Neonatal screening for sickle cell disease in France

J Bardakdjian-Michau,[1] M Bahuau,[1] D Hurtrel,[1] C Godart,[1] J Riou,[1] M Mathis,[1] M Goossens[2]

[1] Service de Biochimie et de Génétique, Unité Fonctionnelle de Génétique, Centre Hospitalier Universitaire Henri-Mondor (AP-HP), Créteil, France; [2] INSERM Unité 841, Equipe de Génétique, Institut Mondor de Recherche Biomédicale, Centre Hospitalier Universitaire Henri-Mondor (AP-HP), Créteil, France

Correspondence to: Josiane Bardakdjian-Michau, Service de Biochimie et de Génétique, Unité Fonctionnelle de Génétique, 51 avenue du Maréchal de Lattre de Tassigny, 94010 Créteil Cedex, France; josiane.michau@hmn.aphp.fr

Accepted 3 October 2008

ABSTRACT

Background: As a result of population growth in African-Caribbean regions of overseas France, and now immigration essentially from North and sub-Saharan Africa to mainland France, neonatal screening for sickle cell disease (SCD) has been performed in France since 1985 in Guadalupe and dependencies, as a universal test. After several pilot studies, screening was gradually extended to mainland France in 1996. Since 2000, the test has been performed at national level for all newborns defined as being "at risk" for SCD based on ethnic origin.

Methods: A dry blood sample is obtained by heel stick and analysed by isoelectric focusing as a first-line method, followed by either high-performance liquid chromatography or acid agar electrophoresis for confirmation, whenever a variant haemoglobin is observed on isoelectric focusing.

Results: In 2007, 28.45% of all newborns in mainland France were screened for SCD. Since 1996, a total of 3890 newborns have been found to have SCD, and they have been followed up by reference paediatricians.

Conclusion: Although screening for SCD at birth in France is not universal, it appears that missed babies are relatively infrequent. Despite obvious sociological problems inherent to the at-risk population, the follow-up of SCD babies is rather successful. Due to the birth prevalence of SCD in France, especially in comparison with other common genetic diseases, screening all newborns regardless of ethnic origin is an issue that is being addressed.

As a result of population growth in African-Caribbean regions of overseas France, and now immigration essentially from North and sub-Saharan Africa to mainland France, sickle cell disease (SCD) has become a major health problem in France.[1] SCD has become the most common genetic disease in this country, with an overall birth prevalence of 1/2065 in 2007,[2] or 1/2415 in mainland France, ahead of phenylketonuria (1/10 862), congenital hypothyroidism (1/3132), congenital adrenal hyperplasia (1/19 008) and cystic fibrosis (1/5014) for the same reference period.[3]

It is now well established that early appropriate patient care reduces morbidity and mortality in the first 5 years of life,[4] thus justifying implementation of neonatal screening. Guidelines have been issued at national level for disease prevention in children and adolescents.[5]

Neonatal screening for SCD in France started in 1985 in the West Indies, in Guadalupe Island and dependencies, where the majority of the population is of African ethnicity. In 1986, a survey was initiated in the Val-de-Marne department, a metropolitan district lying to the south-east of Paris, as well as in Marseilles, a major port area on the Mediterranean coast. From 1990 to 1993, a pilot programme was launched by the National Association for Neonatal Screening in three metropolitan areas: Lille, in the north, Marseilles, and Paris. All newborns from the test birth units of these regions were screened, regardless of their ethnic background. From 1994 to 1995, neonatal screening was extended to a larger number of birth units, but restricted to at-risk newborns. In 1996, screening for sickle cell disease was made part of the national neonatal screening programmes, and was further extended to the whole country in 2000, but continues to be restricted to at-risk newborns.

PATIENTS AND METHODS

In our neonatal screening programme, a newborn is defined as being at-risk for SCD when at least one parent originates from a region where the βS gene is prevalent due to the long-time presence of one of the founder genes (eg, Africa, India and the Mediterranean basin[6]) or due to later population migration (box 1). A newborn is also defined as being at risk for SCD if an abnormal haemoglobin is known to be present in a parent or in the family.

