CJD link prompts ban on brain tissue use

[TOKYO] The Japanese health ministry has belatedly decided to ban the import and use of dura mater grafts, almost ten years after similar action was taken by the US Food and Drug Administration (FDA). The decision highlights major deficiencies in the monitoring for safety of health-care products in Japan.

The grafts, freeze-dried tissue from the outer skin of the human brain that is used in many neurosurgical procedures, are derived from human cadavers and have been linked to cases of Creutzfeldt–Jakob disease (CJD). Last week, an expert committee approved an earlier announcement by the Japanese government recommending that such grafts should be replaced by autogenic grafts or artificial substitutes.

The government's decision follows the results of an epidemiological study that found that infected dura mater could have caused as many as 43 cases of CJD in Japan over the past ten years. The study was commissioned by the ministry, and directed by Sato Takeshi of the National Center of Neurology and Psychiatry.

Although Japanese officials were informed by researchers in 1987 about a report on iatrogenic transmission of CJD by dura mater by the US Centers for Disease Control and Prevention (CDC), they claimed that they became aware of the issue only last year.

Most commercially available dura mater products are fabricated by two German companies, Braun Melsungen and Biodynamics. After 1987, many countries encouraged autografting and the establishment of tissue banks. Only Japan continued to rely heavily on imported dura mater products. The practice of autografting is still rare in Japan, and the only tissue banks in existence are run by research units of university hospitals.

Apart from a single recent Japanese case, where the origin of the graft could not be established, all known cases of transmission of CJD by dura mater have been linked to grafts fabricated by Braun Melsungen before 1987, sold under the name Lyodura.

In contrast, at least three of the Japanese CJD cases related to dura mater appear to have been caused by surgical interventions carried out after an international product recall was issued by Braun Melsungen in March 1989. A representative of BBS, which distributes Braun Melsungen's products in Japan, has been reported as saying that the product recall was not fully applied in Japan because of a linguistic misunderstanding.

The FDA issued a product recall and an import ban on dura mater manufactured by Braun Melsungen as soon as the CDC results became known in 1987.

Japanese experts appear to have known of the relatively high number of CJD cases related to dura mater grafts in their country for some time. But the Japanese ministry took action only after an expert committee of the World Health Organization (WHO) recommended in March that dura mater "should no longer be used" on human patients.

The risk of transmission of CJD through allogenic dura mater has been widely acknowledged since the first such case was reported in the United States in 1987. But the risk of transmission is thought to have been considerably reduced by strict donor screening and quality control protocols, as well as by chemical and physical treatment aimed at inactivating the CJD agent.

Fewer than 20 cases of CJD linked to dura mater allografts had been reported worldwide before the preliminary results of the Japanese study were released last year. By then, 28 Japanese cases had already been identified. European experts say they are "surprised" by the new Japanese data, but that similar high rates of transmission elsewhere are highly unlikely.

The recommendation that all existing cadaveric dura mater products be banned has now been endorsed by both WHO and the Japanese health ministry. But companies that produce the material are resisting the move, claiming that it has not been scientifically demonstrated as necessary.

A spokesperson of Biodynamics, the world's second-largest provider of dura mater, describes the recommendation as "scandalous", and says that the company has urged WHO to reveal the scientific evidence.

The validity of the recommended ban is being investigated by both the US CDC and the FDA. Apparent problems in the communication of scientific information by WHO seem to have been reflected in the fact that an initial version of the press release on the expert meeting on bovine spongiform encephalopathy, CJD and medical products stated mistakenly that "CJD has been found to be transmissible by blood". The statement was later corrected.

Some critics have used the situation in Japan to support their claim that the ministry appears unable to take its own decisions about the safety of medical products, even where there is solid scientific evidence of a potential danger. "They needed an official announcement by WHO to legitimize their action," says Shohei Yonemoto, an independent science policy observer in Tokyo. Yonemoto argues that the ministry needs to improve its decision-making and risk assessment procedures.

There is also a growing feeling that, at a time when public debates on organ transplantation are heating up in Japan (see panel below), the dura mater case reveals severe shortcomings in the regulation and handling of products derived from human donors.

Under present Japanese legislation, most medical products derived from human donors remain unregulated. Until recently, even products treated as "medical devices" — such as dura mater — were not subjected to regular screening and quality control procedures after initial approval.

And Japan still lacks both a legal framework and an independent organization to guide the handling of human tissues, including tissues used for research. **Robert Triendl**

Japan takes step towards organ transplants

[TOKYO] After decades of debate, a bill to provide a legal framework for organ transplants was finally approved last Thursday (24 April) by the lower house of Japan's parliament, the Diet, in what appears to have been its first-ever free vote. The bill, introduced three years ago by an all-party group, still has to be ratified in the upper house, where its fate is by no means certain.

The bill makes it explicitly legal to transplant organs from "brain death bodies". But, although purporting to regulate organ transplants in general, the proposed law covers only main organs, and omits coronary arteries, bone marrow and other tissues – all of which are in far greater demand than hearts or livers.

The use of organs from brain-dead donors has been a controversial issue. Organ transplants are not technically illegal. But no heart transplant has been carried out since Japan's first such operation ended in scandal some 27 years ago.

As a result, many Japanese in need of transplants have been going overseas, and there is a growing population of patients with renal failure who cannot get transplants and have to rely on dialysis.

Cultural factors contribute to the widesread opposition to 'brain death' as the legal definition of death. But some also blame the medical profession. In most countries, organ transplants are not regulated by law but by professional guidelines. It was only last year that the Japanese Society for Organ Transplants started drafting guidelines.

The bill does not cover organs used for research. But it was recently revealed that Japanese university researchers have for at least the past six months been importing livers from brain-dead US donors for use in safety evaluations of pharmaceuticals. **R.T.**