 5 years of age and causes a loss of splenic function, making patients with SCD particularly susceptible to encapsulated organisms (such as Streptococcus pneumoniae, Haemophilus influenzae type b (Hib), and Neisseria meningitidis, which are often responsible for invasive infections. A defect in compliment activation, impaired opsonisation, decreased immune responses and genetic variations among patients with SCD further increase their susceptibility to infections. Genetic polymorphism of the human leukocyte antigen (HLA) system and the haplotype of the β-globin gene cluster modulate the intrinsic susceptibility to bacteraemia in patients living with SCD. While some alleles such as the HLA class II DRB1*15 have been shown to be protective, others like the HLA class II DQB1*03 occur significantly more in patients with major infections, supporting an increased susceptibility of the latter to infections. This high infectious risk justifies the implementation of anti-infectious preventive measures. SCD require a vaccination schedule that is optimized and unique. In December 2014, the High Council of Public Health published vaccine specific recommendations for immunocompromised or asplenic persons. Children and adults with SCD should get all recommended vaccinations, including a flu vaccination (every year starting at 6 months of age). They are considered high risk for certain infections and should follow a special vaccination schedule for the following vaccines: Haemophilus influenzae type b, Pneumococcal vaccines, and Meningococcal vaccines. Despite its low efficacy, the immunization against typhoid fever is recommended because of the specific risk of salmonella infections. There are no vaccinal contraindications in asplenic subjects. These recommendations on the use of conjugate pneumococcal vaccines in people with SCD are based on evidence from observational studies. Two systematic reviews have evaluated the efficacy and safety of the conjugate Hib type b vaccines, and vaccines for preventing invasive salmonella infections in SCD and found no RCTs addressing the subject.

Conclusion: Apart from the usual vaccination schedule which must be scrupulously respected, vaccinations against Streptococcus pneumoniae, Haemophilus influenzae type b (Hib), and Neisseria meningitidis and influenza virus are strongly recommended.

REVIEW OF NEWBORN SCREENING FOR SICKLE CELL DISEASE IN THE ANGLOPHONE CARIBBEAN

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The incidence of sickle cell disease (SCD) in the Caribbean is second only to Africa (4.3% versus 10.1%). The gene entered the populations of the Caribbean from Africa through slavery and from Asia with indentured laborers. All haplotypes have been reported regionally. The islands vary considerably in ethnicity, language, population and sociodemographics, based on their history of colonization. More than half of the region's inhabitants speak Spanish; a quarter speak French and a few Dutch. Despite accounting for the majority of nations and territories in the region, the Anglophone Caribbean includes less than 15% of the region's population. The independent English speaking nations with the largest populations are Jamaica (2,898,677), Trinidad and Tobago (1,372,598), Bahamas (399.285), Barbados (286,388) and St Lucia (179,667). Other islands with populations greater than 100,000 are St Vincent and the Grenadines, Grenada and Antigua and Barbuda.

Newborn screening (NBS) for SCD coverage has not remained static in these islands since the last CAREST conference. Islands partnering with Guadeloupe continue to have strong programs. Screening in Jamaica became islandwide in 2015 but remains precarious as the government has supplied a significant portion of laboratory supplies, but the program has not been fully integrated into the hierarchy of the Ministry of Health. Thus, funding is not guaranteed but identified on an annual basis.Some Regional Health Authorities in Jamaica have been more pro-active than others in providing care for affected infants identified by the program. Screening has started in Trinidad- a pilot that is based on a collaboration between a community based organization (the Society for Inherited Blood Disorders), the North West Regional Health Authority in Trinidad and the Center in Guadeloupe. Screening has stopped in St Vincent and the Grenadines when their pilot project ended and the government has not been willing to support a continuation of screening. There is a strong push to start newborn screening in Antigua, championed by Dr Edda Hadeed and little interest in Barbados where a combination of identifying high risk infants based on antenatal testing and screening of symptomatic infants is employed.

Methodology still varies across the region. In some areas, heel prick sample collection is practiced. In Jamaica cord blood sampling is still the method used.In St Lucia, a heel prick/high throughput liquid chromatography (HPLC) pilot sponsored by the SickKids Caribbean Initiative has ended and the previously used cord blood/ hemoglobin electrophoresis methods continue.In Jamaica the bloods are screened using HPLC and confirmed with isoelectric focusing.

Despite the variability, approximately half of all infants born in the English speaking Caribbean are being screened at birth for SCD. This compares favorably with our French and Spanish speaking neighbors, as some large francophone (Haiti) and Spanish speaking (Dominican Republic) do not currently have SCD NBS. It is significantly better than what obtains in Africa where for example, many countries in West Africa with high incidence rates have no or limited SCD NBS. There still remains much room for improvement. National champions and persuaded policy makers are the keys to progress.

NEONATAL SCREENING FOR SICKLE CELL DISEASE: THE EXPERIENCE FROM THE FRENCH CARIBBEAN AND THEIR COLLABORATION WITH OTHER CARIBBEAN COUNTRIES

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Sickle cell disease (SCD) is a significant problem in the Caribbean since countries share the same origins of population, mainly Africa and Asia where hemoglobinopathies get a high prevalence. However, except in the French islands Guadeloupe and Martinique, none of them has really develop a global care management as recommended by the World Health Organization, including universal newborn screening (NBS), early care program for every new affected baby, specialized centres for sickle patients for regular assessment, clinical research.

One of the main objectives of the Caribbean Network of Researchers on Sickle Cell Disease and Thalassemia (CAREST) is to reduce this inequity by promoting regional collaboration. In fact, CAREST acts as a facilitator, bridging health professionals and health authorities from different Caribbean countries, providing technical and financial support.

As a result, it was possible to benefit from the long experience of Guadeloupe in NBS for SCD. In this country, after a pilot study conducted in the early 80, the universal screening program started in 1984, with very good acceptance by families and a coverage rate around 100%. This experiment made it possible to establish the incidence of the sickle cell syndromes in Guadeloupe, to decrease childhood morbidity and mortality significantly; so many arguments to convince the local health authorities for financial support to the program. Finally, in 1990 the health authorities of Guadeloupe recognized sickle cell disease as a public health priority; since this date, the universal neonatal screening program has been entirely financed by public funds, and a comprehensive sickle cell centre was established to carry on the management program.

Tobago first, experimented with the project developed by CAREST. In 2008, NBS was initiated for a 2- year period as a pilot study subsidized by CAREST with the partnership of the diagnostic laboratory of hemoglobinopathies of the University hospital of Guadeloupe by carrying out tests on the blotters sent by mail from the maternity ward of Scarborough (Tobago).

This step was essential to convince the Tobago Regional Health Authority to include the universal NBS for sickle cell disease in its health planning and subsequently to sustainably fund the screening program until now.

The same policy was developed by CAREST in Grenada by promoting the organization of a two-year pilot NBS program between 2014 and 2016, involving the Ministry of Health of Grenada, the Sickle Cell Association of Grenada, and the diagnostic laboratory of hemoglobinopathies of the University Hospital of Guadeloupe. Although the study was conducted successfully and the health authorities of Grenada were in favour of continuing the screening program, this was not possible because of funding reasons.

CAREST learned from these two experiences. Implementation of neonatal screening results from a long process. Many exchanges between all the partners under the coordination of CAREST, including meetings on-site in the candidate country, are necessary to take into account the local realities before to reach the definitive project. Sickle cell associations are unavoidable and should not be neglected as they generally act effectively to advance the project through their interventions with the public, the local health professionals and health authorities. Similarly, as funding is a key problem, strategies to reduce the test price need to be considered to ensure the sustainability of the program in the countries where it was initiated.

NEW SCREENING STRATEGIES : FROM RAPID TESTS TO HIGH-THROUGHPUT SCREENING PLATFORMS

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Life expectancy of patients with Sickle cell disease (SCD) has steadily increased over the past three decades. Rather than resulting from advanced sophisticated medicines, it is mostly the result of the implementation of newborn screening (NBS) in the mid-80s and of the early prevention of the major SCD complications by rather simple care. Universal NBS has now been established in the US, Brazil, some Caribbean islands and territories and several European countries. However, it is estimated that 80% of the 400,000 infants born every year with the disease are in low-income/lower-middle-income countries of sub-Saharan Africa or India. In these parts of the world, NBS is limited to only a few pilot programs and no country has yet adopted a national universal NBS program. This leads to under-five mortality of a majority of affected infants. Current methods for the diagnosis include classical electrophoresis, isoelectric focusing (IEF), high performance liquid chromatography (HPLC), and capillary electrophoresis (CE). These two latter in particular require expensive laboratory equipment and reagents, and all demand trained laboratory personnel. Thus obstacles to NBS programs in these countries include financial and technical limitations. In addition, test results are often delayed due to transport and batching of samples in a central laboratory. Interestingly, we are witnessing a surge of interest in addressing the global burden of SCD, including improving and optimizing diagnostic capacities. In particular, several point-of-care (POC) diagnostic tests for SCD have been developed with a focus on devices that are inexpensive, simple, and practical at the local level in limited resource settings. On the other hand, due to the present migration crisis, SCD epidemiology is rapidly changing, particularly in Europe, where the burden of the disease increases requiring the extension of the ongoing NBS programs as well as the speeding up of the screening technologies.
Based upon the criteria developed by WHO (in the context of sexually transmitted diseases), an "ideal" POC test for SCD in resource-limited settings should be:

- sensitive, allowing the detection of HbS in newborns with high HbF
- specific, allowing the detection of HbS, HbC, to distinguish trait from disease
- simple to perform and to interpret with minimal training
- equipment-free or compact/portable, with no additional requirements (electricity...)
- rapid to produce results (during a visit/consultation...)
- robust, long shelf-life, not requiring refrigerated storage
- affordable (probably < 5€/test, ideally < 1€/test)

Sickle cell disease and Thalassemia

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Several POC test devices have been produced, supported by various levels of evidence for complying to those criteria. Some are based on the immunological detection of Hb variants and use the lateral flow immunoassay (LFIA) procedure developed for rapid malaria or HIV tests. Formats include the "sandwich format" and "competitive format". The Sickle SCAN® assay (Biomedomics, Inc., Research Triangle Park, NC, USA) uses polyclonal antibodies against HbS, HbC, and HbA in a sandwich format. The HemoTypeSCTM assay (Silver Lake Research Corporation, Azusa, CA, USA) uses monoclonal antibodies for Hb A, S, and C in a competitive format. Both tests show high specificity and sensitivity even in the presence of high HbF, making them appropriate for NBS. Both have been validated in field studies. HemoTypeSCTM cost will probably be easier to lower than that of Sickle SCAN® but interpretation of the results is less intuitive because the test produces a «negative» image in which the presence of a given Hb is indicated by the absence of a band. These two tests are probably foremost towards a routine usage in limited-resource settings or in situations where the result of the test is needed quickly (during a consultation). Several other POC tests have been proposed, based on the different electric charges or solubility of the Hb variants, or on the high density of sickle cells. HemeChip (Hemex Health Inc., Portland, OR) is a portable miniaturized battery-powered version of cellulose acetate electrophoresis that separates the Hb variants based on electric charge. The SCD-AMPS test (Daktari Diagnostics Inc., Cambridge, MA, USA) use aqueous multiphase systems (AMPs), i.e. mixtures of polymers of different density in water. Because sickle red blood cells have a higher density than normal red cells, they can be separated by centrifugation in a microhematocrit tube in a battery-powered microcentrifuge. This test identifies SCD patients (SS and SC) but do not differentiate AS carriers from normal AA subjects. Because of the high HbF content in newborn samples, SCD infants cannot be identified either. Based upon the specific (un)solubility of HbS exploited in the historic Itano's test, a paper-based and visually interpreted POC test has been proposed (Halcyon Biomedical Inc., Friendswood, TX, USA). This test amenable to the lowest cost does not differentiate healthy AS carriers from affected SC individuals. This probably restricts its appropriateness to regions where only HbS (and not HbC) is present, i.e. Central Africa.

On the other side of the scale, in high-income countries, most notably in Europe where SCD burden is increasing, development of automatized high throughput NBS platforms is highly relevant. Besides optimization and improved automation of the classical screening procedures (HPLC and CE), the most striking innovation is the introduction/development of Mass Spectrometry-based (MS) procedures. In this approach, Hb variants are identified based on molecular mass differences. SpotOn Diagnostics Li. (London, UK) proposes a NBS solution using tandem MS/MS separation of the globin chains tryptic peptides. Specificity of the approach is the highest because virtually all the Hb variants can be identified. Tryptic hydrolysis introduces an additional step that prevails full optimization of the throughput. The NeoSickle® solution (Biomaneo, Dijon, France) uses the MALDI-MS procedure to separate variants according to the total mass of the globin chains. At this stage, it identifies the presence of HbS and thus differentiate SS (and S-βThal), from AS and AA newborns. Recent developments will include the identification of HbC and HbE. The fully automatised platform is amenable to the testing of up to 2,000 samples/day.