Information is provided to the parents by nurses in the birth units and a booklet is issued covering all neonatal tests. After subsequent discussion with the parents and based on data present in the medical records from the parturient and her family, it is the nurse who defines whether the newborn is at risk for SCD or not.

Blood is obtained by heel stick at 72 h of life, and blood spots are made on a single dry filter paper card in order to perform the universal tests for phenylketonuria (Guthrie test), congenital hypothyroidism (TSH), congenital adrenal hyperplasia (17-OH progesterone), and cystic fibrosis (immunoreactive trypsin), and then SCD, but only when the newborn is at risk. The cards are processed for the sickle cell test in four neonatal screening units in metropolitan (mainland) France and in a single centre for Guadalupe. The tests for other overseas departments or territories are performed in mainland France (Lille). All newborn babies from Guadalupe and other overseas (African-Caribbean and Indian Ocean) departments are screened regardless of ethnic background or known family risk.

Guidelines for laboratory procedures are determined at national level.[7] Isoelectric focusing (IEF) on agarose gels from PerkinElmer (Waltham, Massachusett, USA) is the first-line test used. Whenever an abnormal haemoglobin is observed on IEF, its identity is provisionally confirmed by

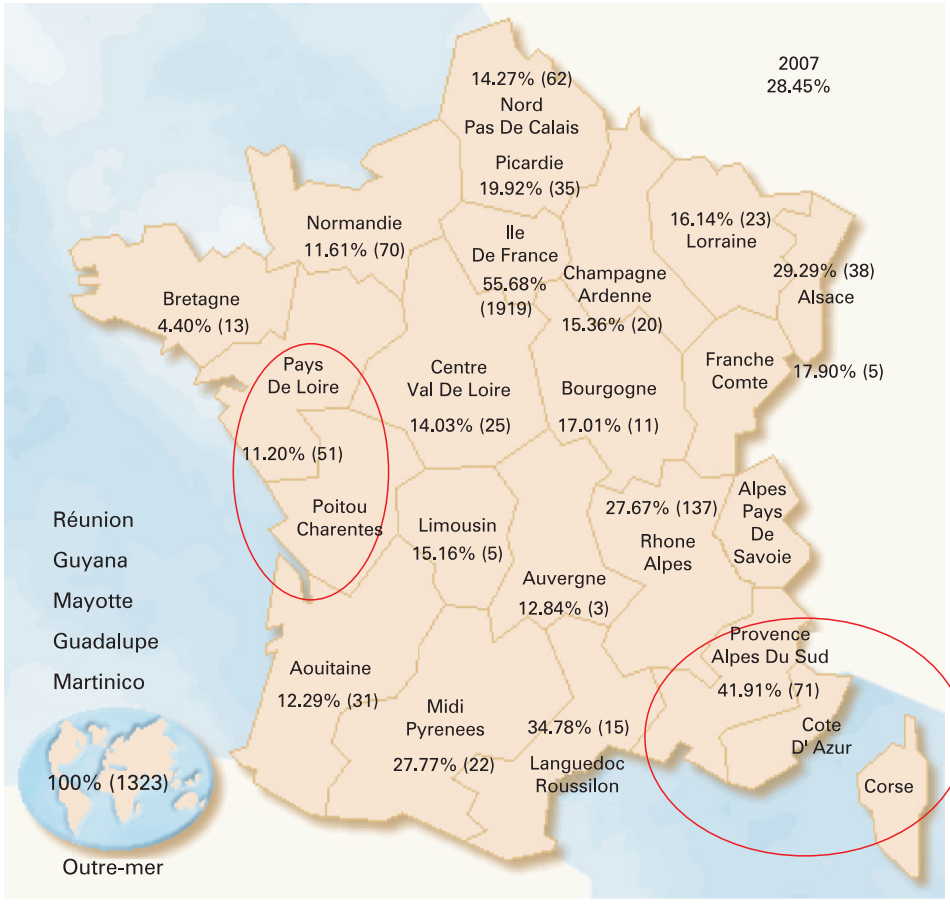

Figure 1 Update for sickle cell disease screening in France, 2007. For each region, the percentage of babies screened among all newborn babies in 2007 is given, and in parentheses, the total number of SCD cases since the screening programme has been introduced. Outre-mer, overseas departments.

either acid agar electrophoresis and/or high-performance liquid chromatography (Bio-Rad Variant I system; Bio-Rad Laboratories, Hercules, California, USA).

