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NEONATAL SCREENING FOR HAEMOGLOBINOPATHIES IN THE EUROPEAN UNION

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The objectives of the ENERCA experts are to obtain epidemiological data on haemoglobinopathies, to facilitate and accelerate cooperation in this field between European experts, and to propose or improve a rational strategy for haemoglobin disorders control within the European Union. Here are presented the results associated with the primary objectives of the Expert Group ENERCA: in countries where the neonatal screening for haemoglobinopathies was introduced, epidemiological data were obtained, strategies for screening were examined and compared.

Haemoglobinopathies are inherited disorders of haemoglobin and are the most common monogenic disorders in humans. The term "haemoglobinopathies" contains two main groups of disorders: the thalassaemias and the haemoglobin variants. The thalassaemias are quantitative defects which arise from a decreased production of structurally normal globin chains, whereas the haemoglobin variants are most often qualitative defects which arise from an alteration in the globin gene structure. Several haemoglobin variants conduct to a thalassaemic phenotype. Haemoglobinopathies are autosomal recessively transmitted affections which mean that the heterozygous individuals are near asymptomatic carriers while the homozygous or compound heterozygous individuals have varying degrees of symptoms. The most severe clinical forms of these disorders are met in the β-thalassaemia major, the haemoglobin Bart hydrops fetalis and the sickle cell disorders (SCD), respectively.

Specific background within the EU

The frequency of different haemoglobinopathies varies in different ethnic groups. Since the carrier condition confers a protection towards the severe forms of malaria, this is the reason why these disorders were first confined on the endemic countries for the malaria. For example the thalassaemias are common to the entire Mediterranean area and the frequency of the carriers reaches rates of 15% in Cyprus. Due to population movements the haemoglobinopathies are now encountered in almost every country in the world. A chart of the frequencies of the diseases by European country could currently be: comparable frequencies of haemoglinopathies throughout the EU with SCD more frequent than thalassaemias and more frequently encountered in Northern and Western European countries *(Modell B, Darlinson M, Birgens H et al. Epidemiology of haemoglobin disorders in Europe: an overview. Scand J Clin Lab Invest 2007; 67:39-70).*

- ***South of Europe, β-thalassaemia and antenatal screening***

This situation explains why health professionals from the South of Europe have been long concerned by indigenous at risk groups for thalassaemias and why national or regional carrier screening programmes exist for decades; the overall aim of antenatal screening being to identify early couples at risk of a pregnancy with a β-thalassaemia major, and to provide these couples all the necessary information regarding the possibility of a prenatal diagnosis and termination of pregnancy in case of an affected fetus. Nevertheless, these countries are more and more confronted with immigrants at risk for SCD, and the screening strategy should probably be soon revised.

- ***North and West of Europe, sickle cell disorders and neonatal screening***

In the countries of Northern and Western Europe, the background is different: haemoglobinopathies are a more recent problem, couples at risk for SCD are more reticent to prenatal diagnosis, and there is substantial evidence that early detection of the affected newborns insure to avoid the high mortality and morbidity rate in this population by severe overwhelming infections, splenic sequestrations crises, acute anemia and cerebrovascular disease. In London, sickle cell disease is now one of the most common reasons for admission to hospital *(London Health Observatory. 2005. Analysis Of Frequent Users, 2002/03, Local Authority Level. [Online] [access 2006 September]. Available from URL http://www.lho.org.uk/viewResource.aspx?id=9736).*

In this context, neonatal screening and clinical care programmes for haemoglobinopathies have been introduced in Northern and Western Europe.

Aims of neonatal screening programmes for haemoglobinopathies: from secondary prevention to an information process

The primary aim is to detect all infants affected with a sickle cell disorder in order to improve outcome through early treatment and care. Other interesting information is delivered by the neonatal screening programme since newborns affected by other clinically significant haemoglobinopathies or those who are simple carriers of a haemoglobinopathy are also detected. So other goals can be reached by the screening:
- The identification of newborn's affected with a major haemoglobinopathy who will benefit from early and dedicated follow-up;

- The identification of the newborn's affected by a minor haemoglobinopathy who will benefit of the knowledge of their own genetic risk;
- The possibility of offering specific tests and genetic counselling to the parents of the affected newborns.

The result of all this is that the power of the neonatal screening as an **information process** should not be neglected; neonatal screening is an excellent tool to fight against the lack of awareness among policy-makers, health professionals, and the public.

Newborn neonatal screening policy within the EU

In the EU, four countries have adopted a neonatal screening programme financed by the authorities in public health: The Netherlands, Belgium, France and Great Britain.

