Meeting reports

Sudden death in sickle cell disease

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Report of meeting of Section of Pathology, 3 November 1992

Contributions to this meeting were heard from both American and British experts and it was attended by about 100 delegates from around the country.

The first speaker was **Professor K Ohene-Frempong** (Philadelphia) whose subject was the American experience of unexplained death in sickle cell disease (SCD). He introduced his talk by outlining the main acute and chronic complications of SCD and which of these cause sudden death. He highlighted acute chest syndromes, cerebrovascular (CVA) events, splenic dysfunction or sequestration and aplastic crises as the main causes of sudden death though he pointed out that almost any presentation of sickling can lead to death if one of these more serious complications then arises.

He then went on to present some figures from a study by Parfrey at Johns Hopkins Hospital who reviewed the data on 74 sickle deaths from 1915-1984. The largest group (26%) died of infection, 12% of uraemia and 12% of splenic sequestration. In 22% the cause was unknown. Looking at events leading up to death, of the 27% of sickle deaths where there had been a definite painful crisis before death, almost half the patients had no obvious cause of death found at post-mortem and they therefore had unexplained deaths.

Following this data, a cooperative study into patients with sickle cell disease (CSSCD) has been set up in the USA to document more thoroughly the course of the disease. To date there are 3000 patients in the under 20 years age group. A total of 73 have died. The causes were as follows: bacterial infections - 28 (40%); CVA - nine (12%); chest sequestration crisis - six (8.5%); aplastic crisis - one (1.3%); splenic sequestration - one (1.3%); and unrelated deaths - nine (12%: these were mainly homicide, AIDS, and accidents). In 19 (26%) the cause was unknown, even though a number had had a post-mortem examination. This data has been published by Leiken *et al.* in *Pediatrics* 1989. In the >20 year group the presence of chronic disease at the time of death has been analysed. Of the 18% with chronic disease, 13% had had a stroke, 58% had chronic renal failure and 29% chronic heart failure. The chronic disease was not necessarily the cause of death.

Professor Ohene-Frempong concluded by saying that there is still much doubt surrounding many sickle deaths and much more information is needed if we are to unravel the cause of unexplained sickle deaths.

The next contribution was from **Dr S C Davies** (London) on the British experience. She opened by considering some general aspects of sickle deaths using quotations from a recent *BMJ* editorial on sudden death in young people by Professor M J Davies to illustrate them. She highlighted the fact that mortality rates are significantly higher in the less than 65 years black population in USA than white, even allowing for socioeconomic status. This could be due to income but could also be due to access or quality of health care or beahvioural risk factors in the black population. Unexpected deaths without explanation in young people are all too common in SCD and are particularly difficult for bereaved families to cope with. Contributory factors to the high number of unexplained deaths are under-reporting of SCD-related deaths, the complex interaction of SCD with other pathologies and the difficulties in separating the effects of antemortem from postmortem sickling at postmortem examinations.

Dr Davies then talked in some detail about the 24 deaths in the Brent sickle population that have occurred since 1974. Twenty-one of the 24 were Hb SS, two Hb SC and one was Hb S beta thalassaemia. Looking at the age distribution: three were <5 years; four aged 5-16 years; 11 aged 16-30 years; and six were in the >30 years age group. The commonest cause of death was pulmonary complications of SCD in 11 patients: three had liver failure; two each had splenic sequestration, CVA and AIDS; one pneumococcal septicaemia; and one had metabolic disease. The other two deaths were completely unexplained. This data showed some similarities but also some striking differences from the American data.

Sixteen of the patients had postmortem examination. Eight of these were in the chest syndrome patients where, not only did they show the expected intrapulmonary sickling effects, but associated isolated findings were right atrial thrombosis, bilateral pleural effusions, necrotic bone marrow and one had coexistent scleroderma. Three of the patients had died within a month of general anaesthesia, two for a gynaecological operation.

Dr Davies then discussed the importance of preventing sickle deaths. Penicillin prophylaxis to all SCD children and neonatal screening to detect haemoglobinopathies early are both very important. Good patient compliance with iron chelation in the transfused patients also prevents early deaths in this sub-population. In terms of treatment for SCD-related infection and chest syndromes, antibiotics, blood transfusions and ventilation or CPAP should all be used early when necessary. Other recommendations which are currently being put into practice to reduce SCD mortality and morbidity are the assessments of the role of upper airways obstruction in strokes, transcranial Doppler techniques to look at cerebral blood flow and neurological and psychometric monitoring of sickle children. Future possible prospects to try and reduce the number of unexplained deaths could include the development of a British 'natural history study' along the lines of that in the USA which would improve documentation, and also the development of a national register of SCD deaths. Haemoglobin electrophoresis and full histology should be carried out in any postmortem where sickled cells are seen. In her conclusion, Dr Davies again referred to the *BMJ* editorial which suggested that to help bereaved

families - and scientific knowledge - a category of sudden unexpected deaths should be recognized.