Sickle cell disease and Thalassemia

Update in clinical care and research

French Guiana University, Cayenne October 24-26, 2018 - Building A, Amphitheater

NEWBORN SCREENING IN CAP HAITIEN, HAITI: PRESENT AND FUTURE

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Objective : Hemoglobinopathy newborn screening (NBS) is not offered in Haiti. The objective was to explore NBS feasibility and sustainability.

Methods: A Haitian team was hired and trained at Hôpital Universitaire Justinien in Cap Haitien and Guadeloupe (supported by CAREST). NBS was conducted by isoelectric focusing from dried blood samples during the first three months of the study, and by dual method (rapid test Sickle SCAN and isoelectric focusing) thereafter obtaining immediate screening results. The hospital Ethics Committee approved the study. Children who were identified had dual method confirmatory testing. SCD children are on oral penicillin, are immunized with pneumococcal 13-valent conjugate vaccine (Prevnar 13) and followed by a pediatrician (RSF).

Results: Beginning in August 2017 until present (June 2018), we have screened 1,800 newborns, of which 10.5% have sickle cell trait, 3.3% have hemoglobin C trait, 0.78% have hemoglobin SS, 0.27% have hemoglobin SC and one child has been confirmed to have sickle beta thalassemia plus. Currently, there are 15 children confirmed and followed at the Center, for a SCD incidence of 0.83% (8 SS, 6 SC and 1 S-beta thalassemia+). Based on this incidence, we estimate that every year around 2,000 children will be born with SCD in Haiti. In order to sustain efforts, we have initiated a network of physicians, nurses, and patient advocates to share information and establish partnerships. The Ministry of Health is involved and a document is being written stating SCD should be a national health priority. Barriers encountered are the lack of local resources such as screening materials, oral penicillin, and the high cost of Prevnar 13.

Conclusions: A hospital-based NBS Program is feasible. SCD is highly prevalent with an incidence of 0.8% among newborns. Academic-governmental partnerships are being established to sustain efforts and generalize NBS, and to enhance supportive care for identified children.

PRESENCE OF NON-AFRICAN HAPLOTYPES IN SICKLE CELL PATIENTS IN COLOMBIA PROBABLY DUE TO ADMIXTURE AMONG AMERINDIAN, EUROPEAN, AND AFRICAN POPULATIONS

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Objective: The objective of this study was to identify the frequency of Beta globin cluster's haplotypes present in Sickle Cell Anemia patients in Colombia, to establish the presence of non-African haplotypes in this population, and to verify variations in the pattern of linkage disequilibrium in the Beta globin cluster.

Methods: It were analyzed 83 individuals affected with Sickle Cell Anemia, the haplotypes were formed using five restriction sites into Beta globin cluster. The haplotype frequency was calculated, as well as the linkage disequilibrium among restriction sites, the genetic similarity among Colombian population and other affected American population was determined.

Results: The haplotypes most frequent were Benin (35,1%) and Bantu (26,5%), both African. However, atypical haplotypes represented 35% in our sample. In this group haplotypes I (- - - - -), frequent in European populations, showed a frequency of 10%. In the same way, the haplotype XII (+ - - - -) typical in Colombian indigenous population is present in our patients. Five haplotypes not reported in others population were observed in our sample of patients. The restriction sites showed low or null linkage disequilibrium among them. When we compared with other populations, the Colombian patients showed higher similarity with Venezuelan population where Benin and Bantu are predominant too.

Conclusions: Our results showed that admixture has facilitated the transit of sickle cell mutation to a non-African genetic context (Amerindian and European). Further, the admixture has also modified the pattern of linkage disequilibrium into the Beta globin cluster generating modifications that could have influence in association studies in this affected population.

MEDICAL MANAGEMENT OF PREGNANT WOMEN WITH SICKLE CELL DISEASE IN WEST FRENCH GUIANA: HISTORICAL ASPECTS, EVOLUTION OF THE MANAGEMENT

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French Guiana has a multiethnic population with a clear predominance in its West part of people with African origins. The fertility rate is the highest one in Europe. There are 3 major maternity hospitals: Cayenne (4200 births per year), Saint-Laurent (3000 births per year) and Kourou 2800 (births per year).

The perinatal mortality rate is still higher than in mainland France, mainly because only 40% of the patients have a regular pregnancy follow-up.
The screening at birth of the sickle cell disease has debuted in 1992. Its incidence rate is 1 per 200 birth in West French Guiana: 61% SS, 36% SC, 3% SB.
In 1982 was conducted an inventory of all the pregnancies in women with sickle cell disease that happened in West French Guyana during the 10 former years; only 6 cases were found. Infantile mortality at the times were so high, only a few women arrived to the childbearing age. Those 6 pregnancies ended with 3 maternal deaths and 5 fœtal and neonatal deaths.
The patients suffered from numerous complications before the pregnancy and the pregnancy itself aggravated their health and caused major complications.
In 1986 are conducted the first prophylactic blood transfusions in patients with the most severe antecedents. The blood transfusions, started at 24-26 weeks of amenorrhea, consisted of 15 milliliters of blood per kilos, given over 2 days, every 15 days. We observed a drastic fall of the number of complications and a better quality of life for the patients.
As time went, the general health of our young patients got better, allowing us to be less systematic in our prophylactic blood transfusions distribution.
Today, in West French Guyana, we observe every year 12 to 15 pregnancies in women with sickle cell disease. Of the patients with SS hemoglobin, 2/3 get a prophylactic blood transfusion, as opposed to ¼ in the patients with SC or SB hemoglobin, in accordance of the presence or not of complications, and the number of anterior vaso-occlusive crises.
Maternal mortality

From 1985 to 2018, only one death (caused by a delayed hemolytic transfusion reaction) out of 238 pregnancies has been observed.
The evolution of the medical management of the sickle cell disease in French Guiana has led to a spectacular improvement of the general health of our patients starting a pregnancy, which must prompt us to adapt our own medical management.

NEW APPROACH IN THE TREATMENT OF ACUTE VASO OCCLUSIVE PAIN IN SICKLE CELL DISEASE (SCD)

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Sickle cell anemia is almost synonymous with pain. Acute painful episodes are its hallmark and the most common cause of hospitalization. Vaso-occlusion is believed to be the root cause of the pain; it causes damage to tissues supplied by the occluded vessel and is also responsible for creating a state of chronic vascular inflammation that explains many features of sickle cell pain. Major gaps in knowledge are identified regarding how sickle pathobiology evokes pain, pathways specific to chronic and acute sickle pain, perception-based targets of "top-down" mechanisms originating from the brain and neuromodulation, and how pain affects the sickle microenvironment and pathophysiology.

Current treatment of moderate to severe acute pain in SCD is mostly reliant upon opioids; however, long-term use of opioids is associated with multiple side effects including nausea, vomiting, pruritus, constipation, mental changes, tolerance, dependence, hyperalgesia, and addiction. Moreover, significantly larger doses of opioids are required to treat pain in SCD as compared to other acute and chronic pain conditions. Clinicians also described perplexing observations in patients with sickle cell anemia. For example, they reported that some hospitalized patients with acute painful crises become refractory to treatment with opioids about 3 or 4 days after admission and continue to have severe pain despite the administration of high doses of opioids (Ballas et al, 2005; Jacob et al, 2003). Due to opioid-induced endothelial-, mast cell-, renal mesangial-, and epithelial-cell-specific effects and proinflammatory as well as growth influencing signaling, it is likely that when used for analgesia, opioids may have organ specific pathological effects. Experimental and clinical studies, even though extremely few, suggest that opioids may exacerbate existent organ damage and also stimulate pathologies of their own.

Thus, from the beginning of the 2010's, by using transgenic sickle cell mouse and clinical studies, several authors studied the other mechanisms of pain in SCD and tried to identify new therapeutic and more efficient approach for analgesia. They found that mast cell activation contributes to neurogenic inflammation, pain and hyperalgesia in sickle mice (Kohli et al, 2010; Ballas et al, 2012; Aich et al, 2016; Vincent et al, 2016). Morphine is highly histaminergic, and is known to activate mast cells. They also found that cannabinoids mitigate chronic and hypoxia/reoxygenation (H/R)-evoked acute hyperalgesia in sickle mice. Cannabinoids have anti-inflammatory effects and provide protection from ischemia/reperfusion injury.

Beside an early and aggressive treatment of acute painful crises, based on this study results, authors proposed and tested on transgenic sickle cell mouse others treatment such as cannabinoids and antihistaminic drugs for better management of acute sickle cell vaso occlusive crisis.

POPULATION PHARMACOKINETICS OF ANTIBIOTICS AND DOSAGE RECOMMENDATIONS IN CHILDREN WITH SICKLE CELL DISEASE.

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Sickle cell disease (SCD) is characterized by vaso-occlusive complications, chronic haemolytic anaemia, splenic dysfunction and defective immunological function predisposing to severe infection. The management of the infectious risk is a major issue in SCD patients. Indeed, infectious complications remain one of the main causes of death, particularly in children under 5 years of age. Before two years of age, invasive infections in SCD patients are mainly due to Streptococcus pneumoniae and Haemophilus influenzae, whereas after 2 years the most frequently germs are minor Salmonellae. In children with SCD, the early initiation of a probabilist antibiotherapy such as suspicion of bacterial infection is recommended. Third generation cephalosporins as cefotaxime are usually prescribed because of their bacterial efficacy against S. pneumoniae, H.influenzae and Salmonella sp., but without specific dosage recommendation, a standard dose is used in SCD patients. Nevertheless, pharmacokinetic data of most drugs, including antibiotics, are lacking in SCD patients although clinical situation and early changes in renal and hepatic functions may impact drug disposition. The aim of this study was to define the population pharmacokinetic parameters and the factors of variability of cefotaxime, in order to optimize dosage in children with SCD.
Cefotaxime serum concentrations were measured in 80 pediatric SCD patients receiving cefotaxime intravenously. A total of 110 concentrations were available for pharmacokinetic analysis.

A population pharmacokinetic model was developed with NONMEM and used for Monte-Carlo simulations.
Patients were aged 0.6 to 18.7 years and weighted 8 to 80.2 kg. Cefotaxime treatment was started on clinical symptoms of fever in all patients. 23 patients had fever without concomitant vaso-occlusive complications. 33 patients had concomitant extra-thoracic vaso-occlusive crisis (VOC) and 22 patients had acute chest syndrome (ACS). Bacterial infection was confirmed in three patients: Escherichia Coli (n=2) and Salmonella (n=1). All patients were hyperhydrated with an intravenous infusion of polyionic solution (2 liters/m2/24 hours). Some children were concomitantly treated with acetaminophen, morphine, hydroxycarbamide, nalbuphine and/or non-steroidal anti-inflammatory drugs.

Cefotaxim is a time-dependent antibiotic, meaning that its major killing effect against bacteria is produced by the extensive amount of time the antibiotic binds to the microorganism. The inhibitory effect can be effective because its concentration exceeds the Minimum Inhibitory Concentration (MIC) for the microorganism. For time-dependent drugs, the pharmacodynamic parameter can be simplified to the time that serum concentrations remain above the MIC during the dosing interval (t>MIC). If we consider that, the aim of the predictive antibiotic treatment in SCD children is to reach 80% t>MIC (in order to treat a potential bacteriemia), with the prescribed median dosing regimen of 63 mg/kg/8h (190 mg/kg/day), **only 50.5%, of our pediatric population reached the target attainment of 80% T > MIC** for the breakpoints MICs0.5, corresponding to sensitive Streptococcus pneumoniae. In case of infection with a decreased susceptibility bacteria (MICs1 and MIC2), only 30.4% and 13.1% of the children respectively reached the target attainment of 80% T > MIC. The target attainment rates as a function of dose for MICs0.5, MICs1 and MIC2 susceptibility breakpoints are shown for 80% T > MIC in Figure 1.

Last, **cefotaxime clearance was higher in our patients** (0.38 L/h/kg) that the one reported for normal subjects (0.23-0.31 L/h/kg). It was increased by **22% in the presence of concomitant Acute Chest Syndrome (ACS),** highlighting the possible impact of inflammation, tachycardia, or hypoxia on antibiotic clearance in SCD patients.

In SCD patients, many organ dysfunctions occur that may impact drug disposition including age, weight, clinical presentation of the disease, renal and hepatic function, inflammation. Renal dysfunction with glomerular hyperfiltration appears early in the course of SCD in children and in adults. The increase in glomerular filtration rate appears at the age of one with gradual changes until the second decade. In the pre-adolescent, the lack of urine concentration is almost constant, leading to irreversible anatomical lesions at the adult age.

In our study, the high glomerular filtration rate most probably results from both glomerular hyperfiltration as a consequence of SCD nephropathy and hyperhydratation as treatment or prevention of VOC.

In addition, early hepatic dysfunction occurs in SCD patients without correlation with an elevation of classical liver function biomarkers. Due to chronic haemolytic anaemia, hepatic blood flow increases and an induction of hepatic glucuronidation enzymes (UGT and P450 enzymes) has been reported. Additional studies have highlighted an impairment of hepatic metabolism for some drugs in SCD and this phenomenon seems to increase with age. Furthermore, SCD is characterized by chronic inflammation at steady state and worsening during the VOC leading to an increase in plasma concentration of many proteins and modifications of the distribution volume of many drugs.

