Heterogeneous geographic distribution of patients with aortic valve stenosis: arguments for new aetiological hypothesis

G Le Gal, V Bertault, E Bezon, J-C Cornily, J-A Barra, J-J Blanc

Calcific aortic valve stenosis is far the most common valve disease in developed countries. The first clinical symptoms usually appear in the late 60s. Prosthetic aortic valve replacement is the only effective treatment at present. The reasons for the occurrence of calcifications of the aortic cusps leading eventually after many years to aortic valve stenosis are unknown. Some risk factors, mainly those already recognised in vascular disease, have been found to be associated with aortic valve stenosis and are considered to cause the disease. However, these factors are totally non-specific and may be confounded with factors leading to other illnesses. Recently a genetic hypothesis has been proposed after observation of a few familial cases but remains largely challenged in the absence of gene determination. The aim of our study was to evaluate whether epidemiological data collected in a selected region of France could provide evidence in favour of this hypothesis.

PATIENTS AND METHODS

The list of all patients who had undergone aortic valve replacement for calcific aortic valve stenosis in the cardiac surgery department of the Brest University Hospital between January 1996 and June 2003 was obtained from the central computerised registration of medical diagnosis and surgical procedures of the hospital, coded according to the International classification of diseases, 10th revision. This list was compared, and if necessary completed, with the diary registries of all the surgical interventions performed in the cardiac surgery department.

For each patient, the following data were collected: name, sex, date of surgery, date of birth, and social security number. The social security number is a 15 digit number allowing identification for sex, year and month of birth, and geographic origin (region and commune). France is administratively divided into 22 provinces, about 100 regions, and 36 000 communes. The commune is the smallest French administrative division. The canton is an intermediate division comprising four to eight communes. Only patients who where born in the region of Finistere were included in our analysis. The nature of the aortic valve disease was verified by examining every surgery report, which always describes the macroscopic aspect. When the surgeon mentioned that aortic valves were bicuspid the patient was excluded from analysis.

Our goals were, firstly, to establish the proportion of the population from each commune who had undergone aortic valve replacement for calcific aortic valve stenosis; secondly, to map the prevalence in the communes within the region to identify geographic clusters; and lastly, to detect significant differences between communes.

To assess the prevalence of the disease it was necessary to know the exact number of patients who had undergone aortic valve replacement originating from each commune during the study period. The choice of the reference population was an issue, as various options were possible. We could have used the number of inhabitants living in a commune at the time of the surgical intervention in the patients originating from this commune. This was not considered a good option, as it did not take into account major population movement in the preceding decades (urbanisation, second world war). Another possibility was to use the number of births in the commune during the year of the birth of each patient to obtain the incidence for each year in each commune. However, some little communes had only a few births in one year and experienced a few cases, leading to very variable results. Ideally, to assess more accurately the prevalence of surgical cases of aortic valve stenosis, the reference population could have been the number of people born in the commune during the same year as the patients and who were still alive at the time of the surgical interventions. These data are not available. We decided to use the population of the commune at the approximate date of birth of the patients and chose the 1926 census, which corresponds to the mean age (74 years) of patients who had undergone surgery between 1996 and 2003. These data were obtained from the 1926 census, which recorded 753 801 inhabitants in the region.

The results were expressed as the ratio of patients who had undergone aortic valve replacement for calcific aortic valve stenosis to 10 000 inhabitants living in the commune in 1926. The relative risk was assessed as the risk of surgery in the commune as compared with the risk in the rest of the region. A 95% confidence interval was estimated for each relative risk.

Visual study could not indicate the significance of observed clusters—that is, whether the geographic aggregations could have occurred by chance alone. Therefore, we used the method recommended by the Centers for Disease Control and Prevention. By this approach we assessed the deviation from chance expectation of the geographic pattern we observed as described by Ohno and colleagues. For this test, each commune was classified into one of three categories (0–9 cases, 10–19 cases, and ≥20 cases for each 10 000 inhabitants living in 1926) and each pair of adjacent communes was identified. The statistical test analyses the number of adjacent concordant pairs—that is, the number of pairs of communes that were adjacent and had ratios in the same range. The expected number of adjacent concordant pairs is calculated by a simple formula given by Ohno and colleagues. The observed adjacent concordant pairs are compared with the expected number by a simple \( \chi^2 \) test.

