The Increasing Frequency of Hemoglobin Disorders in Europe

Second European Hemoglobinopathy Forum
Madrid, November 29, 2011
The endemic world of Hemoglobinopathies

Traits selected as protective factors during human evolution in tropical and subtropical populations are virtually absent in indigenous Northern populations....
How indigenous are northern populations?

Protohistoric migrations.
More than 400 years Roman empire.
Middle age trade

Gene migration in ancient history
Gene migration in more recent history

Slave trade and commerce
leading to multi ethnic admixtures

HbS, HbC, HbE, HbD
\(\alpha\) and \(\beta\) Thal
Examples of gene migration to non-endemic countries

Recent post-colonial migration

Holland

Recent multi-ethnic economic migration

Colonial slavery and post-slavery migrations to Holland and to the western Dutch colonies

HbS, C, β- en α-thal

HbE, β- en α-thal

HbS, D, β- en α-thal

α- and β-thal. and HbE

Africa

South America

China

India

Indonesia

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www.hbpinfo.com
Other examples of gene migration to non-endemic countries

Recent post-colonial migration

HbS, C, β- en α-thal

β- thalassemia

HbS, E, D, β- en α-thal

Post-war and recent multi-ethnic economic migration

Belgium

Congo
Rwanda

www.hbpinfo.com

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The UK: another examples of Multi-ethnic migrations

HbS, C, β- en α-thal
HbS, C, E, D, β- en α-thal
HbS, D, β- en α-thal
Spain and Portugal…
New globin genes migrate also to endemic countries

Immigrants represent > 10% of the Italian population where local mutations are mixing with imported multi-ethnic traits
Gene migration to endemic countries

Immigrants represent > 10% of the Italian population where local mutations are mixing with imported multi-ethnic traits.
Migration from endemic to non-endemic areas is bound to increase.
Already in 2007 the incidence of severe hemoglobinopathies was estimated higher in non-endemic Europe then in the South European endemic countries

<table>
<thead>
<tr>
<th>European Areas</th>
<th>Annual conceptions: SCD</th>
<th>Annual conceptions: Severe Thal</th>
<th>Annual conceptions: Harmless</th>
<th>Total requiring risk assessment</th>
<th>Estimated % primary prevention</th>
</tr>
</thead>
<tbody>
<tr>
<td>Northern</td>
<td>434</td>
<td>101</td>
<td>81</td>
<td>2464</td>
<td>≈ 50</td>
</tr>
<tr>
<td>Western</td>
<td>401</td>
<td>119</td>
<td>86</td>
<td>2460</td>
<td>&lt; 10</td>
</tr>
<tr>
<td>Southern</td>
<td>234</td>
<td>402</td>
<td>14</td>
<td>2600</td>
<td>&gt; 90</td>
</tr>
<tr>
<td>Total</td>
<td>Over 1.000</td>
<td>Over 600</td>
<td>Over 180</td>
<td>Over 7500</td>
<td>Less than 50</td>
</tr>
</tbody>
</table>

Without interventions: suffering for patients and families. Increasing burden for public health and social care.

Therefore prevention must be offered to couples at risk in the all of Europe

Adapted from Model et al. Scand J Clin Lab Invest 2007
The terminology of prevention

Secondary

Morbidity prevention in all phases

From prenatal care to NBS, vaccinations, to stopping unsafe habits

Primary

Preventing severely affected progeny

Prospective

Offered to parents at risk before the birth of the first affected

Genetic risk / informed choice

Retrospective

Offered to parents at risk after the birth of the first affected

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The tools of prevention

Information  Carrier detection  Counseling
The tools of prevention

Information  Carrier detection  Counseling
The elements of prevention

Information  Carrier detection  Counseling

Tools
CBC
HPLC
DNA

α-Thalassemia
M.H. anemia and normal ferritin


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The elements of prevention

Information
Carrier detection
Counseling

β-Thalassemia
M.H. anemia

Tools
CBC
HPLC
DNA

Confirmation

* Stephens et al Int J Lab Hematol. 2011
** Mantikou et al Clin Biochem. 2009

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The elements of prevention

Information  Carrier detection  Counseling

Tools

CBC  SCT (HbS)  No anemia unless + α

HPLC

DNA  Confirmation


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# The elements of prevention

## Information

- Carrier detection
- Counseling

## Carrier Detection

<table>
<thead>
<tr>
<th>Tools</th>
<th>SCT (HbC)</th>
<th>No anemia unless + α</th>
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<tr>
<td>CBC</td>
<td></td>
<td></td>
</tr>
<tr>
<td>HPLC</td>
<td></td>
<td></td>
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<tr>
<td>DNA</td>
<td></td>
<td></td>
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</table>


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The elements of prevention

Information  Carrier detection  Counseling

Tools
- HbE: SC and β-Thalassemia
- Mild MH anemia

CBC

HPLC

DNA Confirmation

** Bouva et al. J Med Screen. 2010

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Improving carrier detection

By introducing in all Labs:

1) Basic protocol as summarized

2) Explanation accompanying the results

By implementing national or regional screenings based on previous and new experiences....
Experiences on carrier screening

How ?  Where ?  When ?

- School screening
- Preconception screening
- Following NBS
- In early pregnancy

Free and informed reproductive choice

Which method is most appropriate and where ?