In conclusion, the prescription of a standard dosage of cefotaxime (75 mg/kg/8h) in SCD children in case of suspicion of bacterial infection may be inappropriate considering the risk of severe infectious complication in this population. Physicians must keep in mind that in case of sever bacterial infection, particularly associated with vaso-occlusive complication as ACS, the dose of 100 mg/kg/6h may be necessary in order to reach a t>MIC of 80% in 80% of patients when targeting sensitive Gram positive cocci and Gram negative bacilli with MICs of 1 mg/L or below.

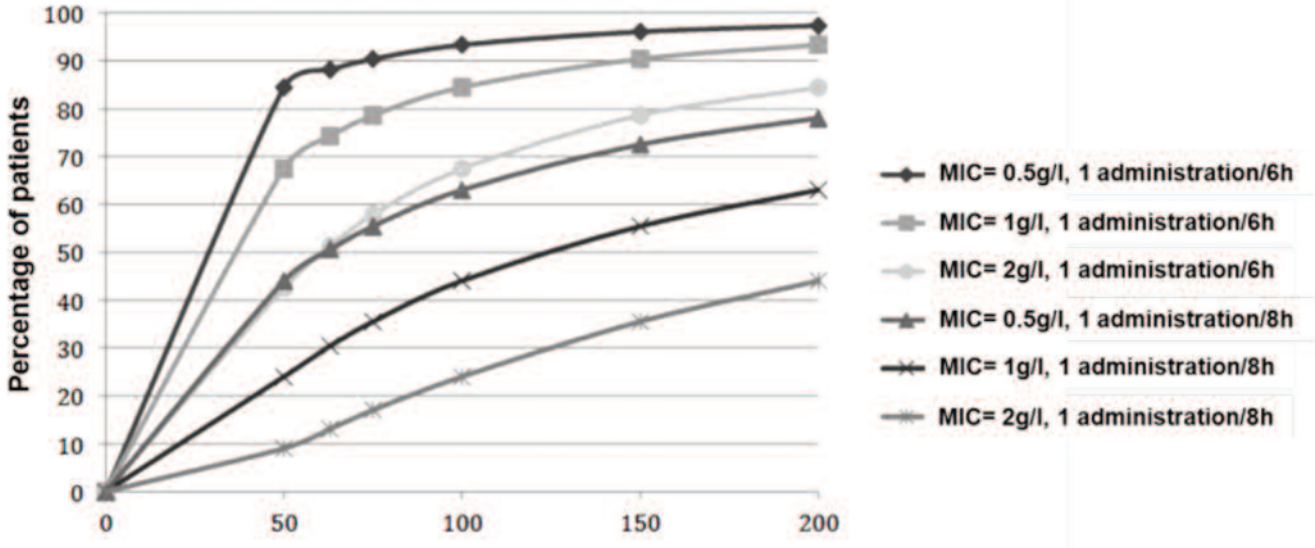

Figure 1: Target attainment rates for the 1000 simulated trials for MIC0.5 (0.5 mg/L), MIC1 (1 mg/L) and MIC2 (2 mg/L) are presented as a function of dose (mg/kg) administered three (TID) or four times (QID) per day. The Time > MIC target is 80%.

TRANSCRANIAL DOPPLER SCREENING: ANALYSIS AT DISTANCE, EXPERIENCE DEVELOPED BY DOMINICAN REPUBLIC.

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Background

The prevalence of Sickle Cell Anemia (SCA) in the Dominican Republic (DR) is almost 4 times that in the United States. The probability of primary stroke is about 10 percent of children with SCA at the Hospital Infantil Dr. Robert Reid Cabral (HIRRC), the main children's hospital located in Santo Domingo, the capital of DR.

Transcranial Doppler (TCD) is an effective screening tool for primary stroke risk and has been demonstrated to identify the risk of primary stroke in other countries such as the United States. Unfortunately, this screening is not routinely available in the DR, where stroke is a significant cause of morbidity and mortality in children with SCA.

Hydroxyurea is an important disease modifying therapy for SCA. It can reduce TCD velocities and prevent the conversion from conditional to abnormal velocities. There is availability of hydroxyurea in DR, but most of the families cannot afford the cost of this medication. Healthcare providers also do not have experience using TCD screening to identify children with highest stroke risk, or with proper dosing and monitoring of this potent disease-modifying therapy.

Objectives

- Conducting a prospective open-label screening and treatment research trial: Stroke Avoidance for Children in REpublica Dominicana (SACRED). Specific aims include:
- Screening a large cohort of children with SCA living in DR, building local capacity with TCD to identify elevated stroke risk;

- Obtaining longitudinal data on the natural history of TCD velocities in this cohort;
- Determining the prevalence of elevated conditional and abnormal TCD velocities in children of DR with SCA;
- Identifying in children with SCA and conditional TCD the effects of hydroxyurea for stroke prevention

Methods

- The SACRED trial (NCT02769845) is a research partnership between Cincinnati Children's Hospital and Hospital Infantil Dr. Robert Reid Cabral in Santo Domingo, Dominican Republic. The protocol, consent forms, and REDCap database were prepared collaboratively and translated into Spanish, and then IRB approval was obtained at both institutions.
- Training for the local hematology team in principles of clinical research was provided on-site and remotely.
- Certification of local staff in TCD screening techniques, according to the NHLBI guidelines established in the STOP and STOP2 trials. This training is conducted in a systematic way using continuing analysis at distance by experts who support the local team with information, communication and technology (ICT) resources.
- TCD screening is performed at the clinical site by the DR research team. TCD velocities are scored by experts at Cincinnati Children's, who provide feedback to the site team and provide recommendations based on TCD category.
- Children had TCD screening in the first year over a 12-month period. Children with conditional velocities (170-199 cm/sec) receive fixed dose hydroxyurea at 20 mg/kg/day over a 6-month period, followed by escalation to maximum tolerated dose. TCD is performed in this group every 6 months.
- Children with abnormal TCD velocities (more than 200 cm/sec) receive monthly transfusions for primary stroke intervention per local clinical guidelines.
- Education is provided to local healthcare providers about appropriate dosing and monitoring of hydroxyurea for children with SCA and conditional TCD.

Results

- A total of 283 children from the local sickle cell clinic were enrolled over the first year.
- The initial TCD screening results were normal for 200 children (70.7%), but 63 (22.3%) conditional and 11 (3.1%) abnormal.
- There were 50 eligible children for hydroxyurea and 48 initiated open-label therapy.
- Repeat TCD screening after 6 months of hydroxyurea treatment documented reversion to normal velocities in 30 of 48 children (63%), and after 12 months of treatment in 35 (74%).

The median TCD velocity was 177 cm/sec at baseline but was reduced to 159 cm/sec after 6 months of hydroxyurea treatment and 154 cm/sec after 12 months.

- No clinical strokes occurred in the first 12 months of hydroxyurea treatment.

Conclusions

1. SACRED is an important collaborative trial that features local capacity building to prevent stroke among children with SCA in DR.
2. The prevalence of conditional TCD velocities is >20%, supporting the observation of an elevated stroke risk among children in DR with SCA.
3. Hydroxyurea treatment is effective for lowering the TCD velocities and reducing the risk of primary stroke.
4. The SACRED trial experience suggests that it is feasible to carry out research by local groups with external support through communication and education technology. This strategy has been possible by continuous interaction between both teams, such as training of the local team in TCD screening, monitoring of the results of this procedure, as well as the initiation and adjustment of hydroxyurea doses with the advice of experts.

Sickle cell disease and Thalassemia

Update in clinical care and research

French Guiana University, Cayenne October 24-26, 2018 - Building A, Amphitheater

SCHOOL IMPACTS OF SICKLE CELL DISEASE

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IMPLICATIONS OF A PAEDIATRICIAN-PSYCHOLOGIST TANDEM FOR SICKLE CELL DISEASE CARE AND IMPACT ON COGNITIVE FUNCTIONING

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Sickle cell disease (SCD) necessitates a paediatric treatment plan that considers the influence of psychological, family and intercultural factors. In 2005, we introduced at Colombes hospital an original paediatric-psychological partnership that implies a rethinking of traditional roles in the SCD treatment care plan as a clinical psychologist accompanies the paediatrician at programmed consultations.

The aim of our study was to objectively evaluate children and their parents treated in Colombes (C1) and in two other paediatric units (Evry (C2) and Clamart (C3)) using clinical interviews and standardized culture-free tools including the Rey-Osterrieth Complex Figure Test (ROCF) that evaluate different cognitive functions important for successful performance in school.

129 families with 155 children were included between February 2013 and April 2014. The average number of days spent hospitalized annually for vaso-occlusive crisis (VOC) was 3.66 (CI95: 2.55-4.77) with no significant difference between centres. 51.7% of the children were severely symptomatic.
The centres significantly differed on the percentage of children with ROCF recall scores 25 percentile (C1=72.73%, C2=60.61%, C3=42.86%; p<0.05); the expected threshold is 75% with lower scores reflecting a poorer outcome. The scores did not significantly differ by geographical origin. Cognitive performance was low for the ROCF recall model with a marginally significant difference between the centres for ROCF mean scores (C1=41.74, C2=36.46, C3=25.81, p=0.053). Qualitative analysis of the parent data showed that 64% of parents stated they felt shame; death was a recurrent theme that appeared in the interviews. The initial diagnosis remained a traumatic event even many years after.

The paediatric-psychologist partnership is a novel promising approach for long-term care of SCD shown in improvement of children's cognitive performance. To our knowledge, this is the first study of a medical-psychological partnership and the first to use standardized culture-free assessments to evaluate the psychological and cognitive repercussions of SCD.

COPING WITH: CONTRIBUTION OF NEW TECHNOLOGIES (LIVING WITH SICKLE CELL DISEASE IN THE AGE OF MEDICINE 2.0)

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HYDROXYCARBAMIDE: USA EXPERIENCE WITH MAXIMUM TOLERATED DOSE

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Hydroxycarbamide (hydroxyurea) is a potent disease-modifying therapeutic agent with proven efficacy for the treatment of both children and adults with sickle cell anemia. When administered as a once-daily dose, oral hydroxycarbamide induces fetal hemoglobin, which inhibits erythrocyte sickling and reduces acute vaso-occlusive complications including pain crises and acute chest syndrome. However, the optimal dosing strategy for hydroxycarbamide treatment has not been determined. In the United States, the dose is typically escalated to maximum tolerated dose (MTD) based on mild marrow suppression, typically 20-30 mg/kg/day, while in Europe the dose is typically limited to 15-20 mg/kg/day, which still provides clinical benefits. Limited experience from Nigeria and India have suggested some clinical benefits can be achieved even with low-dose hydroxycarbamide at 10 mg/kg/day.

Using retrospective review of published reports, comparison of these dosing strategies indicates that hydroxycarbamide escalation to MTD is associated with better laboratory changes including higher hemoglobin, HbF, and MCV as well as lower neutrophils and reticulocytes. The threshold for neutropenia toxicity has changed over time, and lower thresholds allow more consistent dosing and better HbF responses. But any potential benefits from dose escalation must be weighed against the time require to reach MTD, the risks of developing extra hematological toxicities, and the costs of laboratory monitoring. Current research trials in the Caribbean (SCATE and EXTEND in Jamaica, plus SACRED in Dominican Republic) and also in Africa (REACH) have included a two-step treatment strategy involving fixed-dose hydroxycarbamide for six months, followed by escalation to MTD. These study results allow a more direct comparison of both laboratory and clinical effects and confirm benefits with both treatment approaches but further improvement at MTD. The lack of a randomized trial has prevented definitive conclusions, but the current NOHARM extension trial in Uganda is directly comparing a fixed-dose versus MTD escalation strategy.

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Newer dosing strategies in the USA are attempting to predict the hydroxycarbamide MTD at the time of dose initiation, using a pharmacokinetics-based dosing algorithm. If successful, this personalized dosing strategy could reduce the time, costs, and risks involved with dose escalation and help achieve the goal of optimal dosing. Data will be presented to provide a fuller understanding of the pros and cons of hydroxycarbamide dose escalation, and to support evidence-based conclusions on this important topic.

HYDROXYUREA IN SICKLE CELL DISEASE-INDIAN EXPERIENCE

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Sickle cell disease is the most common haemoglobinopathy worldwide. It is an inherited blood condition which is most common among people of African, Arabian and Indian origin . Sickle cell disease in north and South America, the Caribbean and much of Europe occurs in people of African origin. This is mostly of the Benin Haplotype and this form of disease is well documented, relatively severe, and successful interventions have been developed to improve outcome of the disease.
Sickle cell disease was first described in India 64 years ago in Tamil Nadu and was subsequently identified in many locations across the country. It was initially thought to be a particular feature of the tribal people, but it has now been found in all populations. The distribution is very uneven even across small areas, although it seems to be more prevalent in western and central parts of India. 3 It has been estimated that 44,000 children are born in India with sickle cell anemia which is the third highest birth rate in the world after Nigeria and democratic republic of Congo.