RESULTS

During the study period 756 patients born in Finistere had undergone aortic valve replacement for calcific aortic valve stenosis in our institution. This gives a proportion of 10.03 patients in 10 000 inhabitants living in 1926.

Figure 1 summarises the proportion of aortic valve replacement according to the commune of birth. In this map of

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Finistere, each commune is shaded according to the proportion of cases. There is great heterogeneity among the communes, ranging from 0–52 cases in 10,000 inhabitants. It seems that there are several clusters of high proportion communes concentrated in a geographic area. This is more obvious when considering the highlighted communes, which are the communes that have a significantly higher proportion of cases—that is, a relative risk of surgery significantly greater than 1.

Lastly, two areas are clearly prevalent: one in the southwest area of the region and the second in the northwest part.

After the division of the 283 communes into three ratio categories, we obtained 135 communes of low prevalence (<10 cases in 10,000 inhabitants in 1926), 96 communes of intermediate prevalence (10–19 cases), and 48 of high prevalence (≥20) (four islands were excluded). The total number of adjacent pairs in the full set of 283 communes was 712. The observed numbers of adjacent concordant pairs were 178, 95, and 32 within the low, intermediate, and high ratio category subsets, respectively. The expected numbers were 161, 81, and 20, respectively. The observed global number of adjacent concordant pairs was significantly higher than expected (305 vs 262, p = 0.009). In the high risk category, the observed number of adjacent concordant pairs was 32, as compared with 20 expected (p = 0.008).

DISCUSSION

The main result of this study is evidence of a clear heterogeneous distribution of aortic valve replacement in the region of Finistere. The highly significant differences raised many issues.
to be a random phenomenon. The geographical and historical particularities of the region of Finistere strengthen this conclusion and support new aetiological approaches to this disease.

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**IMAGES IN CARDIOLOGY**

**Right to left shunt 20 years after sinus venous atrial septal defect closure**

A 29 year old woman with hypoxia of unknown aetiology, which was found one day after she underwent a knee joint operation, was admitted to our hospital. She had undergone an atrial septal defect (ASD) closure 20 years previously. Arterial PO2 (PaO2) was 74 mm Hg despite administration of 10 ml/min of oxygen (PaO2 was 58 mm Hg in room air). She had no symptoms and was not cyanotic. Chest x ray was normal and there were no ECG abnormalities. There were no findings of pressure overload in the right atrium (RA) and right ventricle (RV) by transthoracic echocardiography (TTE). TTE revealed continuous abnormal flow signal, flowing into the left atrium (LA) on colour and pulsed Doppler, located just in the anterior side of the right pulmonary artery. Intravenous contrast (Levovist, Schering) injected from both upper limbs reached the LA normally (upper panel). Transoesophageal echocardiography showed distal superior vena cava (SVC) stenosis with SVC dilatation, and incomplete closure of sinus venous ASD. An SVC to LA (right to left) shunt flow signal was revealed by colour Doppler (lower panel). Mean pressures measured by using cardiac catheterisation were as follows: SVC 9 mm Hg, LA 5 mm Hg, RA 2 mm Hg.

As a result of distal SVC stenosis and residual ASD after inappropriate sinus venous ASD closure, SVC pressure exceeded LA pressure, and hence, SVC to LA shunt occurred through the residual ASD. This right to left shunt resulted in the patient’s chronic hypoxia. Intravenous contrast echocardiography was useful for detecting that this patient had right to left shunting from the SVC to the LA, and transoesophageal echocardiography clearly revealed the complicated anatomical and physiological abnormality.

Fortunately, the patient had no history of systemic embolism for the preceding 20 years, or symptoms of hypoxia. After the successful corrective surgery, her hypoxia improved dramatically and she is doing well.

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