(Gulbis B, Ferster A, Cotton F, Lebouchard MP, Cochaux P, Vertongen F. Neonatal haemoglobinopathy screening: review of a 10-year programme in Brussels. J Med Screen. 2006;13(2):76-78; de Montalembert M, Girot R., Galacteros F. Sickle cell disease in France in 2006: results and challenges. Arch Pediatr. 2006;13:1191-1194; Modell B, Darlinson M, Birgens H et al. Epidemiology of haemoglobin disorders in Europe: an overview. Scand J Clin Lab Invest 2007; 67:39-70)

The screening policy varies from one country to another:

- Screening is national except in Belgium where it is financed only in Brussels
- Heel prick is used except in Belgium;
- A systematic screening (all newborns) is offered except in France;
- Methods of screening are high-performance liquid chromatography or iso-electric focusing;
- Carriers are reported except in France.

The procedures are almost identical between the different countries but three significant differences deserve to be commented:

- ***Specimen collection***

Cord blood has been used in Belgium since it has been implemented in a reference laboratory for haemoglobinopathies and not in a reference laboratory of screening for congenital hypothyroidism, phenylketonuria and inborn errors of metabolism. In the latter case, heel prick is the standard specimen collection. In France, neonatal screening is also performed in reference laboratories for haemoglobinopathies, but the specimen collection is common for all the neonatal screening laboratories which explain the choice of heel prick. There are advantages and disadvantages to both type of specimen collection, but cord blood provides the option of a control sample in case an affected newborn is identified, and to give the result of the screening to the parents before discharge of the baby.

- ***Universal versus targeted screening***

In European countries apart from the ethics, equity and discrimination issues that may arise if universal screening is not applied, it has been demonstrated that universal screening identifies more newborns with disease and prevents more deaths. The choice of the screening method is based on cost-effectiveness and it has been demonstrated that at prevalence and incidence of at least 16 sickle cell traits/1000 and 0.5 SCD/1000 there is no significant identification cost difference between universal and targeted screening programs. All European countries where a neonatal screening programme has been implemented should apply a universal screening.

- ***Reporting of carriers***

A neonatal haemoglobinopathy screening programme is an opportunity to provide information to health-care practitioners and families, and withholding information from parents is not justified. Nevertheless, some have highlighted the potential risk of neonatal identification of carriers like inadvertent exposure of non-paternity, social stigma for the individual and family, as well as adverse psychological effects for the individual and family. Those aspects imply that delivering these results should be done by a trained healthcare staff.

- ***National linked antenatal and neonatal screening programme for haemoglobinopathy and sickle cell disease***

In the United Kingdom, a commitment was made in 2000 to implement "effective and appropriate screening programmes for women and children including a new national linked antenatal and neonatal screening programme for haemoglobinopathy and sickle cell disease" *(http://www.nhsia.nhs.uk/nhsplan/nhsplan.htm)* ; a general policy has been implemented towards sickle cell and thalassaemia antenatal screening programme.

	Heel prick	Universal	Report carriers	Year	SCD (/birth))
	Y	Y	Y	2007	1/4298
	N	Y	Y	1994 *(Bru.)*	1/1586 *(Bru.)*
	Y	N	N	1992	1/4125
	Y	Y	Y	1985	1/2400

Although facilities for control and management of haemoglobinopathies are available in Northern and Western European countries and although one can benefit from the experience of health practitioners from the South of Europe or from the UK, providing national programmes for prevention and clinical management is a challenge. The reason is that haemoglobinopathies are not officially recognized as a significant health problem in each EU countries. However recently, haemoglobinopathies have been recognized as a public health priority by the World Health Organization (WHO) *(117 session – EB117/34 26 May 2006 - http://www.who.int/genomics/publications/WHO-MODreport-final.pdf)* and European dedicated networks like for example the "Euromediterranean network of research centres conducting molecular and clinical research of thalassaemia and related haemoglobinopathies" *(http://www.ithanet.eu)*, the "European Network for Rare and Congenital Anaemias" *(http://www.enerca.org)*, and the European Organisation for Rare Diseases *(http://www.eurordis.org)* are supported by the European Commission.

Proposed strategy for haemoglobinopathies screening in the EU

It seems reasonable to adapt the prevention strategy to the local situation encountered in each EU country. In those concerned by haemoglobinopathies a clear message should be delivered at a national level: an integrated programme should be implemented. But one should be always aware that it outlines many challenges since it implies to implement effective procedures for primary and secondary prevention, diagnosis, education, information, and clinical care. In this context, working together within the EU is a necessity but it constitutes another challenge.