The second part of the presentation was based on the pathology findings at postmortem in sickle cell patients. **Dr S Leadbetter** (Cardiff) reminded us that unexpected deaths were not confined to patients with SCD and raised the controversial point that maybe they were no commoner than in the normal population. The problem of definition was also raised: 'sudden' death depends on the amount of recent antemortem data available, whereas 'unexplained' was taken to imply unexplained following a complete postmortem analysis. In most postmortem examinations at least a few pathological conditions are identified: the most likely cause of death can be inferred by the pathologist on the basis of past experience and epidemiological studies. Therefore, a large population of SCD patients must be studied at postmortem and compared to a normal matched population to see if SCD predisposed the patient to death from a specific cause.

The technical difficulties faced by the pathologist doing postmortems on SCD patients were also discussed. Little metabolic information is available after death though hydration can be assessed by analysing the vitreous humour. Lungs and brain should ideally be fixed in formalin and then examined, the individual chambers of the heart should be weighed to assess hypertrophy, the conduction system should be studied and necrotic bone marrow emboli should be looked for. Finally, a full microbiological and toxicological screen should be performed as well as haemoglobin electrophoresis in all black patients. If sickling is found, it is impossible to assess whether the sickling occurs ante- or postmortem. On the basis of this type of postmortem examination, death in SCD can be divided into three groups - those with sufficient SCD-related pathology to cause death, those in which SCD-related pathology in association with unrelated pathology caused death and finally patients in whom SCD-related pathology is insignificant and therefore unlikely to have caused death.

Dr P Vanezis (London) was the second pathologist to speak. He used a case history to illustrate how factors insufficient to cause death in a normal person can lead to death in SCD. A young male patient with known Hb SC disease and schizophrenia was held in police custody for 4 days after an alleged crime while having delusions. During that time the patient refused to drink and eat properly and died from sickling secondary to dehydration. In contrast to Dr Leadbetter, Dr Vanezis appeared confident about his ability to distinguish ante- from postmortem sickling.

Professor A Bellingham (London) then gave an overview of the discussion. He commented that prevention and early treatment of infection was of paramount importance in decreasing mortality in young patients with SCD. The importance of collecting data on large cohorts of patients with SCD was also emphasized and he suggested that a protocol for an adequate postmortem examination on SCD patients should be developed. A consensus opinion from pathologists on whether ante- and postmortem sickling could be differentiated would also be of value.

A round table discussion took place at the end of the meeting, during which time delegates discussed their opinions about the topics discussed during the afternoon. The definition of 'sudden' was described by **Professor S Charache** (Baltimore) as unexpected based on the previous clinical course and by **Dr M Brozovic** (London) as 'sudden' based on the clinical course of the previous 24 h. **Dr Leadbetter** disagreed with the term 'unexplained' as he felt all causes of death could not be excluded even after a complete postmortem. **Professor G Jenkins** (London) felt that whether sickling had occurred ante- or postmortem could not be determined at postmortem examination, and **Professor Bellingham** suggested that this problem could be addressed by doing postmortem examinations on sickle cell patients who died in road traffic accidents. **Dr D Bevan** (London) pointed out that conditions causing death in individuals with Hb AA such as massive pulmonary emboli or left ventricular hypertrophy with outflow obstruction should be excluded in patients with SCD. **Professor S Machin** (London) suggested that bowel ischaemia, which might be missed at postmortem examination, could lead to endotoxaemia, complement activation and cytokine release which could cause widespread cellular dysfunction and death in some cases. **Dr Ohene-Frempong** returned to the problem of preventing sudden deaths, suggesting that indices giving reliable information about a patient's clinical course should be developed. This would give useful information when dealing with the sickle chest which according to **Professor Charache** developed over a few days but which according to **Dr Davies** had a variable speed of onset. **Dr A Yardumian** (London) was concerned that narcotic analgesics could contribute to development of the sickle chest syndrome in patients hospitalized for painful vaso-occlusive crises. However, both Professor Bellingham and Dr Davies felt that this was unlikely to be the case.

Professor Charache summed up the session by reiterating that the cause of death must be sought in all sickle cell patients as far as is practicable, and that close communications between pathologists and clinicians would help in elucidating the cause of death. The meeting concluded with expression of the great need for more postmortem examinations in patients with SCD, more detailed postmortems, and perhaps the referral of histological slides with clinical data to pathologists with a particular interest in SCD. Such a study has begun in the USA and should be considered in the United Kingdom.

R J Liesner
E A Vandenberghe
Department of Haematology
Central Middlesex Hospital
Acton Lane
London NW10 7NS, UK