All positive tests are handled locally by a reference paediatrician and confirmed using a fresh blood sample from the baby and his or her parents.

RESULTS AND DISCUSSION

A total of 3890 newborns have been found to have SCD in a period extending from 1996 to 2007 (table 1). The Paris metropolitan district (Ile-de-France) is the region that accounts for the largest number of at-risk and affected newborns. Indeed, in 2007, nearly 56% of all newborns in this area were screened for SCD (fig 1). It is national policy that ethnicity cannot be put on records, whether paper or electronic. Therefore, ethnic data are unfortunately missing for France. The medically relevant information reported on the test card includes birth date, weight and gestational age, date of sampling, and presence or absence of a blood transfusion. All neonatal tests in France are free of charge for the families and supported financially by the Caisse Nationale d'Assurance Maladie des Travailleurs Salariés (CNAMTS), which is the national medical insurance system for salaried persons.

Because the family data are often incomplete, especially for the father, many babies remain with the SS or Sβ^0 thalassaemia diagnostic tag, unless a genetic test is eventually performed. All SCD cases are registered at national level and are managed clinically in a dedicated hospital department. These cases are followed up by the reference paediatrician at least until they reach the legal age of maturity of 18 years.

In addition to handling SCD cases and their families, a letter of information is sent to the families of all carriers (AS, AC and

Box 1: Regions of origin defined as "at-risk" for sickle cell disease

French overseas departments and territories: French West Indies, French Guyana, Réunion Island, Mayotte
Africa: North Africa, sub-Saharan Africa, including Cape Verde and Madagascar Islands
America: African ethnics from North, Central and South America, including the West Indies
Southern Europe: Portugal, Corsica, Southern Italy including Sicily, Greece
The Near and Middle East: Turkey, Syria, Lebanon, Arabian peninsula (Kingdom of Saudi Arabia, Yemen, etc)
The Indian sub-continent: Pakistan, India, Maldives, Sri Lanka

Table 1 Newborns screened from 1996 to 2007

Abnormal haemoglobin	Number
SCD (all)	3890
SS or Sβ^0 Thalassaemia	2917
Sβ Thalassaemia	245
SC	718
Others	5
AS	64 269
AC	15 986
Total number screened	2 622 870

other), in which a familial haemoglobin screen is suggested, with a view to offering genetic counselling. There is a substantial network of dedicated social and health workers so that this familial screen is totally free of charge.

Because of the methods used for the test, and relatively broad inclusion criteria to define at-risk newborns, other haemoglobinopathies can be diagnosed at birth; these include haemoglobin H disease or severe β thalassaemia. However, severe α and β thalassaemias are relatively rare disorders in France,[8] with ~5 β^0 thalassaemia major cases identified yearly. Although screening for SCD at birth in France is not comprehensive, it appears that missed babies are relatively infrequent. Despite obvious sociological problems inherent to the at-risk population, the follow-up of SCD babies is rather successful. One of the major difficulties of this screening programme lies with the heterozygotes (1/30 AS in the target population), who appear to be too numerous to be successfully taken care of. Indeed, families with a genetic risk for SCD are liable to be identified through a heterozygous newborn rather than by identification of heterozygosity in a parent. Due to the birth prevalence of SCD in France, especially in comparison with other common genetic diseases, screening all newborns regardless of ethnic origin is an issue that is being addressed.

Acknowledgements: The authors are grateful to the Association Française pour le Dépistage et la Prévention du Handicap de l'Enfant (AFDPHE) for the 2007 data, and to Dr Catherine Badens (Faculté de Médecine de La Timone, Marseille) for the β thalassaemia data.

Competing interests: None.