It is believed that Indian sickle cell anemia patients have milder manifestations compared to western counterparts. This is particularly attributed to high baseline HbF levels, however significant number of Indian sickle cell anemia patients, particularly those from non-tribal communities in central India present with severe manifestations despite high baseline HbF levels. Studies have suggested that high HbF levels were linked to the presence of HbS mutations on the Arab-Indian Beta globin Haplotype, and the Xmnl polymorphism , although the exact mechanism of high HbF in Indian population is still not understood.

Hydroxyurea is a powerful inducer of HbF production and is one of the main therapeutic agents in the management of SCD. It has been found to be effective in decreasing the painful episodes, blood transfusion requirements and rate of hospitalizations. ‘ The majority of the studies that have proved the efficacy of hydroxyurea therapy in SCD have been in patients with the African Haplotype with lower baseline HbF levels , and there are limited data on the efficacy of hydroxyurea in patients with SCD, many of whom have manifestations despite high HbF levels. Primary toxicity related to myelosuppression reverses upon cessation of the drug. However, parents of the children requiring hydroxyurea should be well informed and strict hematological monitoring should be done by complete blood count and reticulocyte counts. As a remedial measure, low fixed dose hydroxyurea therapy was started in severely affected Indian children in low dose of 10mg/kg/day and was continued on the same dose.

Therapeutic response was comparable with that of standard therapy even with issues of lack of proper monitoring, compliance and toxicity profile.
Studies in India have reported that fixed low dose at 10-15 mg/kg/day without dose escalation is as effective as the recommended schedule[9 10] .

There are many studies in India with respect to hydroxyurea treatment in SCD patients. In one of them 77 severe SCD patients were enrolled for hydroxyurea therapy. A significant clinical response was seen in majority of the patients. There was a significant but variable increase in HbF and F cells along with a significant increase in gamma-mRNA expression. The hemoglobin and MCV levels increased with some reduction in White blood cells and platelet counts, reticulocyte counts and serum bilirubin levels. The reduction in bilirubin levels were higher in patients with (TA)7/7 repeats in the promoter region of UGT1A1 gene after hydroxyurea therapy. No significant toxicity was seen [11 12] ' . The maximum tolerated dose of hydroxyurea was not required for therapeutic effect. Similar findings were shown in other studies from Chhattisgarh, Odisha, Gujrat; however, the dose of hydroxyurea was higher. [13]

The recently concluded pediatric hydroxyurea phase III clinical trial in infants (9-18 months) has proved the efficacy and safety of hydroxyurea.[14]

According to a study conducted in Maharashtra state [15] nearly 53% of HbSS patients were prescribed hydroxyurea at low doses @10mg/kg/day; but there were no clear guidelines on the use of this drug and probably most prescriptions were inappropriate.

The details of Indian studies would be discussed while presentation.
[16]. Despite the fact that hydroxyurea improves survival and quality of life in SCD patients , compliance to therapy is poor in Indian patients.. There are many potential contributing factors which include physicians concern about potential long term mutagenic effects and the lack of familiarity of primary care providers with the use of chemotherapeutic agent.

The majority of the studies in America have used higher doses escalating to maximum tolerated doses [17] . In India a low dose should be more acceptable and economically more viable as the majority of the patients are from low-income group.

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Sickle cell disease and Thalassemia

Update in clinical care and research

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HYDROXYCARBAMIDE AND STROKE JAMAICA EXPERIENCE

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Cerebral vasculopathy in sickle cell anemia (SCA) begins in childhood[1]. One manifestation of cerebral vasculopathy is elevated transcranial doppler (TCD)velocity which path ophysiologically may be due obstructive arteriopathy, impaired haemodynamic dilatation, abnormal vascular tone, and endothelial dysfunction [2]. Notwithstanding aetiology, cerebral vasculopathy is associated with a high risk of ischaemic stroke and TCD screening with subsequent treatment with chronic transfusion therapy reduces this risk[3, 4]. The highest risk of stroke occurs in children with maximum time-averaged mean velocity (TAMV) greater than or equal to 200 cm/sec (abnormal) in the cerebral vessels but the risk is also increased among children with TAMV of 170 - 199 cm/sec (conditional)[3-5]. In Jamaican children, the prevalence of abnormal TCD velocities was 13.1% and prevalence of conditional velocity 6.7% [2].

However, the approach to treat such a large at risk group with chronic transfusion is impractical in many developing countries such as Jamaica because of high cost, blood safety and scarcity as well as limited health system capacity both in terms of human and physical resource capacities. Notwithstanding, there is accumulating evidence that supports the use of hydroxyurea for the primary and secondary prevention as well as treatment of cerebrovascular disease in children with SCA. For example, in Jamaica, we reported that in children with SCA and prior stroke, and observed for 111 person-years, stroke recurrence was reduced to 2/100 person-years in those treated with hydroxyurea compared with 29/100 person-years in those untreated[6]. Additionally, treatment was associated with less disability, cognitive impairment and was more cost-effective [6, 7].

Further, we also reported that for primary prevention of stroke, hydroxyurea treatment reduced TCD velocities by on average 15.cm/sec after 10 months of therapy in those children with baseline conditional level TCD velocities [8]. We are expanding these observations through the implementation of the EXpanding Treatment for Existing Neurological Disease (EXTEND) clinical trial (ClinicalTrials.gov NCT02556099) which will provide additional data on the effectiveness of hydroxyurea in both primary and secondary prevention of stroke [9].

EXTEND will also provide data on the effects of hydroxyurea on other health outcomes such as growth and nutrition, neurocognition, pulmonary function, and quality of life.
These and other reports have influenced the Sickle Cell Unit to include the use of hydroxyurea in its treatment guidelines for cerebrovasculopathy and to advocate for the consideration of hydroyurea as a cost-effective therapeutic option to manage stroke risk in developing countries.

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EXPLOITATION OF HU-ESCORT DATA (French Caribbean)

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HEPCIDIN-BASED THERAPEUTIC STRATEGIES

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Iron is an essential element critical for a multitude of biological processes at the cellular level (including catalyzing essential enzymatic reactions and electron transport) and at the systemic level for oxygen transport. Both iron excess and iron scarcity have important consequences. Excess iron accumulation leads to the production of dangerous free radical species, responsible for epithelium injury and increasing the risk for cancer, while iron deficiency is one of the most frequently observed diseases in the world today, affecting as many as two billion people. Therefore, iron levels need to be tightly regulated in the organism.

At a systemic level, iron homeostasis depends on the regulated absorption of dietary iron by mature enterocytes of the duodenum and iron recycling by macrophages, which supply most of the serum iron through recovery of the metal from senescent erythrocytes. These two fundamental processes are regulated by the iron-dependent hormone hepcidin, a 25-aminoacid peptide, produced mainly by the liver and secreted in the circulation.

In brief, hepcidin controls plasma and tissue iron levels by inhibiting cellular iron export through degradation of ferroportin, the sole known iron exporter, in the intestine and macrophages. Hepcidin is thus a hyposideremic hormone decreasing the transfer of iron into the circulation. Hepcidin expression is regulated by tissue and serum iron (through the BMP/Smad pathway) and by the erythroid drive, through a recently identified bone marrow-made hormone, erythroferone, Erfe. Erfe is produced by erythroblasts in response to erythropoietin, EPO, and acts a negative regulator of hepcidin expression allowing iron mobilization for hemoglobin synthesis.

Mutations affecting hepcidin regulators, or the hepcidin gene itself, cause hereditary hemochromatosis, HH, a common genetic disorder, characterized by iron-induced tissue damage resulting in serious illnesses including cirrhosis, hepatomas, diabetes, cardiomyopathy, arthritis, and endocrinopaties characterized by excess iron accumulation.
Interestingly, in β-thalassemia, hallmarked by ineffective erythropoiesis, anemia and iron overload, marked hepcidin suppression has also been reported. Erfe expression is greatly increased in a mouse model of thalassemia intermedia, where it contributes to hepcidin suppression and the systemic iron overload characteristic of this disease.

In both conditions, primary (HH), as well as secondary iron-overload (β thalassemia), hepcidin deficiency thus represents the key molecular event responsible for the iron accumulation that may cause illness and death. Iron overload is usually treated by phlebotomy for HH and iron chelators for thalassemia. Very promising alternative therapeutics have been reported in animal models using hepcidin-based therapeutics.

Current knowledge of hepcidin regulation and pathological involvements as well as current progress on hepcidin-based therapeutics in humans will be discussed.

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Sickle cell disease and Thalassemia
Update in clinical care and research

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FETAL HEMOGLOBIN IN SICKLE CELL DISEASE : NEW INSIGHTS INTO THE EXPRESSION, CELLULAR DISTRIBUTION AND THE EFFECT OF HYDROXYCARBAMIDE ON THE CELLULAR LEVEL

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In sickle cell disease, fetal hemoglobin (HbF) is known to act as a modulator of the disease manifestations, since HbF is capable of interfering with HbS polymerization. We studied the expression and distribution of HbF in SS and Sβo patients treated or non-treated with hydroxycarbamide (HC). Using imaging flow cytometry, we set up a method to (i) study the F+RBCs and subdivide them into Low-F+RBCs and High-F+RBCs (ii) measure the percentage of irreversibly sickled cells (ISCs) and (iii) the surface area of each cellular population. We analyzed RBCs from 36 non-treated patients and showed that most of the F+RBCs were categorized in the Low-F+RBCs. We observed a high percentage of ISCs in the non-F cells and in the Low-F+RBCs. The latter validates that a minimum amount of HbF is required per cell to avoid sickling. Using a microfluidic device, we observed that only High-F+RBCs were protected from hemolysis. 9 out of the 36 patients were later under HC. During HC treatment we observed a significant increase in F+RBCs with a median of 50% (21.5% before HC). Note that this increase was mainly in the High-F+RBCs. Microfluidics analysis of HC-treated RBCs showed a moderate level of hemolysis with no enrichment of F+RBCs. Thus we tested the following hypothesis: treatment with HC increases the volume of all RBCs leading to a dilution of HbS. We measured the surface area of F+ and F-RBCs. We observed that both populations had increased area during HC, and that the area of F-RBCs was similar to that of F+RBCs before the treatment. Our study presents an innovative approach to determine HbF distribution per RBC. It shows that HC treatment increases HbF content per RBC, together with increasing the cell volume of all RBCs, which has a beneficial anti-sickling effect even in the absence of HbF induction.

IDENTIFICATION OF COMPONENTS OF THE MECHANISTIC TARGET OF RAPAMYCIN COMPLEX 1 (MTORC1) PATHWAY AS POTENTIAL REGULATORS OF FETAL GLOBIN

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Objective: In patients with sickle cell disease (SCD), the ability to postnatally reactivate the expression of fetal γ-globin is an effective way to reduce disease symptoms.
Our goal is to identify new and safe means of reactivating the expression of γ-globin.

Methods: We used the Nan mouse model to identify new genetic regulators of βh1 expression, the mouse ortholog of human γ-globin. The Nan mouse carries a mutation in the gene encoding Klf1 (Krüppel-like factor 1) transcription factor resulting in a corrupted transcriptome that produces anemia and a ~100-fold increase in βh1 expression in adult Nan spleen and bone marrow. We performed eQTL (expression quantitative trait locus/loci) mapping in Nan. By integrating genes falling within eQTL confidence intervals with ChIP-seq data obtained using an immortalized Klf1-null fetal erythroid cell line expressing either WT or Nan Klf1, RNA-seq data from sorted WT and Nan adult spleen erythroid precursors (pro-, baso-, poly- and orthochromatic erythroblasts), and available functional annotations (DAVID and Ingenuity pathway analysis), we identified several strong candidate genes.

Results: We identified genetic loci modifying βh1 expression on chromosomes 7, 4, 11, and 17. Gene ontology (GO) functional annotations analysis showed that the mTORC1 pathway controls the top GO term annotations associated with differentially expressed genes between Nan and WT mice. The integration of the confidence intervals and bioinformatic analysis with the RNA-seq and ChIP-seq datasets revealed strong candidate genes potentially influencing the expression of βh1. Among the strongest candidates several genes encoding components of the mTORC1 pathway including Rptor (regulatory associated protein of MTOR complex), Rragd (Ras-related GTP binding) and Ampd3 (adenosine monophosphate deaminase 3).

Conclusion: We identified the mTORC1 pathway and several of its components as potential regulator of βh1 expression in Nan. These data may point to new targets to increase fetal globin in patients with SCD.

HYDROXYUREA TREATMENT IN SICKLE CELL ANEMIA INDUCES CHANGES IN MICROPARTICLES CHARACTERISTICS AND THEIR IMPACT ON ENDOTHELIAL CELL PHENOTYPE

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Objective: To determine, in sickle cell anemia (SCA) patients, the impact of hydroxycarbamide (HC) treatment on the effect of microparticles (MPs) on endothelial cell (EC) phenotype.
Methods: ECs (TrHBMECs) were incubated with MPs isolated from 15 longitudinally followed SCA patients at steady state, before (t=0m) or 2 years (t=24m) after HC treatment onset, and from healthy controls. After various incubation times, expression levels (MFI) of endothelial VCAM-1, ICAM-1 and E-selectin were evaluated by flow cytometry. For SCA patients' MPs, sICAM-1 levels in culture supernatants were also determined by ELISA and unbound MPs were analyzed after 1 hour of incubation.

