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THE INDUSTRIAL INJURIES ADVISORY COUNCIL

POSITION PAPER 20

ASBESTOS EXPOSURE AND RETROPERITONEAL FIBROSIS

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Asbestos Exposure and Retroperitoneal Fibrosis

Position paper 20

Summary

1. Retroperitoneal fibrosis (RPF) is a relatively rare disorder in which parts of the renal tract become blocked and compressed by a build up of fibrous tissue in the retroperitoneum (the compartment of the body containing the kidneys, aorta and renal tract), potentially leading to kidney failure. In a recent court judgement a claimant's RPF was judged, on the balance of probabilities, to have been caused by asbestos exposure.

2. Subsequently the Council was asked to consider the case for prescription of RPF associated with occupational exposure to asbestos. This paper describes the position of the Council in relation to RPF following an evaluation of the available evidence in terms of the requirements for prescription.

3. A number of non-occupational factors, including certain medicinal drugs, increase the risk of RPF. The case for prescription therefore rests on the availability of epidemiological evidence that the risk of the disorder is more than doubled in those with a history of asbestos exposure.

4. Five published reports on the subject were identified, of which four contained only case descriptions and one described the results of a case-control study.

5. Although the results of the case-control study indicated a more than doubling of risk in those with previous asbestos exposure, the study was small and currently represents the only epidemiological evidence of an association between asbestos exposure and RPF. The Council normally looks for strong and consistent evidence from several independent studies to support the case for prescription.

6. The Council concludes that, while there is a suggestion of an association, prescription cannot be recommended on the basis of currently available evidence. The Council will, however, review the position should other relevant epidemiological evidence emerge in the future.

Introduction

7. The possible association between asbestos exposure and retroperitoneal fibrosis (RPF) was brought to the attention of the Council by Mr. Tony Whitston of Greater Manchester Asbestos Victims Support Group. He noted a recent court judgment in which a claimant's RPF was judged, on the balance of probabilities, to have been caused by exposure to asbestos.

8. Retroperitoneal fibrosis (also known as Ormond's disease) is a disorder characterised by the proliferation of fibrous tissue in the retroperitoneum, the compartment of the body containing the kidneys, aorta and renal tract. The ureters, which carry urine from the kidneys to the bladder, may become compressed and blocked by excess tissue leading to kidney failure. A number of non-occupational factors have been linked to the disorder including cancer, radiation therapy, infection, aortic aneurysm and the use of certain medicinal drugs, notably methysergide (used in the treatment of migraine), and a number of antihypertensive agents such as hydralazine and beta blockers. It has also been suggested that RPF may represent an autoimmune response to the components of atheroscelortic plaques which result from a build up of cholesterol in the arteries. It is a relatively rare disorder, for example the annual age-standardised incidence in three districts of Finland has been reported as 1 per million persons per year (Uibu *et al* 2004). In England and Wales approximately 30 deaths per year occur in which RPF is cited as an underlying cause.

The Industrial Injuries Disablement Benefit Scheme

9. The Industrial Injuries Advisory Council (IIAC) is an independent statutory body set up in 1946 to advise the Secretary of State for Social Security on matters relating to the Industrial Injuries Scheme. The major part of the Council's time is spent considering whether the list of prescribed diseases for which benefit may be paid should be enlarged or amended.

10. The Industrial Injuries Disablement Benefit (IIDB) Scheme provides a benefit that can be paid to an employed earner because of an industrial accident or Prescribed Disease.

The legal requirements for prescription

11. The Social Security Contributions and Benefits Act 1992 states that the Secretary of State may prescribe a disease where he is satisfied that the disease:

    i. ought to be treated, having regard to its causes and incidence and any other relevant considerations, as a risk of the occupation and not as a risk common to all persons; and

    ii. is such that, in the absence of special circumstances, the attribution of particular cases to the nature of the employment can be established or presumed with reasonable certainty.

12. In other words, a disease may only be prescribed if there is a recognised risk to workers in an occupation, and the link between disease and occupation can be established or reasonably presumed in individual cases.

13. In seeking to address the question of prescription for any particular condition, the Council first looks for a workable definition of the disease. It then searches for a practical way to demonstrate in the individual case that the disease can be attributed to occupational exposure with reasonable confidence. For this purpose, reasonable confidence is interpreted as being based on the balance of probabilities according to available scientific evidence.

14. Within the legal requirements of prescription it may be possible to ascribe a disease to a particular occupational exposure in two ways – from specific clinical features of the disease or from epidemiological evidence that the risk of disease is at least doubled by the relevant occupational exposure.

Clinical features

15. For some diseases attribution to occupation may be possible from specific clinical features of the individual case. For example, the proof that an individual's dermatitis is caused by his/her occupation may lie in its improvement when s/he is on holiday, and regression when s/he returns to work, and in the demonstration that s/he is allergic to a specific substance with which s/he comes into contact only at work. It can be that the disease *only* occurs as a result of an occupational hazard (e.g. coal workers' pneumoconiosis).