REFERENCES

1. **Bardakdjian J,** Wajcman H. Epidémiologie de la drépanocytose [Epidemiology of sickle cell anemia]. *Rev Prat* 2004;**54**:1531–3.
2. **Bardakdjian-Michau J.** Le dépistage néonatal de la drépanocytose en France. *Arch Pediatr* 2008;**15**:738–40.
3. **Association Française pour le Dépistage et la Prévention du Handicap de l'Enfant**. Bilan d'activité 2007 (personal communication). http://www.afdphe.asso.fr (accessed 4 November 2008).
4. **Bardakdjian-Michau J,** Guilloud-Bataille M, Maier-Redelsperger M, *et al*. Decreased morbidity in homozygous sickle cell disease detected at birth. *Hemoglobin* 2002;**26**:211–7.
5. **Haute Autorité de Santé**. Recommandations pour la pratique clinique: Prise en charge de la drépanocytose chez l'enfant et l'adolescent (September 2005). http://www.has-sante.fr/ (accessed 4 November 2008),
6. **Trabuchet G,** Elion J, Baudot G, *et al*. Origin and spread of beta-globin gene mutations in India, Africa, and Mediterranean: analysis of the 5′ flanking and intragenic sequences of beta S and beta C genes. *Hum Biol* 1991;**63**:241–52.
7. **Bardakdjian-Michau J,** Dhondt J-L, Ducrocq R, *et al*. Bonnes pratiques de l'étude de l'hémoglobine. *Ann Biol Clin* 2003;**61**:401–9.
8. **Haute Autorité de Santé**. Guide – Affection de Longue Durée: Syndromes thalassémiques majeurs et intermédiaires. Protocole national de diagnostic et de soins pour une maladie rare. 2008. http://www.has-sante.fr/ (accessed 4 November 2008).