Results: Compared to t=0m MPs, we detected a decrease of sICAM-1 level at 2 hours (p=0.0151) and a lower expression of transmembrane ICAM-1 at 4 hours with t=24m MPs (p=0.0227). This latter decrease was also observed when capping t=0m MPs externalized phosphatidylserine (PS) with Annexin V (p=0.0215), or with healthy controls' MPs (p=0.0072). Both concentration (p=0.0269 or p=0.0068) and PS density (p=0.0107 or p=0.0034) of the remaining unbound t=0m platelet- or erythrocyte-derived MPs (RBC-MPs) were decreased after 1 hour of incubation, when compared to the same condition but without ECs.

Conclusions: We showed that MPs from SCA patients not treated with HC trigger the endothelial overexpression of ICAM-1, a protein involved in the abnormal adhesion of neutrophils to EC in SCA. This MPs-mediated pro-adhesive phenotype was abolished after a 2 year-long HC treatment. We also presented evidence supporting that MPs binding to ECs is facilitated by PS exposure of these extracellular vesicles. Since we have previously shown that HC treatment in SCA patients decreases RBC-MPs PS exposure, our results suggest a new beneficial effect of HC treatment through its impact on MPs. Further experiments are warranted to test the functional effect of SCA MPs on neutrophil adhesion on EC.

INFECTIOUS RISKS AND TRANSFUSION: THE BRAZIL EXPERIENCE

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Introduction

Blood safety is based on two principles: the proper selection of blood donors and serological and molecular screening tests on donated blood. This traditional approach is effective in the prevention of classical pathogens – HIV, HCV, HBV, T. pallidum and T. cruzi.
However, for many other pathogens, especially - but not exclusively - the so-called emerging and reemerging pathogens, no tests are available, and at-risk blood donors cannot be eliminated based on behavior or risk situations, which may compromise transfusion safety.

Situation in Brazil

Since the early 90's, federal regulation requires in Brazil requires to test the donated blood for anti-HIV1+2, anti-HTLV-I/II, HBsAg, anti-HBc, anti-HCV, anti-T. cruzi and syphilis tests. In 2012, multiplex NAT for HIV and HCV became mandatory; finally, in 2015, NAT for HBV were included in the list of required tests.

The federal regulation also imposes donor deferral based on previous exposure to risk situations, such as multiple sexual partners, MSM, drug addiction etc.
This strategy was very successful in increasing blood safety in Brazil; in the last five years, only two cases of transfusion-transmitted "classic" pathogens were notified to health authorities. The prevalence of transfusion-transmitted of tested blood borne pathogens is much higher than in Europe or USA. For most agents, this is a reflex of Brazilian epidemiological situation; however, for HIV, the explanation is related to seeking-test donors, which is still an issue in Brazil. In Brazil, the residual risk for HIV after NAT introduction, in 2012, 4.2 per million of blood donations, a risk 5 to 10 times greater than the north-american one.

Brazil has experienced in recent years, large outbreaks of dengue, Chikungunya, Zika and yellow fever. In 2016 alone, 779,468 cases of dengue, 80,686 cases of Chikungunya and 119,241 cases of Zika were registered in Brazil. In 2017, 800 cases of Yellow fever were conformed in Brazil.

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These viruses can affect transfusion safety and cause severe diseases, with high morbidity and mortality, and. In 2016, there were 5,373 severe forms of dengue in Brazil (0.7% of cases) and 344 deaths (0.04% case fatality rate).

Chikungunya mortality is very low, but the infection leaves intense joint pain as a sequel, which can last up to two years. The virus can persist in synovial membranes, causing that symptom.
The Zika virus, in turn, causes two very serious complications: fetal microcephaly, better known as congenital Zika syndrome, when the infection occurs in pregnant women, and Guillain-Barré syndrome (GBS). In Brazil, 10,623 cases of microcephaly associated with the Zika virus have already been reported, with 602 deaths.

The clinical selection of safe blood donors in endemic country is relatively ineffective: half of the cases of dengue are asymptomatic; even worse, about 75 to 80% of people infected by Zika do not have signs or symptoms - and therefore can be accepted as blood donors.
The majority of Chikungunya infections are symptomatic, but 15 to 20% of cases may be accompanied by clinical evidence of acute infection. In a recent study conducted in blood donors in Rio de Janeiro city, we found a 6% prevalence of IgM anti-Chik, which means that the viremic donors may be completely asymptomatic.

No molecular tests for those virus are available to blood Banks; licensed serological tests are ineffective in the context of donor blood screening, since in these infections viremia is very short.
Reports of transfusion-transmitted Zika and dengue have been published in Brazil. For dengue, there are several reports of transmission of the disease by transfusions outside Brazil. The first report was in Hong Kong in 2007. Since then, there have been several reports in Singapura6, Puerto Rico and Brazil8. A large multicenter prospective study Brazil, published in 2016, showed six cases of transfusion-transmission of dengue virus in susceptible individuals, with a 37% efficiency rate of transmission.

For Zika virus, there are four cases of transfusion-transmission in Brazil, during the 2015-2016 outbreak. In all cases, the patients had an asymptomatic infection. In three cases, donors called the blood bank two or three days after the donation to inform that they had a fever and fever with rash (this donor made a double donation of platelets, which were transfused to two recipients. In the fourth case, the recipient had an unexplained thrombocytopenia, which led to the presumption of viral infection transmitted by blood transfusion.

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At the end of 2016, 2017 and 2018, there were outbreaks of the sylvatic form of yellow fever (YF) in some Brazilian states, including Rio de Janeiro and Sao Paulo. The sylvatic YF vector is Haemagogus and Sabethes mosquitoes, arthropods whose habitat is the forest, not urban areas.

So far, no case of YF transfusion-transmitted was suspected or notified in Brazil. Nevertheless, the YF re-emergence in some urban areas adjacent to forests caused some Brazilian states, including Rio de Janeiro resulted in a mass vaccination campaign. This public health measure could have a major impact on blood donations, because donors are deferred for 4 weeks, after vaccination.
These emerging and re-emerging pathogens are not the only risks that affect blood safety in Brazil and other Latin American countries. For example, there are two diseases caused by protozoa that are particularly important in this context: malaria and visceral leishmaniasis.

Malaria is endemic in some areas of Brazil, particularly in the Amazon region, whose annual rates are high, in some localities. The risk of Plasmodium transfusion-transmission does exist, especially in endemic areas, because no molecular test applicable to blood banks is available. Although there are no prospective studies to measure this risk, there are several reports of malaria transmission through transfusion in Brazil.

With respect to leishmaniasis, a recent study by de Moraes Souza found that 8 (1.31%) out of 615 samples of blood donors from endemic areas for Leishmania had Leishmania chagasi in its plasma, detected by molecular assays. Two of the 8 patients who received these bags seroconverted for Leishmania, by PCR, although they have not yet developed any Leishmania symptoms.
In summary, transfusion infectious risk for traditional pathogens is totally under control in Brazil; risk for emergent or re-emergent agents is a very important public health issue. The risk is difficult to quantify and preventive measures not so easy to apply, in blood donation context.

STORAGE LESION; SHOULD WE TRANSFUSE YOUNG BLOOD BAGS?

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After collection and processing, RBC concentrate is commonly stored à 2-6 °C for up to 42 days before transfusion, depending on the additive solution and local policy or regulation. During this process, storage lesions of RBC leading to the progressive loss of biochemical, morphological and mechanical properties occur and are mostly due to irreversible changes in the membrane. Seminal studies suggested that in patients undergoing cardiac surgery, transfusion of RBC that had been stored for more than 2 weeks is associated with a significantly increased risk of postoperative complications as well as reduced short-term and long-term survival. However, several subsequent studies as well as a systematic review of the results obtained from sixteen trials randomizing more than 30 000 patients led to the conclusion that transfusion of fresher RBCs compared to older RBCs is not associated with decreased risk of death in critically ill patients, while increased rates of transfusion reaction and possibly infection were observed. It was therefore concluded that there is no evidence for a change from current transfusion practice.

However, storage lesions should be taken in consideration in transfusion medicine since they are likely to induce the rapid clearance of up to 25% of transfused RBC in the recipients. Improvement of transfusion yield is important when transfusion of RBC concentrates from donors with rare blood group phenotypes or transfusion of multi-transfused patients, as SCD patients, is concerned.

The underlying mechanisms leading to RBC membrane changes during storage are poorly known and a quantitative, whole cell-based predictor of transfusion yield is lacking. We have shown that Band 3 phosphorylation and clusterization likely initiates membrane micro-vesiculation.

This could represent the primary event leading to the formation of a "small cells" subpopulation of altered RBCs that we have shown to accumulate during storage.
We propose that "small RBCs", for the detection of which we have developed an operator-independent quantification using imaging flow cytometry, are preferentially cleared from the circulation shortly after transfusion of long-stored blood and may therefore provide a marker of storage lesion potentially predictive of transfusion yield. In this context, we have recently shown that treatment of the RBC concentrate with a rejuvenation solution known to restore RBC metabolism markedly reduces the storage-induced spherocytic small cell population and partially restores RBC morphology. These results provide the rational for undergoing specific clinical studies assessing transfusion yield and efficacy and tissue oxygenation when "rejuvenated" RBCs are used.

The new storage lesions that we have identified will be also evaluated in the course of a collaboration study with the French Anti-Doping Agency aiming to detect autologous blood transfusion (ABT) in high-level athletes ("blood doping"). Indeed, blood transfusion (homologous or autologous) are prohibited in sports by the World Anti-Doping Agency (WADA) and ABT is a particular matter of concern for anti-doping laboratories because its detection is still a challenge at the moment since no clear-cut markers are reported and no reliable detection method has emerged yet.

A CHALLENGE FOR FRENCH GUIANA: HOW CAN DONOR BLOOD COLLECTION MEET THE DEMAND WITH RESPECT TO THE REGULATIONS IN FORCE?

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Technically, blood transfusion (BTx) service comprises of entry and exit operations, to and from a Blood Component (BC) inventory. Exit interventions consist in attribution of a BC to a given beneficiary patient, named "recipient" in the transfusion jargon; attribution—termed "delivery"—is immunologically matched between recipient's and BC's characteristics, based upon a number of defined parameters such as ABO, Rhesus (RH) and other important blood groups and on the absence of patient antibody (Ab) reactive to any of the known and significant (donor) blood group antigens (Ags). Such Abs, collectively terms irregular Abs, are formed by patients immunized after BTx but also pregnancies and controlled by a set of complex mechanisms that are not all well understood; such mechanisms seem to comprise of patient intrinsic factors (genetics, underlying disease...) and extrinsic factors such as BC characteristics, dose, perhaps freshness (age of blood), presence and concentration of residual leukocytes etc. Of notice, patients presenting with haemoglobinopathies are particularly prone to manifest with allo-immunization after BTx, and to complement fraction activation leading to often severe hemolysis crises that can even be fatal.

In all, the BTx process is overviewed in full respect of several safety check-points: The very first one is inventory, as BCs must be quantitatively enough to serve every patient in need in the reference facility (public and private hospitals). Next, BCs must be safe with respect to the carriage of infectious agents that can be blood transmissible and deleterious in an immunocompromised or a fragile patient even if innocuous in the donor; this step also overviews bacterial safety of BCs all along the process, including during shelf-life preservation. Then, BCs must bring the needed factors in amounts enough (e.g. Hb) and not be responsible for any type of overload (metabolites, anticoagulant, volume, etc.). Last, the BC must be immunologically compatible, which is slightly distinct from immunologically identical as identity can barely be reached, because everyone is unique considering that there are more than 35 blood group families (and 10-fold more antigens) whose genes are transmitted independent from each other.

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Good transfusion practice and guidelines assist transfusion practitioners in providing the best care to patients needing either unique or repeated BTx; this is particularly care sensitive in BTx-dependent patients such as β-Thalassemic and sickle cell patients (and also myelodysplactic syndrome patients, and patients undergoing myeloablative chemotherapy).

Having those restrictions in mind, especially the immunologic restriction, the BTx service—in general the French Blood Establishment EFS in France (or the army BTx service CTSA)—faces a challenge: how to build-up an inventory large enough to match the quantitative and qualitative demand while avoiding overstock for ethical, logistical, and economical reasons? This is theoretically quite easily achievable in settings where the immunological profiles of blood donors and recipients are similar; this is a particularly difficult task when profiles differ, especially in areas where the populations that cannot fulfill medical conditions for donating (or whose collective psychology refrains from blood donation; or both) but account for a non-negligible percentage of recipients (with frequent haemoglobinopathy traits, for example).