Doubling of risk

16. Other diseases are not uniquely occupational, and when caused by occupation, are indistinguishable from the same disease occurring in someone who has not been exposed to a hazard at work. In these circumstances, attribution to occupation on the balance of probabilities depends on epidemiological evidence that work in the prescribed job, or with the prescribed occupational exposure, increases the risk of developing the disease by a factor of two or more. The requirement for, at least, a doubling of risk is not arbitrary. It follows from the fact that if a hazardous exposure doubles risk, for every 50 cases that would normally occur in an unexposed population, an additional 50 would be expected if the population were exposed to the hazard. Thus, out of every 100 cases that occurred in an exposed population, 50 would do so only as a consequence of their exposure while the other 50 would have been expected to develop the disease, even in the absence of the exposure. Therefore, for any individual case occurring in the exposed population, there would be a 50% chance that the disease resulted from exposure to the hazard, and a 50% chance that it would have occurred even without the exposure. Below the threshold of a doubling of risk only a minority of cases in an exposed population would be caused by the hazard and individual cases therefore could not be attributed to exposure on the balance of probabilities. The epidemiological evidence required should ideally be drawn from several independent studies, and be sufficiently robust that further research at a later date would be unlikely to overturn it.

Available evidence

17. RPF has been associated with a number of non-occupational causes and it is not possible to determine occupational causality from particular clinical features of individual cases. In these circumstances, therefore, the case for prescription rests on the identification of a body of epidemiological evidence which indicates a doubling or more of risk in those with previous exposure to asbestos.

18. In the case referred to by Mr. Whitston, an expert opinion was provided by Professor David Coggon, who reviewed the available evidence on the subject. For the period 1966 to 2005 Professor Coggon identified four published papers which examined a possible association between RPF and asbestos exposure. Two of these were case reports, one was a case series and one was a case-control study. A subsequent literature search conducted by the Council's Research Working Group did not reveal any further published evidence on the subject. However, an additional report was brought to the Council's attention in February 2008. A summary of the information contained in the five papers thus identified is provided below.

Case reports

19. Maguire *et al* (1991) reported a case of a 72 year old man who developed RPF resulting in acute renal failure. The patient was reported to have no known risk factors for RPF. However, he had been exposed to asbestos between 1941 and 1945 when he worked as a machinist in a shipyard. He may also have had further asbestos exposure in 1970 when he worked as a pipe fitter for several months. It was noted that the development and progression of RPF occurred at the same time as diffuse bilateral pleural thickening, a condition associated with asbestos exposure. Thus there was a temporal relationship between RPF and the manifestation of other effects of asbestos exposure, which might indicate a common cause for the two conditions.

20. Boulard *et al* (1995) reported two cases of RPF in men who had previously been occupationally exposed to asbestos and who also showed evidence of chest disease typically associated with asbestos exposure. A 51 year old man had worked for 25 years in road building. Chest radiographs showed bilateral diaphragmatic calcified pleural plaques. A 54 year old man had been exposed to asbestos for 20 years as a boiler maintenance engineer. Chest radiographs showed unilateral chronic pleural thickening. No other known causes of RPF could be identified in either patient.

21. Cottin *et al* (2008) reported two cases of pleural and mediastinal fibrosis with additional retroperitoneal fibrosis. Both patients were slightly or moderately exposed to asbestos and no other explanation was found for their condition.

Case series

22. Sauni *et al* (1998) reported on all cases of RPF diagnosed at one hospital in Finland (with a catchment area of approximately one million people) between 1987 and 1995. 13 cases of RPF were identified. Of the 13 cases, 7 were men, all of whom reported previous occupational exposure to asbestos. The authors note that generally only 5%

of the Finnish working population has exposure to asbestos. Radiograph findings showed bilateral pleural plaques in 4 of the 7 male cases, and unilateral pleural plaque in one case. In these five cases, the duration of asbestos exposure ranged from 11- 40 years. Of the two male patients with normal radiography findings, one reported 3 years of asbestos exposure. The other reported 37 years of work involving sawing fire insulation plates which 'sometimes contained asbestos' In the case of this patient, however, RPF appeared to be associated with aortic aneurysm. Three of the six female patients were also found to have other risk factors for RPF. In all the female cases asbestos exposure was reported to be either absent or not known.

23. The authors argue that the rate of bilateral pleural plaques (a radiological feature of asbestos exposure) in these male RPF patients was 8 times greater than that in the Finnish male population.