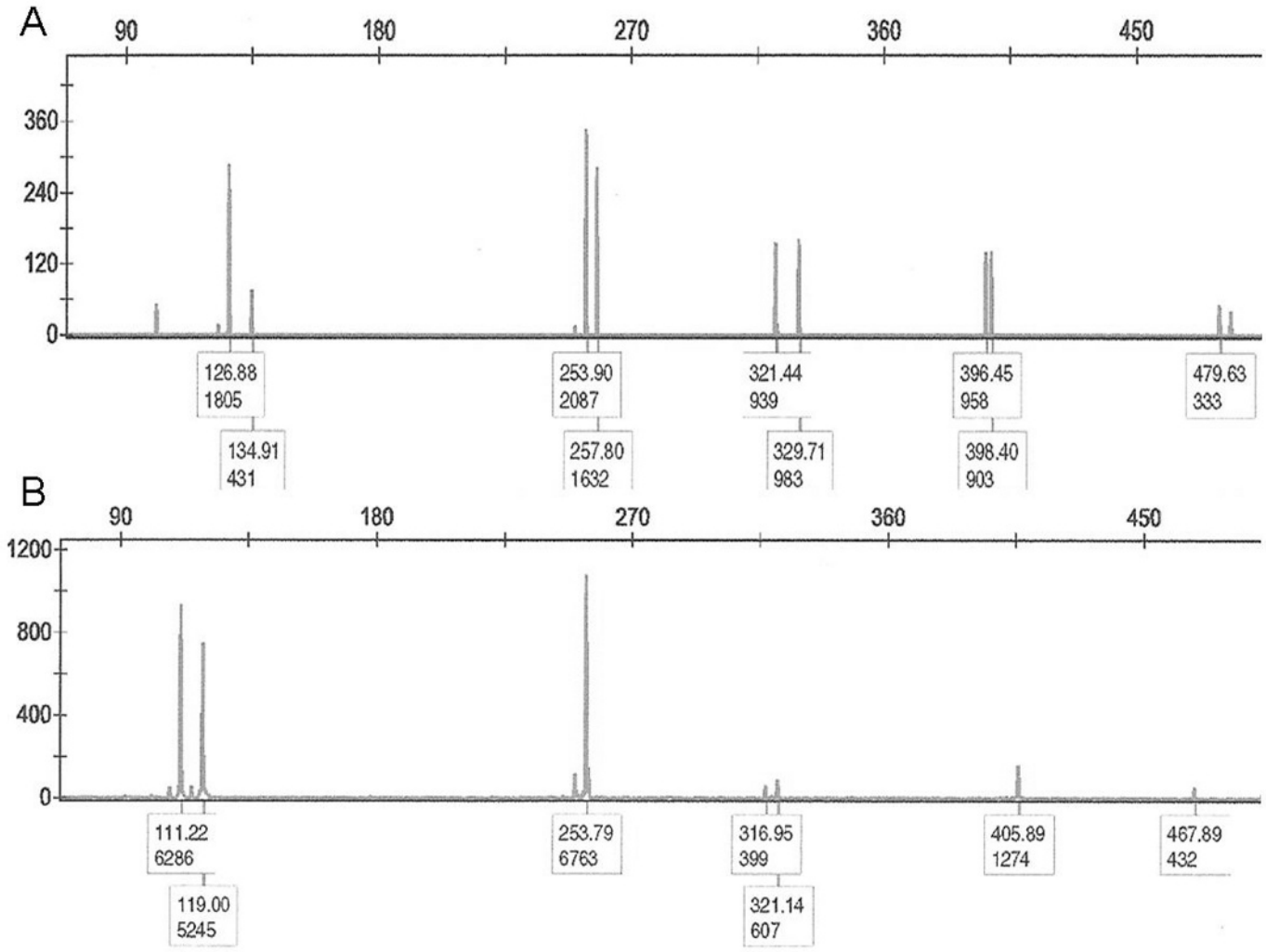

Figure 2 Illustration of 5 of the 12 microsatellite markers employed. All markers showed a clear mismatch between the bone marrow biopsy (A) and the core of chronic lymphocytic leukaemia (B).

L J Christie,[1] L J Bayer,[2] R Smith,[3] M J Pippard,[4] D A Levison[1]

[1] Division of Medical Sciences, University of Dundee, Dundee DD1 9SY, UK; [2] East of Scotland Regional Genetics Service, Ninewells Hospital and Medical School, Dundee DD1 9SY, UK; [3] Department of Respiratory Medicine, Ninewells Hospital and Medical School, Dundee DD1 9SY, UK; [4] Division of Clinical and Population Science and Education, University of Dundee, Dundee DD1 9SY, UK

Correspondence to: Dr Lesley J Christie, Department of Pathology and Neuroscience, Ninewells Hospital and Medical School, University of Dundee, Dundee DD1 9SY, UK; l.y.christie@dundee.ac.uk

Funding: Lesley Christie's Fellowship is supported by the Royal College of Pathologists and the Jean Shanks foundation.

Competing interests: None.

Provenance and peer review: Not commissioned; not externally peer reviewed.

Accepted 7 May 2009

J Clin Pathol 2009;**62**:862–864. doi:10.1136/jcp.2009.067660

REFERENCES

1. **Christie LJ,** McKay FJ, Purdie CA, *et al*. A simple and rapid approach to the problem of tissue contamination and patient identity in histopathological specimens. *Hum Pathol* 2006;**37**:1536–42.
2. **Kessis TD,** Silberman MA, Sherman M, *et al*. Rapid identification of patient specimens with microsatellite DNA markers. *Mod Pathol* 1996;**9**:183–8.

CORRECTION

doi:10.1136/jcp.2008.058867cor

In the paper, Neonatal screening for sickle cell disease in France (*J Clin Pathol* 2008;**62**:31–3), the following people should be added as co-authors: C Badens[1], R Ducrocq[2], J Elion[2] and JM Perini[3]. Their affiliations are as follows: 1. Laboratoire de Génétique Moléculaire, Hôpital d'enfants de la Timone, Marseille, France; 2. Laboratoire de Biochimie Génétique, Hôpital Robert Debré, Paris, France; 3. Laboratoire de Dépistage Néonatal, Hôpital Calmette, Lille, France.

Neonatal screening for sickle cell disease in France

J Bardakdjian-Michau, M Bahuau, D Hurtrel, et al.

J Clin Pathol 2009 62: 31-33
doi: 10.1136/jcp.2008.058867