Blood donation has been discontinued in French Guiana for more than a decade, because of an exceeding percentage of disqualification for low Hb levels, and high infectious markers, and for a non-negligible risk of parasite carriage, whose biological testing was not secured at this time; further on, additional BCs could not be filtered because of a significant % of variant Hb red blood cells (sickle cell disease trait) that slows down the filtration that cannot be achieved within the acceptable time frame according to the regulation. The main consequence for this is that since then, BCs are chiefly imported from Metropolitan France (and the French Caribbean Island La Guadeloupe). The vast majority of red blood cell concentrates (RBCCs) imported from Metropolitan France are donated—offered—by donors presenting with genetic background of diverse origin representing populations living in this country and not presenting contraindications, of which low Hb count. The latter requisite disqualifies numerous blood donor candidates of African ancestry, either from intertropical Africa and from the Caribbean area, alongside with past malaria infection antecedent or exposure. The main consequence for this is the build-up of an ad hoc inventory suitable for populations with majority African traits based on BCs from populations with majority Caucasian traits. This can often be met in proposing Rhesus D negative blood independent on the Rhesus D status of the recipient, which presents an imbalanced Rhesus CeEe—actually within the RHCE gene—linkage, and frequent C and E negative phenotypes, more often found in African origin populations; however, this leaves unsolved the issue of all other frequent blood group Ags such as Duffy, either a and/or b positive in Caucasian populations and often a and b negative in African populations, etc. This has another consequence, which is the overuse of Rhesus D negative blood, and the overcollection of such blood in the 15% Rhesus negative population in Metropolitan France, with pressure on Rhesus D negative blood donor candidates etc.

The case of the D antigen is just an example of the overall difficulties in matching bloods between Guianese recipients and Metropolitan French donors.
What could the remedies be? Firstly, to reconsider collecting in French Guiana, in spite this would need much effort to reorganize blood collection, and foremost to communicate with populations having in mind that many candidates will not be authorized to donate form medical reasons; this latter can be perceived as a general discouragement. Next, to anticipate on technological developments: pathogen inactivation technologies for whole blood and RBCCs have been developed and are being tested in particular in Africa, with very encouraging results (two such processes have been promoted so far); this step would get rid of the reported infectious over-risks. Next again—perhaps the most difficult task to achieve—would be to beg for a European Commission regulation exemption, for adjusting the Hb count to the African physiological standards which are known to be lower than the Caucasian's; and to seek for CE marked filtration filters better suited to sickle cell disease trait blood. Implementation of technique rupture scenarios would be a step further, with engineered universal blood, or techniques that can cut or mask the immunogenic parts of blood Ags.

In conclusion, the proposed challenge is technically and administratively difficult; however, it corresponds to a public health safety issue (to maintain some self-sufficiency in case a civilian breakthrough prevents the shipping of blood in due time) and justice and sanitary democracy, with perhaps political interventions. Technical progress would help alleviating the present situation and be the after-tomorrow solution; in the meantime, a solution for tomorrow is still to be envisioned.

HEMATOPOIETIC STEM CELL TRANSPLANTATION : GLOBAL EXPERIENCE

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In 2018, hematopoietic stem cell transplantation (HSCT) from mainly sibling donor (i.e. HLA fully compatible brother or sister) still remains the only available curative therapy for severe sickle cell disease (SCD). The most and widest report from both EBMT and Netcord consortium described a 5-year overall survival of almost 93% and a 5-year event-free survival of 91% about 1000 patients with a median follow-up of more than 5 years. There is no other disease associated with so good results in HSCT setting. These results are similar to those currently reported by local or national cohort. Interestingly, those data were obtained in patients suffering of severe SCD. The severity stage may vary among studies but globally describe patients with either cerebral vasculopathy, alloimmunization or with several and repeated acute chest syndrome and/or vaso-occlusive disease. Others are those under transfusion program (with or without exchange) and those after failure of hydroxycarbamide treatment. Despite this disease severity and the related comorbidity, these high-quality results were obtained after using myelo-ablative conditioning regimen, i.e. very toxic chemotherapy drug association based on alkalyting agents. These regimens induce acute toxicity (mainly digestive and renal injuries) as well as long-term side effect mainly on fertility, hypofertlity or sterility, and as ever in allogeneic HSCT frame, the rare (less than 5%) but debilitating extensive chronic graft versus host disease. In the French cohort, since year 2000, the cumulative incidence of chronic graft versus host disease is about 10% for any cGvHD and 2% for extensive. The mortality rate is around 7% in this widest report and may be lower but never null in other series as the French one with less than 2% of treatment related mortality for patients transplanted since year 2000. From 2000 to 2012, 197 patients were transplanted in France. The calculated 5-year event-free survival is 97%.

The other important information from the Gluckman's report regards the impact of age at transplantation, the lower age, the better overall survival. Finally, this paper drawn the most important questions we have to discuss and answer in the closed future: how to select, how to define the good candidate and the good conditions to perform HSCT leading to the best results:

- the best time, probably before scholar age i.e. before SCD induced organ injury as well as before SCD-related scholar impact, and surely before adolescence.

- the best conditioning regimen, probably reduced toxicity regimen in order to decrease the acute toxicity and late effect but keeping mind the risk of graft failure (rejection) by decrea sing too strongly the conditioning intensity.

- the consensual indications: only severe SCD patients at time of HSCT or more widely every patient requiring any intensive therapy defined by either hydroxycarbamide or transfu sion program initiation or extensively, and considering the high morbidity of SCD at adulthood whatever the severity of symptoms during childhood, every patient with S/S, or S/β0thal SCD and with available non-SCD related full compatible donor?

- In the same time, we have to discuss the development of alternative transplantation for either patients with severe SCD but without sibling donor or patients with comorbidity excluding myeloablative conditioning regimen. These alternative HSCT were developed for 5 to 10 years now with interesting results however remaining inferior to those obtained and des cribed above. If it appears very important to develop non myeloablative conditioning regimen (for example based on irradiation and alemtuzumab, as reported by Hsieh et al) and HSCT from alternative donor as described by Bolanos-Meade et al or by Corbacioglu et al, it is very important to keep in mind that those options still remain experimental, have to be conducted in prospective trial and do not represent current standard of care. Currently, in France, we have chosen to keep myelo-ablative conditioning regimen for patients younger than 15 years in regards to the excellent results obtained from year 2000.
For patients above 15 years, we propose for using NIH reduced intensity conditioning regimen (based on low dose total body irradiation and alemtuzumab).
However, this procedure is under investigations.

BID CLEAVAGE PATTERN DEPENDENT ON ERYTHROPOIETIN-INDUCED CASEIN KINASE - 1α DETERMINES THE FATE OF ERYTHROID PRECURSORS

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Objective: Red blood cell production is negatively controlled by the rate of apoptosis at the stage of CFU-E/pro-erythroblast differentiation, depending on the balance between Erythropoietin (EPO) levels and activation of the Fas/Fas-L pathway. At this stage, transient caspases activation through mitochondrial depolarization (MOMP) is also required for terminal erythroid differentiation. Molecular mechanisms regulating the differential levels of MOMP, during differentiation and apoptosis, however, remain poorly understood.

Method: Erythroblasts were generated with a two-step culture of CD34+ cells from cord blood. We used an shRNA-mediated knockdown approach (shBID, shCASP-10, shCK1α) in addition to BID mutant constructs transduced at day 5 of the CD34+ cultured. MOMP was assessed by the cyanine dye DiIC1(5) and differentiation by was assessed morphological and FACS analyses of KITlow/GPA-high and Band3high/CD49dmed expression.

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Results: Here, we show that caspase-10 is fully activated at the onset of erythroid terminal differentiation, resulting in BID successive cleavages. A first truncated P18-tBID is phosphorylated on serine residues in part by EPO induced CK1α expression, preventing cleavage that generates the classical apoptotic Myr-P15-tBID fragment. Then, phospho-P18-tBID is ultimately cleaved in a P13-tBID fragment, which induces the transient, but no definitive, mitochondrial depolarization and terminal differentiation.

Likewise, transduction of P13-tBID fragment induced strong erythroid terminal differentiation after 3 to 4 days, rather than the 8 to 10 days observed in controls (mean proportion of Band3high/CD49dmed cells: 28.89 ± 2.4% for P13-tBID vs. 1.26 ± 0.27% for controls).

Conclusions: EPO levels by modulating CK1α expression and the pattern of BID cleavage controls MOMP (definitive vs transient) and determines the fate of erythroblasts (apoptosis vs differentiation). In beta-thalassemia, GDF11 overexpression induced by ROS production down-regulates Fas-FasL expression in immature erythroblasts. Caspase-10 activation and the resulting BID cleavage pattern could be altered in ineffective erythropoiesis of beta-thalassemia.

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VASCULOPATHY IN SUB-SAHARAN AFRICA

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Sickle cell disease (SCD) hallmarks includes chronic hemolysis, inflammation and increase of cell-derived microparticles (MP), resulting in a systemic vasculopathy characterized by chronic organ damage. In this study, we analyzed cell-derived MP in an African cohort and their association with clinical complications.

This cross-sectional case-control study is nested in the CADRE cohort (Cœur Artère Drépanocytose, clinical trials.gov identifier NCT03114137), a large cohort of SCD patients from five countries in Sub-Saharan Africa. Here, we analyzed 219 SS adults, recruited in two African centers: Bamako (Mali) and Dakar (Senegal). These patients were stratified according to six vascular complications: tricuspid regurgitant jet velocity (TRJV) > 2.5 m/s -which may indicate pulmonary arterial hypertension-, microalbuminuria, leg ulcer, priapism, aseptic osteonecrosis and retinopathy, or none. MP from red cells, leukocytes, platelets and endothelial cells were isolated in Bamako and Dakar and characterized using a flow cytometer in Paris. We analyzed the associations between the different cellular types of MP and the six vascular complications. We studied 28 controls, 27 retinopathies, 43 priapisms, 105 microalbuminuria, 55 increased tricuspid regurgitant jet velocity, 51 osteonecrosis and 34 leg ulcers. The number of erythroid MP are significantly associated with an increased TRJV, microalbuminuria, priapism and leg ulcer, in contrast to other MP. This strong association is observed also for retinopathy and avascular osteonecrosis. These results strongly suggest that the presence of erythroid MP, a marker of hemolysis is not only associated with hyperhemolytic sub-phenotype but also with hyperviscosity phenotype at least in an African context.

In conclusion, our results highlight a correlation between erythroid MP and all vascular complications in African SS patients. This study is the first to describe the setting up of relevant experiments (flow cytometry, plasma preparation) from blood samples in a large cohort of African patients thus enabling the implementation of these technologies in Africa for the research of pertinent markers of vasculopathy in SCD patients.

GENE THERAPY FOR HEMOGLOBIN DISORDERS

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The β-hemoglobinopathies, sickle cell disease (SCD) and β-thalassemia (β-thal) major, the latter defined clinically as transfusion-dependent β-thalassemia (TDT) regardless of the underlying genotype, are the most prevalent inherited disorders worldwide and affect millions of people. They fall into two large groups of β-globin gene mutations that results in either abnormal hemoglobin (Hb) structure such as HbS in SCD or highly reduced (β+) / absent (β0) production of β-globin chains in TDT. The only available curative treatment is allogenic hematopoietic stem cell transplantation (AHSCT) which is recommended for patients with severe Hb disorders who have a healthy, HLA-matched sibling donor. Although outcomes are improving, a substantial risk of severe adverse events and mortality still exist. Furthermore, most patients lack a suitable HLA matched donor. Hence, gene therapy by one-time addition of the missing gene in autologous hematopoietic stem cells followed by engraftment is an attractive approach for the treatment of β-hemoglobinopathies. The key objective of gene therapy to cure SCD and TDT are similar but not strictly identical. In TDT, the aim is to achieve cellular levels of β-globin expression that are sufficient to bind much of the unpaired α-chains and this level varies whether there is complete absence of β-globin (β0) or not (β+). In SCD, the goal is to inhibit intracellular HbS polymerization. Whereas wild-type human β-globin is a relatively weak inhibitor of HbS polymerization because it acts by mere dilution, we demonstrated that a β-globin chain modified at position 87 (βT87Q) is able to disrupt HbS tetramer formation. We therefore conceived a lentiviral vector promoting high level expression of the βT87Q-globin chain. Transplantation of genetically modified mouse HSC from β-thalassemic donors in myelo-ablated recipients resulted in pan-cellular and long-term expression of human β-globin, high enough to correct ineffective erythropoiesis and anemia, and to prevent iron overload. In mouse models of SCD, we observed inhibition of HbS polymerization and red blood cell sickling, and correction of hematological parameters.

To prepare for human clinical trials, safety modifications were made to yield the vector referred to as HPV569. It is a self-inactivating (SIN) vector, encoding the βT87Q-globin under the control of the human β-globin locus control region (LCR) and the β-globin promoter, containing two copies of the core element of the chicken chromatin insulator cHS4. The first clinical trial (LG001) with this vector was initiated in 2006 in France and brought invaluable proof-of-concept for the potential of lentiviral vectors. One subject sustained clinical benefit as evidenced by long-term transfusion independence that was achieved approximately 1-year post-transplant and sustained so far.

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Partial clonal dominance was observed upon vector integration within the HMGA2 gene a few months after transplantation but the clone progressively moved aside.

