16 year follow-up of surgically exposed contacts of patients with CJD in the UK

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INTRODUCTION

Transmission of Creutzfeldt-Jakob disease (CJD) by surgical instruments has been documented [1]. In the UK, since 2000, the surgical histories of patients newly diagnosed with CJD are investigated to identify past procedures that could have exposed other patients to a risk of prion transmission [2].

If any are identified, instruments that may still be contaminated are removed from use and individuals exposed to potentially contaminated surgical instruments are traced. Surgical contacts are informed and asked to take public health precautions. Long term follow-up of these surgical contacts to detect any transmissions of CJD continues. Here, we present the findings after 16 years of this public health surveillance in the UK.

METHODS

The elements which determine whether a surgical incident has occurred and how many surgical contacts should be traced and informed are outlined as "Index Patient and Operation Factors" in Figure 1.

CJD status of index patient. Surgical contacts may be informed in connection with index patients who are:
- Diagnosed with confirmed or probable CJD
- At risk of variant CJD through treatment with blood components from a donor who later developed variant CJD
- At risk of familial/inherited prion disease

Time from procedure to symptom onset. The surgical lookback period is 8 years for patients with sporadic, inherited or iatrogenic forms of CJD, and extends to 1980 for patients with or at risk of variant CJD.

Tissue infectivity. Central nervous system tissues of the brain, posterior eye and spinal cord are defined as high infectivity and olfactory epithelium as medium infectivity for all types of CJD. In addition lymphoid tissues are defined as medium infectivity for variant CJD. More surgical contacts are traced for higher infectivity tissues.

Public health follow-up of surgical contacts includes records flagging and annual review to identify date and cause of death. Periodic cross-referencing with the national CJD surveillance records and a post mortem review of notes by a neurologist is done to identify any indication of neurological disease prior to death. Person years of follow-up to 31st December 2016; years of survival post operation and causes of death among those patients who have died were summarised.

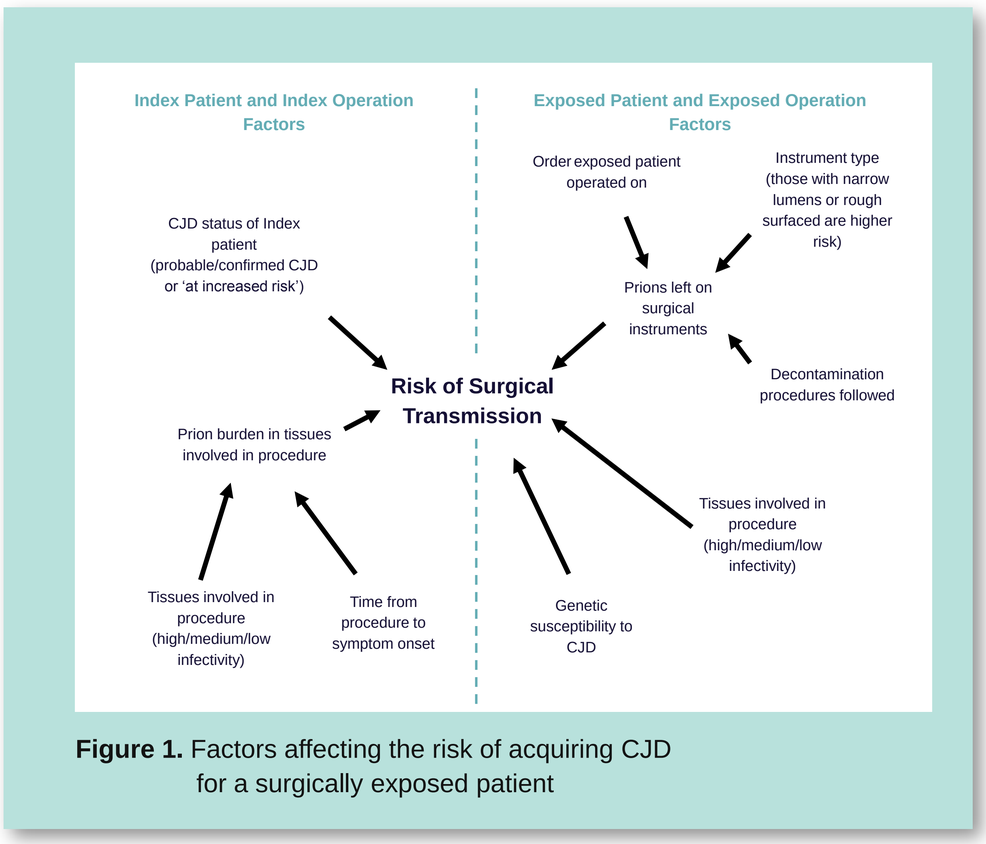


Figure 1. Factors affecting the risk of acquiring CJD for a surgically exposed patient

RESULTS

Between 2000 and 2016, CJD incidents involving 18 index patients and 39 surgical procedures led to 231 surgical contacts being traced and informed. Half of the index patients had been diagnosed with confirmed/probable CJD (6 sporadic, 2 variant and 1 genetic) and the remainder were at risk of developing CJD.