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## Carrier screening

<table>
<thead>
<tr>
<th>How</th>
<th>In endemic areas</th>
<th>When</th>
</tr>
</thead>
</table>
| School screening  | One of the 20 Italian “regioni”  
> 17,000 Km  
> 5.6 million inhabitants | Ferrara    |

- Ferrara
- Latium
- Sardinia
- Sicily

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Amato et al. prenat diag 2009

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School screening in Latium*
Ida Bianco

Detecting young carriers and couples at risk

* Courtesy of dr. Antonio Amato

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School screening in Latium*

- Local population
- Recent immigrants

Prospective and retrospective prevention

* Courtesy of dr. Antonio Amato
Carrier screening

How

School screening

In endemic areas

Successfully applied also in Southern France (1978-1985) but interrupted for lack of funds *

When

Not available so far in Northern Europe


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Detecting carriers and couples at risk

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<th>How</th>
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<th>When</th>
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<tr>
<td>School screening</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Preconception</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Successful</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Successful</td>
<td></td>
<td></td>
</tr>
<tr>
<td>In Latium</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Successful</td>
<td></td>
<td></td>
</tr>
<tr>
<td>in endemic areas</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cyprus</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Iran</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Greece</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Turkey</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Southern France</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Italy</td>
<td></td>
<td></td>
</tr>
<tr>
<td>............</td>
<td></td>
<td></td>
</tr>
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Detecting carriers and couples at risk

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<th>How</th>
<th>In endemic areas</th>
<th>When</th>
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<tr>
<td>School screening</td>
<td>Preconception screening</td>
<td>Incidence reduction (%) in Sardinia*</td>
</tr>
<tr>
<td>Successful in Latium</td>
<td>Successful in endemic areas</td>
<td></td>
</tr>
</tbody>
</table>

* Courtesy of Prof. Renzo Galanello

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Detecting carriers and couples at risk

How, In non-endemic areas, When

School screening
Mostly not available

Preconception screening?
Based on ethnicity in immigration countries?
Detecting carriers and couples at risk

How, Non-endemic areas When

School screening

Mostly not available

Preconception screening

Based on ethnicity in immigration countries?

How to define ethnicity?

Structures are absent. GP’s unprepared

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Detecting carriers and couples at risk

**How, Non-endemic areas When ?**

- School screening
  - Mostly not available
- Preconception screening
  - Political decision. Organization. Stigmatizing
- Following Newborn Screening ?
  - Needs referral of all carriers, collaboration of GP’s and local Labs ....

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Detecting carriers and couples at risk

<table>
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<th>How,</th>
<th>Non-endemic areas</th>
<th>When</th>
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<tr>
<td>School screening</td>
<td>Mostly not available</td>
<td>Following Newborn Screening ?</td>
</tr>
<tr>
<td></td>
<td>Political decision. Organization. Stigmatizing</td>
<td>Possible in UK Netherlands, France, Belgium, Spain *.... however ....</td>
</tr>
</tbody>
</table>

* Eloísa Urrechaga 25/6/11: El Departamento Vasco de Sanidad ha ampliado el cribado neonatal
No more than a theoretical 50% of the couples at risk can be reached for prospective prevention after NBS.

\( \frac{1}{4}, \text{if reported might get prospective prevention} \)

\( \frac{1}{4} \text{ is not detected} \)

\( \frac{1}{4} \text{ get retrospective prevention} \)
Earlier screening needed as in endemic areas

<table>
<thead>
<tr>
<th>How</th>
<th>In endemic areas</th>
<th>When</th>
</tr>
</thead>
<tbody>
<tr>
<td>School screening</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Successful</td>
<td>In Latium</td>
<td></td>
</tr>
<tr>
<td>Early pregnancy</td>
<td>successful in endemic areas</td>
<td>Incidence in Greece:</td>
</tr>
<tr>
<td>screening</td>
<td></td>
<td>From ~130 expected to ~10 affected newborn</td>
</tr>
</tbody>
</table>

Courtesy of Joanne Traeger-Synodinos
Early screening

How, in non-endemic areas When

School screening
- Mostly not available

Preconception screening
- Political decision. Stigmatizing

Following NBS
- Not more then 50% prospective prevention

In early pregnancy?
Early pregnancy screening

How,

In non-endemic areas

When

The most sensible alternative?

High participation.

Ongoing in England and part of NL*.

To be offered at the individual level or by screening?

To be organized selectively or as a universal screening?

If offered at the individual level other obstacles will be present …

- How to inform couples to ask the GP
  Ethic minorities, difficult to inform, to reach and to convince

- Are GP’s willing to offer carrier diagnostics.
  Many are still not aware and / or refuse to collaborate

- Are all Labs able to identify a couple at risk
  Many are not and it is much safer to centralize this service in specialized labs

Therefore national screening in early pregnancy seems the most logical alternative …. Structures are present in the all of the EU Nevertheless….
**PSIE** is a Dutch abbreviation for:
“Prenatale Screening Infectieziekten en Erytrocytenimmunisatie”
“Screening for infectious / sexual diseases and rhesus antagonism”

As in the rest of Europe this screening is offered also in The Netherlands to all pregnant at the first control

Hemoglobinopathies could easily be included. The method (HPLC) could be the same as for NBS…. Midwifes and gynecologist’s are very much in favor…

… but Public Health Authorities are still reluctant…

…. Their arguments: it could be interpreted as an invitation to interrupt affected pregnancies!
This in a country with the most liberal abortion policy…
… and one of the lowest abortion figures!
In conclusion, for a better prospective prevention in the EU

Better Better Better Better Better Better
Information carrier detection Counseling

• Basic diagnostic protocol in all labs
• Explanation accompanying the (+) results

• Reporting all carriers found with NBS
• Including hemoglobinopathies into the national early pregnancy screening for Rhesus and I.D.
• Offering partner analysis to all carriers
Thank you for your attention

Second European Hemoglobinopathy Forum
Madrid, November 29, 2011
2nd European Hemoglobinopathy Forum

Insights on the diagnosis of hemoglobin disorders

November 29th, 2011 – Madrid, Eurostars Madrid Tower Hotel