To overcome the relatively low titer and modest transduction efficacy limited to about 10-20% of hematopoietic cells, also following the advice of the US and European regulatory agencies, the HPV569 vector was recently modified and chromatin insulator removed. A comprehensive mouse study that demonstrated absence of toxicity and increased efficacy with the new generation BB305 vector, provided the bases for initiating three new clinical phase II trials in patients with TDT and SCD (HGB-204, HGB-205, HGB-206). In the first SCD patient to be treated (HGB-205, France), biological parameters improved, consistent with a clinical benefit. No SCD-related complication occurred 15 months after gene therapy despite a history of numerous vaso-occlusive events and acute chest syndrome before treatment. All but one non-β0/β0 TDT patients with at least one year of follow-up stopped transfusion and transfusion requirement was considerably reduced in TDT patients with the β0/β0 genotype (HGB-204 and HGB-205). On the basis of these results, phase III multi-center clinical trials (HGB-207, HGB-212) have been initiated with the same vector for TDT patients and slight modifications of the protocol. New pre-clinical studies are also achieved with the aim to increase further the percentage of corrected cells.

Gene therapy for hemoglobin disorders has made major progress, from early discovery of β-globin regulatory elements, development of lentiviral vectors including the HPV569 and BB305 vectors described here, efficient transduction of hematopoietic stem cells, proof of principle of efficacy in mouse models, the first conversion to multi-year transfusion-independence of a patient with TDT, and early clinical benefit now observed in SCD. The implementation of gene therapy in clinical practice will depend on long-term benefit/risk/cost ratios, which will be carefully evaluated over the next few years.

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GENETICS, GENOMICS AND SICKLE CELL DISEASE

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CURATIVE TREATMENT VERSUS IMPROVING CARE IN SICKLE CELL DISEASE WHY GIVING DRUGS WHEN CURE IS POSSIBLE?

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Even if median life expectancy in patients with homozygous sickle cell anemia (SCA) is increasing up to about 60 years, the disease remains severe in many patients, affected with chronic pain, unpredictable painful events, or undergoing multiple treatments. Median age at death is very low in the US (38 years) and in France (37 years).

Hydroxyurea (HU) has been shown to decrease pain and acute chest syndrome rates and transfusion needs in children and adults. The effects are more dramatic in younger patients, but even so, a significant proportion of children still suffer from daily pain (Kanter J et al, Br J Haematol 2018). Although HU is licensed in the US since 1995, chronic pain syndrome develops in up to 30-40% of adults (Brandow AN & DeBaun MR, Hematol Oncol Clin North Am, 2018), and depression, associated with lower quality of life and daily pain, in 35.2% of them (Adams SS et al, Blood advances 2017). Effects on mortality are controversial. These results may be partly explained by a rather low adherence to HU therapy (Zhou J et al, Br J Haematol 2018). Chronic transfusion is more effective than HU to reduce pain and ACS rates, but exposes to allo-immunization risks, venous access difficulties, hepatic iron overload, and lassitude.

Faced to the absence of real hope, parents and patients may consider taking transplant-related risks. In 2018, more than 1000 hematopoietic stem cell transplants have been performed (Gluckman E et al, Blood 2016). In the best case, when stem cells originate from an HLA-identical sibling, risks for death, acute GVH, and chronic GVH are respectively around 5%, 15%, and 10 to 20%. Infertility risk is high. These issues must be exposed to the families. The risk/benefit ratio does not favor HSCT in low-severity patients and in patients well-controlled with HU (no pain, no ACS). In all other cases, HSCT must be considered.

CURATIVE TREATMENT VERSUS IMPROVING CARE IN SICKLE CELL DISEASE HELP THE PATIENTS AND SAVE LIVES, WHILE SEARCHING FOR A CURE!

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An estimated 100,000 persons in the United States are living with sickle cell disease (SCD), and an additional 2,000 affected babies are identified each year in the US through newborn screening. Establishing the diagnosis of SCD early in life allows prompt initiation of penicillin prophylaxis, timely pneumococcal immunizations, repeated family and caregiver education, and proper fever management. These simple and inexpensive interventions have increased the survival of children with SCD to >95% in the US and other developed countries. The advent of transcranial Doppler (TCD) screening for primary stroke prevention, judicious use of blood transfusions, and access to hydroxyurea treatment has further reduced both the morbidity and mortality of SCD.

Worldwide, approximately 400,000 babies are born annually with SCD and the vast majority occur in Africa and India. Few will be identified correctly through newborn screening, and without a proper diagnosis or treatment plan, many will die at an early age. It is estimated that 50-90% of babies born with SCD in Africa will die before age 5 years. Simple and inexpensive interventions including early diagnosis, penicillin, immunizations, education, and hydroxyurea would be transformative for children with SCD born in lower-resource settings.

Stem cell transplantation is now recognized as a curative intervention for SCD and is successful in about 85-90% of published cases. Recent progress with gene therapy and potentially gene editing is also encouraging, by allowing early correction of the genetic abnormalities and potentially providing a curative treatment. But focusing solely on the expensive cure of a few patients forces the discussion away from improving the health and lives of millions of existing patients with inexpensive approaches. It is inappropriate and unethical to divert attention and funding away from proven successful interventions, to chase the dream of future cure while forgetting about the current suffering. Help the patients and save lives, while searching for a cure!

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ABSTRACT POSTERS

ECHANGES TRANSFUSIONNELS AU CENTRE HOSPITALIER DE CAYENNE : LES PROBLEMES TECHNIQUES D'ACCES VASCULAIRES : ETUDE PROSPECTIVE SUR 553 ECHANGES PEDIATRIQUES (DEPUIS 2012) ET 364 CHEZ L'ADULTE (DEPUIS 2014).

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Introduction : Depuis avril 2012, l'erythrocytaphérese automatisée est utilisée au Centre Hospitalier de Cayenne pour traiter les complications aigues ou chroniques de la Drépanocytose. Cette technique nécessite un abord veineux périphérique adéquat ; en cas de réseau périphérique inaccessible, un abord veineux central est utilisé par l'insertion d'un cathéter veineux central double voie par la veine fémorale sous sédation ou courte anesthésie générale, cathéter retiré immédiatement après l'échange.

But : Etudier la faisabilité de ponctions itératives fréquentes de la veine fémorale chez les patients présentant un syndrome drépanocytaire majeur.
Matériel : 553 échanges pédiatriques ont été réalisés d'avril 2012 à juin 2018 avec 312 accès centraux (56 %). 19 enfants ont été inscrits sur un programme d'érytrocytapherese (467 échanges au total). 364 échanges d'adultes ont été réalisés de septembre 2014 à juin 2018 avec 147 accès centraux (40 %). 22 patients adultes ont été inscrits sur un programme chronique (285 échanges au total).

Résultats : Tous les échanges ont pu être réalisés, sans difficultés insurmontables. Les problèmes de ponction et de dilatation, et les incidents techniques sont détaillés. 2 complications graves aigues à type de phlébite sont apparues chez 2 enfants (cathéter laissé en place plus de 3 jours par nécessité, sans anticoagulant). Le suivi des patients sous échanges programmés est détaillé.
Le contrôle systématique par echodoppler de la veine fémorale n'a montré aucune sténose secondaire aux ponctions.

Conclusion : La ponction itérative, même sur une longue période, de la veine fémorale est possible chez les patients avec un réseau veineux périphérique de mauvaise qualité, et permet de réaliser des échanges dans de bonnes conditions.

AIR DREP – A RETROSPECTIVE STUDY EVALUATING THE INFLUENCE OF WEATHER CONDITIONS AND THE IMPACT OF VIRAL EPIDEMICS ON VASO-OCCLUSIVE CRISIS IN PATIENTS WITH SICKLE CELL DISEASE LIVING IN FRENCH GUIANA

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Objectives: French Guiana is the French territory most affected by sickle cell disease (SCD). This study investigated the associations between different environmental factors relative to climate, infectious outbreak, and emergency visits or weekly hospital admissions for vaso-occlusive crisis (VOC). The highlighting of a causal link would lead to better patient care and patient management in the hospital, and a more targeted prevention and therapeutic education for patients with SCD in French Guiana.

Methods: This study was performed using data collected from PMSI (medicalized information system program) and from DMU (medical files from emergency) of Cayenne General Hospital, between 01/01/2010 and 12/31/2016. ARIMA models were used to investigate the potential impact of weather conditions, and flu and dengue epidemics on VOC occurrence.

Results: During the study period, 1739 emergency visits were recorded among 384 patients, of which 856 (49.2%) resulted in hospitalization, 811 (46.6%) resulted in a return home and 72 (4.2%) in another orientation. Decreased temperature and decreased humidity were both independent factors associated with an increase of VOC cases (p=0.0128 and p=0.0004 respectively). When studying severe VOC (leading to hospitalization, with or without prior emergency visit), 2104 hospital admissions were recorded among 326 patients and the only associated factor in the multivariate analysis was flu epidemics (p=0.0148).

Conclusion: This study showed a link between environmental factors such as climate or flu epidemics and VOC in French Guiana. A particular patient's awareness of risks related to climate and flu epidemics should be encouraged, thus home prevention measures could avoid some painful crisis. Moreover, physicians should incite patients to have influenza vaccine every year.

HOPE FOR CHILDREN WITH SICKLE CELL DISEASE IN HAITI : A PILOT PROJECT USING HYDROXYUREA AT SAINT DAMIEN HOSPITAL

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Purpose: Preliminary data indicates that the prevalence of sickle cell disease in Haiti is high. The combination of extreme poverty and chronic debilitating diseases place children with sickle cell disease in a significantly vulnerable position. Due to limited access to preventing care and disease management measures, hydroxyurea is a compelling option for the amelioration of complication of this disease in Haiti due to its relatively low cost and proven safety and efficacy. The primary objective of this study is to examine the acceptability of the use of hydroxyurea. The secondary objective includes documenting the effects of hydroxyurea on renal, hepatic and bone marrow functions.

Design Methods: This is an open label single arm pilot study set in a single institution in Port-au-Prince, Haiti with inclusion and exclusion criteria.
Results: The data shows that hydroxyurea is feasible, safe and effective. No patient was removed from the study due to toxicity of the drug. We observed significant change in Mean Corpuscular Volume (MCV) and Fetal Hemoglobin (HF) percentages for most of the patients. In addition, we observed that patients had less frequent hospital stays.

Conclusions: It appears that using hydroxyurea as a mean to control sickle cell crises symptoms is a locally acceptable and feasible intervention for children in Haiti.

ALPHA THALASSEMIA DIAGNOSIS OF THE -SEA DELETION IN A COSTA RICAN FAMILY WITH CHINESE ANCESTRY

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Objective: To detect alpha thalassemia mutations in a Costa Rican family with Chinese ancestry that presents a microcytic hypochromic anemia

Methods : A familiar study was designed for a possible alpha thalassemia case. General hematologic studies were carried on in a Sysmex 1800i and Wright stain for smears.
Electrophoresis was carried by capyllary electrophoresis in a Minicap Flex Piercing, Sebia. Heinz bodies were analyzed with brilliant cresyl blue stain. The molecular studies were carried by α-globin strip assay, Vienna Lab kit. This kit includes detection for -SEA, -3.7, -4.2, -20.5, -MED. -Fil, -Thai deletions and other single mutations.
The family was initially studied because of a persistent hypochromic anemia in a 32 years old female (propositus), her brother and parents. The parents arrived to Costa Rica from Guangzhou, China.

Results: Heinz bodies were detected in the propositus, her brother and father, with a microcytic hypochromic anemia. They were negative for the mother that has a normocytic normochromic anemia. The only mutation detected was the -SEA deletion. The -SEA was identified in the propositus, her brother and the father. The mother shows no genetic alteration for alpha thalassemia. The other mutations that can be detected by the kit were negative. This result was confirmed in Boston University with GAP PCR and nucleotide sequencing, just for the father and mother.

Conclusions: The -SEA deletion is frequently associated with alpha thalassemia in oriental populations. It was detected in three members of a Costa Rican family with Chinese ancestry.

PATIENT'S PERSPECTIVE: HYDROXYUREA THERAPY FOR SICKLE CELL DISEASE

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Objective: This study sought to comprehend the experiences of clients who have been diagnosed with sickle cell disease and were being treated with hydroxyurea medication in an effort to gain an understanding into the client's knowledge, attitudes and practices of their chronic disease management. The study sought to understand the impact that treatment made on their lifestyles including their daily routines and overall quality of life through:

1. Identification of the adherence practices

2. Determination of the relationship between use of Hydroxyurea medication and perceived impact on quality of life

3. Challenges in adherence practices; and

4. Impact of Hydroxyurea therapy on the family.

Method: A mixed method approach utilized data collection through questionnaire and in depth, semi-structured interviews. The population consisted of patients registered at the CAIHR who had been on a regiment of Hydroxyurea for a minimum of two months. Data was obtained from participants during their routine visits to the CAIHR.

Results:

Hydroxyurea Regularity

Response	Number	%
Every Day	32	74.4
Every Other Day	2	4.7
A Few Times A	4	9.3
When I Remember Week	5	11.6
Total	**43**	**100.0**

SD± 4.38
CI = 95%

Perception of Hydroxyurea as an Improvement to Quality of Life

Response	Number	%
Agree	21	48.8
Disagree	1	2.3
Neutral	4	9.3
Not Sure	2	4.7
Strongly Agree	13	30.2
Strongly Disagree	2	4.7
Total	**43**	**100.0**

SD± 2.26 ; CI = 95%

Conclusion : This study confirms that most of the patients being treated at the CAIHR had good adherence practices which may relate to the overall improvements being witnessed by the individual and their family members.