24. They suggest that asbestos exposure should be considered an important aetiological factor in RPF.

Case-control study

25. The only epidemiological study to investigate the association between asbestos exposure and RPF was a case-control study carried out by Uibu *et al* (2004) in three hospital districts in Finland. The area covered a population of 3.6 million people. The study involved 43 cases (out of 50 identified) treated for RPF in the three districts between 1990 and 2001. Occupational exposure to asbestos was graded in terms of three levels, 'no notable exposure', slight exposure of <10 fibre-years and moderate to high exposure of 10+ fibre-years (where a fibre-year was defined as working for 40 hours per week for 1 year at an average dust level of 1 fibre/ml). There was some overlap in the authorship between this paper and that by Sauni et al (1998), and the possibility exists that some of the cases from the earlier cluster were common also to this study.

26. After adjustment for other risk factors (medication use, abdominal aortic aneurysm and smoking for more than 20 pack years) exposure to asbestos was strongly associated with RPF. For <10 fibre-years the Odds Ratio (OR) was 5.54 (95% CI 1.64-18.65).[1] For 10+ fibre-years OR was 8.84 (CI 2.03-38.50).

27. The mean latency between first exposure and diagnosis was 30.8 years for slight exposure and 33.3 years for moderate to high exposure. In all but 2 cases latency exceeded 20 years.

28. Other factors associated with higher relative risks include: use of migraine medications such as methysergide (OR 9.92), smoking >20 pack years (OR 4.73), abdominal aortic aneurysm (OR 6.73), abdominal surgery (OR 2.06) and use of beta-blockers (OR 2.36).

[1] An odds ratio is the odds of disease in those with exposure relative to the odds in those without; for rare diseases it is approximately equal to the relative risk. A 95% confidence interval gives a plausible range in which the true population value lies allowing for statistical uncertainty. Roughly speaking, it represents a one in twenty chance that the true value is outside the stated range.

29. Since Uibu et al (2004) represents the only epidemiological evidence in this field the quality of this particular study is a critical factor. Despite the small sample size the study appears to have been well-designed and executed. Cases were confirmed on the basis of medical records and histopathological reports. Cases (response rate 86%) were matched to 179 controls, (response rate 83%) with up to five controls per case, matched for sex, age and hospital district, selected at random from the general population. Exposure assessment was relatively detailed, involving retrospective assessment of occupations by an industrial hygienist, enabling grading of exposure to assess dose-response relationships. Exposure information was collected by postal questionnaire and follow-up telephone interview. It was noted that the hypothesis of an association between asbestos exposure and RPF was not publicised and not well-known to subjects which reduced the possibility of bias from differential recall of certain exposures. Following interviews, asbestos exposure was estimated from the occupational histories by an occupational physician blind to the case/control status of the subject. Information on other potential risk factors was also collected and adjusted for in the analysis of the relationship between asbestos and RPF.

Consideration of the evidence

30. The cause of RPF is currently unknown but a number of possible risk factors have been identified. These five papers address the question of whether some cases of RPF may arise as part of an asbestos-induced fibrotic process similar to that which causes the development of pleural plaques or lung fibrosis.

31. Details of three of the case history reports provide some support for the view that RPF may be part of an asbestos-induced process, while that by Cottin et al illustrates how fibrosis can extend between body compartments (adding weight to the biological plausibility of the putative effect). However, case histories cannot by themselves demonstrate an association between an exposure and a disease. Since asbestos exposure is relatively common in the working population it is to be expected that some cases of RPF would also give a history of asbestos exposure. Individual case histories provide information which can generate hypotheses about disease causation, but such hypotheses must then be tested by purpose-designed studies.

32. The case series provides stronger suggestive evidence. All 13 cases in a particular area during an eight year period were identified. Of these, all of the 7 male cases reported occupational exposure to asbestos and this was supported in 5 of these cases by radiographic evidence of asbestos-related effects (pleural plaques). Set against this, there was no evidence of asbestos exposure in the female cases. However, in 3 of the female cases other potential causes of the disease were identified. Although the comparison is crude, in the case of the male cases of RPF there was100% reported exposure to asbestos, while in the general male Finnish population exposure is estimated to be 5%. This evidence is stronger than that provided by the case histories but again cannot alone support the case for a causal association between asbestos and RPF.

33. The case-control study provides the only strong test of a causal relationship. The results indicate more than a doubling of risk of RPF in those with asbestos exposure, including exposure of less than 10 years, with a mean latency for disease development of around 30 years. The study was small in terms of the number of cases and the degree of overlap in cases between this study and the case series by

the same authors is unclear. However the study was otherwise well designed and executed and provides some persuasive evidence of a link between asbestos exposure and RPF.

34. In determining the case for prescription, however, the Council normally looks for consistent evidence from several independent studies. In this case, the study by Uibu et al represents the only evidence of sufficient quality to be considered in this context. While, therefore, the results are suggestive of an association, currently available evidence is insufficient in quantity to the support the case for prescription.

Conclusion

35. The Council has concluded that current evidence is insufficient to support a case for prescription. However, the Council strongly encourages further high quality research in an area where evidence is very limited and will continue to monitor closely new research reports.

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