"MY SIBLING HAS SICKLE CELL DISEASE". PSYCHOLOGICAL EXPERIENCES OF CAMEROONIAN CHILDREN WITH A DIAGNOSED SIBLING

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Objective: Sickle cell anemia is the most common genetic disease in the world and a source of suffering for the sick child and his family. This communication aims to understand the experiences of siblings of children with sickle cell disease in an African cultural context.

Method: 13 siblings of children with this condition were interviewed at their parents' homes in Cameroon during which they were asked to do the family drawing test. They themselves were free from the disease.

Results: The results show the psychological suffering of these children, as they feel guilty and helpless about the crises of their sick sibling. There was a presence of fear of looming death of the sick child coexisting alongside the desire for their death. The children experienced a sense of loneliness within their families and a feeling of strangeness about the sick child and his illness.

Discussion: The suffering expressed by these children suggests a need to listen to them more and to offer them psychological support.

Key words: Sickle cell disease; experience; siblings; culture; sub-Saharan Africa.

TEACHING SELF-HYPNOSIS TO SICKLE CELL DISEASE ADULTS IN ORDER TO MANAGE PAIN AND ANXIETY : A CLINICAL STUDY

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Objective: According to previous studies from the 90's, self-hypnosis has been investigated as an interesting tool for people suffering from sickle cell disease to manage not only the acute and chronical pain caused by the pathology, but also to release the anxiety related to it.

Methods: The aim of this study was to evaluate the benefit of teaching this method on 10 patients, along 5 individual sessions. Every session started with a protocolar session of hypnosis, followed by an adapted and personal technic: every patient has been told to have a daily practice between the sessions.

Results: All the patients claimed to feel more restful after practicing the self-hypnosis exercise and to feel less anxious about the incoming pain crisis. Also, they declared getting a better self-efficacy feeling regarding the management of the acute and the chronical pain by using the self-hypnosis method.

Conclusions: This study suggests that self-hypnosis, such as others psychocorporal therapies, should be more considered as valued methods and more used to help sickle cell disease patients regarding their frequent powerlessness feeling related to the disease.

EVALUATION OF A POINT-OF-CARE TESTING DEVICE (HEMOTYPESC™) FOR SCREENING OF SICKLE CELL DISEASE

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Universal neonatal screening for sickle cell disease (SCD), promoting early enrollment into comprehensive care programs and institution of appropriate preventive measures, has proven to be extremely beneficial by reducing mortality and morbidity in early childhood and improving the quality of life. This newborn screening (NBS) requires clinical laboratories specialized in the diagnosis of hemoglobin abnormalities and equipped with expensive instruments which are hardly available in resource-limited settings where SCD is most prevalent. This is particularly the case in the Caribbean region where the need for a low-cost, easy-to-use diagnostic test for sickle cell disease is critical to foster early medical intervention for the patients.
In this study conducted in the framework of the Caribbean cooperation coordinated by CAREST*, we tested the performances characteristics of a novel point-of-care test (HemoTypeSC™) as a screening test in diagnosing the relevant Hb phenotypes (A/A, A/S, A/C, S/S, S/C, and C/C) as compared to "gold-standard" HPLC/IEF methods.
HemoTypeSC™ (Silver Lake Research, Azusa, California, USA) is a competitive lateral flow assay incorporating monoclonal antibodies.

The study was conducted at the Sickle cell children Center and maternity services, Wife and children Hospital (MFME), University Hospital Martinique, with the inclusion of 39 newborns (1 to 4 days old), and 7 infants (5 to 17 months old) of whom 22 were girls and 24 boys. The HemoTypeSC test was made on whole blood picked up from skin prick. At the same time, a whole blood sample (cord blood sample for newborns, venous blood sample for infants), was tested by laboratory conventional techniques (IEF and HPLC); the results of the 2 tests were compared.

This preliminary evaluation of the HemoTypeSC test showed the rapidity to have a result (10 minutes), the simplicity of use and interpretation of this test, which was performed by 2 nurses. A second reading by a physician confirmed the result delivered by the nurses.

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The HemoTypeSC test results and those of the laboratory performed with the "gold-standard" methods were concordant for 45 tests out 46. The result obtained for 1 of the 46 HemoTypeSC tests has been less easy to interpret but compatible with that obtained by the standard methods indicating the presence of a Sβ+Thalassemia.

The HemoTypeSCTM allows the detection of the phenotypes AA, SS, SC, CC and of carriers of the S and C traits.

A larger study is needed to confirm these findings and determine the specificity and sensibility of the test.
*CAREST: Caribbean network of REsearchers on Sickle cell disease and Thalassemia

RARE HEMOGLOBIN PRESBYTERIAN FOUND IN A NICARAGUAN FAMILY.

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Introduction: Hemoglobin (Hb) is the protein responsible for oxygen transportation. It is a tetrameric protein comprising two α- and two β-globin subunits. In the literature, a large number of mutations in the α- and β-globin genes have been documented [1]. Among these mutations, Hb Presbyterian (HbPres) is a naturally occurring mutant exerting low oxygen affinity. C to G exchange (AAC>AAG) in codon 108 of the β-globin gene (β108) results in the substitution of asparagine (Asn) by lysine (Lys).

Objective: Detection and identification of abnormal hemoglobin in a 6-year-old female patient and her family.
Method: Hemoglobin lysate from peripheral blood from the patient and her family was analyzed. Detection of the abnormal hemoglobin was performed by cellulose acetate electrophoresis and HPLC. A heat stability test and p50 measurement were accomplished. Genomic DNA from leucocytes was extracted and genomic DNA sequencing analyses were conducted.

Results: A variant hemoglobin fraction migrating near HbA, between HbA and HbS, was found by the cellulose acetate electrophoresis (figure 1). Furthermore, a flocculent precipitate was detected in a heat stability test on the propositus' hemolysate. The hemoglobinopathy was also confirmed by HPLC analysis. The β-globin gene sequences for both, father and daughter, disclosed the heterozygous mutation in codon 108 for HbPres (figure 2).
Correspondingly, p50 of the propositus' blood was determined by using a blood gas analyzer (Nova-biomedical) and found to be 31.1 mmHg which is increased compared to the normal range of 25-29 mmHg.

Conclusion: Herewith, we document the identification of HbPres in a 6-year-old female patient from Nicaragua. The hemoglobinopathy was also detected in her father, a 28-year-old Cuban, who never showed any symptoms indicating anemia or other hematologic pathologies. The mutant HbPres has been previously reported for four families from North America, Germany, Japan, and Spain. This is the fifth family with HbPres described to date [2-5], and the first report in Latin America

Keywords : Hemoglobin Presbyterian; Unstable hemoglobin; DNA sequencing

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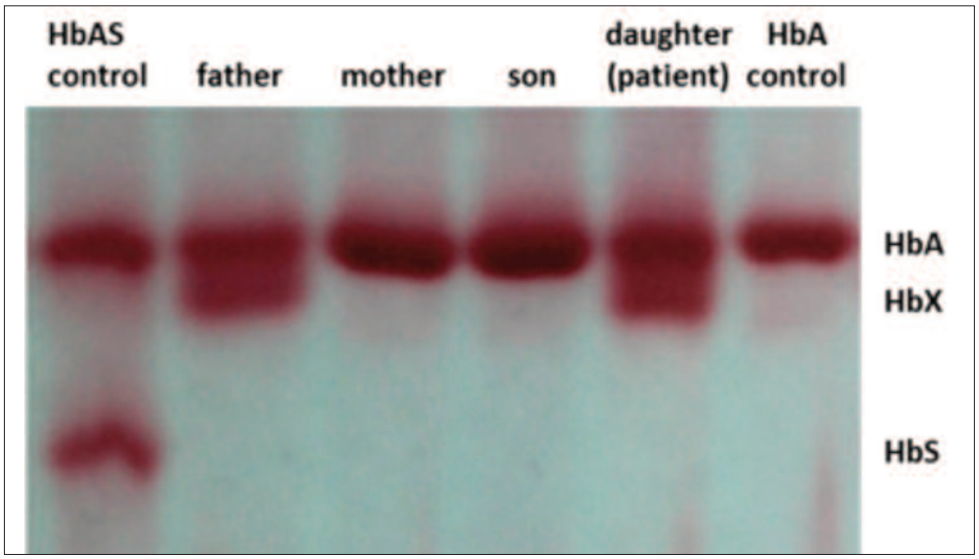

Figure 1 : Cellulose acetate electrophoresis of hemolysates (TBE-buffer, pH 8.4) indicating presence of abnormal hemoglobin in the propositus (daughter) and her father. From left to right : HbAS control, father, mother, son, daughter, HbA control.

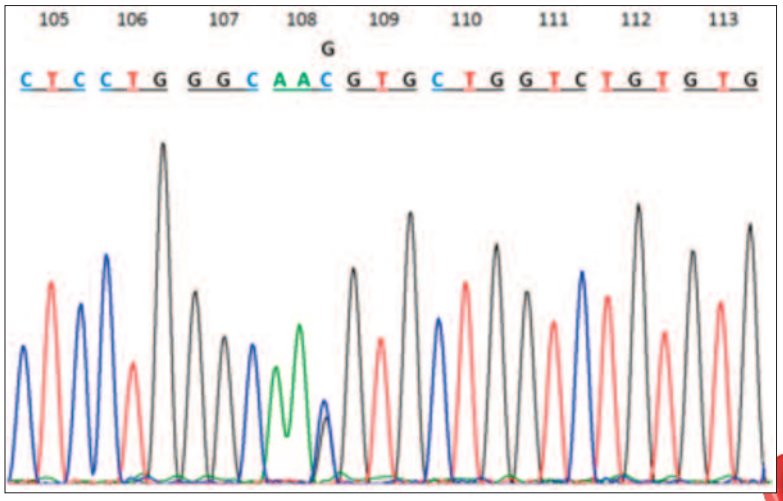

Figure 2 : Nucleotide sequencing of the proband's β-globin gene, codons 105 - 113 revealing codon 108 with C>G heterozygosity (AAC>AAG).

SUBCLINICAL EVIDENCE OF INFLAMMATORY BIOMARKERS IN SICKLE CELL TRAIT.

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Objective: Sickle cell trait (Hb AS) frequency in our population is around 3.5%, being considered asymptomatic due to the presence of normal hemoglobin (Hb A) in erythrocytes. Several studies suggested that this condition could increase the risk of different clinical complications. Our goal was to establish the possible presence of inflammatory biomarkers in sickle cell trait individuals without any pathological event.

Methods: Levels of IL-6, IL-8, IL-10 were measured by an enzyme immunoassay and C reactive protein (CRP), α1-antitrypsin by a turbidimetric method in 26 sickle cell trait adults individuals. Thirty normal adults were included as a reference group.

Results: An increased level of IL-6, IL-10, CRP and α1-antitrypsin were demonstrated ($p < 0.004$) in the sickle cell trait group compared with the normal controls.

Conclusion: The results obtained suggest that inflammation is permanently present as a subclinical condition in sickle cell trait. This could be an explanation why sickle cell trait individuals under a stress situation could precipitate to a more or less severe clinical event.

ANTI NEUTROPHIL CYTOPLASMIC ANTIBODIES (ANCA): ANTI MPO AND ANTI PR 3 IN SICKLE CELL DISEASE

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Objective: There is increasing evidence that suggest the role of activated neutrophils in the pathogenesis of vaso-occlusion in sickle cell disease (SCD). Inflammatory stimuli by cytokines as IL-8 could activate neutrophils moving myeloperoxidase (MPO) and proteinase 3 (PR 3) from the cytoplasm to cell surface membrane acting as neo antigens. Anti-neutrophil cytoplasmic antibodies (ANCA) could also be produced in these patients due to an inefficient apoptosis of neutrophils, being exposed molecules normally hidden, that is MPO and PR 3. This abnormal situation could be related with the finding that in SCD patients there is an increased level of aged neutrophils. The aim of this study was to demonstrate the possible participation of ANCA, anti MPO and anti-PR 3, in the vascular occlusion phenomenon in a group of SCD patients at different clinical stages.

Method: Levels of anti-PR 3 and anti MPO were measured by an enzyme immunoassay in 20 SS adult patients during vaso-occlusive crisis and 25 SS adult patients in steady state. Thirty normal donors were included as a reference group.

Results: An increased level of anti MPO ($p < 0.001$) was demonstrated in the group of patients during painful vaso-occlusive crisis compared with steady state patients and normal controls.

Conclusion: High levels of anti MPO in SCD patients during vaso-occlusive crisis could favor the adherent capacity of activated neutrophils, thus amplifying the endothelial lesion.

Notes

Merci à nos partenaires
Thanks to our partners

Prévention des crises vaso-occlusives douloureuses récurrentes, y compris celle du syndrome thoracique aigu chez l'adulte, l'adolescent et l'enfant âgé de plus de 2 ans souffrant de drépanocytose symptomatique*.

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