Five index patients had neurosurgery; three had surgery on posterior eye tissues; one invasive nasal surgery and the remaining procedures involved gut associated lymphoid tissues in patients with or at risk of variant CJD.

Table 1 shows follow-up details of the 231 surgical contacts identified. Most (80%) were potentially exposed to high infectivity tissues and 31% (59) of these operations were within a year of the index patient developing symptoms of CJD.

Figure 2 shows the causes of death for the 76 surgical contacts who have died. Eighteen neurological causes of death were reported. These were often related to the diagnosis for which the original surgery was done. For 18 patients, the cause of death was not ascertained, 13 of whom had died before the incident investigation determined they should be traced and informed.

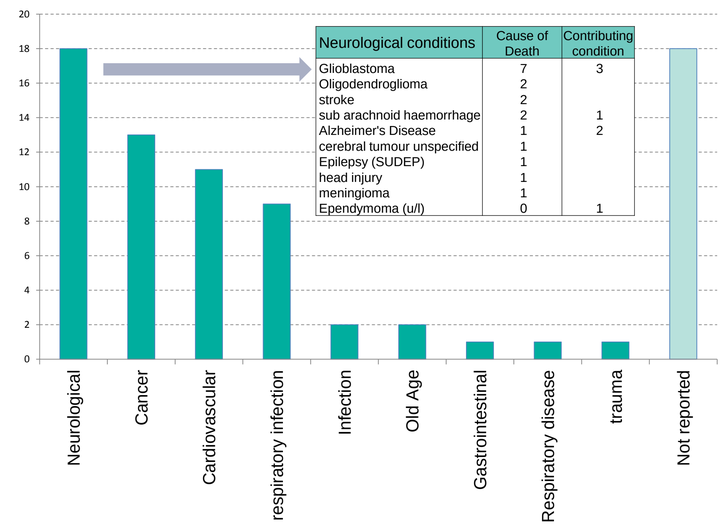
Neurosurgical patients had a higher and earlier mortality rate than other patients: 40% (48) of the neurosurgical contacts have died, 13 of whom within a year of surgery. This compares with 25% (28) of the other surgical contacts who have died, four within the first year.

The average follow-up time for remaining patients is 9.3 years, with a range of 3.1 to 21.3 years. A total of 1,886 person years of follow-up time has been accumulated, during which no clinical cases of surgically transmitted CJD have been identified.

Index patient CJD status	Index tissue infectivity[1]	Instrument order	Years from index patient procedure to symptoms (if confirmed CJD) or death / 31st Dec 2016 (if at risk)	Alive	Dead	Survived at least one year post exposure[2] n (%)	Survived at least five years post exposure[2] n (%)	Years of follow-up patients currently alive median (range)[4]	Age of patients currently alive median (range)[4]
confirmed CJD	High	1-2	<1	7	8	13 (100)	8 (62)	14.4 (3.1,14.4)	53 (34, 72)
			>4-8	17	6	23 (100)	20 (87)	8.9 (8.5,11.9)	64 (33, 81)
		>2	<1	21	23	38 (93)	31 (76)	7.8 (6.9,15.0)	66 (21, 90)
			>4-8	26	8	30 (88)	28 (82)	8.9 (7.8,11.9)	56 (24, 91)
	Medium	1-2	<1	2	1	3 (100)	3 (100)	15.0 (8.7,21.3)	82 (70, 95)
			>4-8	1	0	1 (100)	1 (100)	13.9 -	88 -
at increased risk[3]	High	1-2	>4-8	4	1	4 (80)	4 (80)	9.7 (9.6,9.7)	42 (33, 88)
			>8	4	0	4 (100)	4 (100)	9.3 (9.1,9.4)	74 (63, 92)
		>2	>4-8	17	12	23 (79)	19 (66)	9.5 (7.9,9.6)	71 (27, 93)
			>8	27	5	32 (100)	30 (94)	9.1 (8.1,9.4)	75 (35, 93)
	Medium	1-2	<1	2	2	4 (100)	2 (50)	9.5 (9.5,9.5)	62 (48, 77)
			>1-2	0	1	1 (100)	1 (100)	- -	- -
			>2-4	3	1	3 (75)	3 (75)	7.2 (7.2,14.7)	42 (34, 61)
			>8	24	8	29 (94)	28 (90)	12.6 (11.8,14.5)	57 (24, 89)
Total				**155**	**76**	**208 (92)**	**182 (81)**	**9.3 (3.1,21.3)**	**65 (21, 95)**

Table 1. Individuals exposed to CJD through surgery, summarised by elements considered at risk assessment[4]

1. High infectivity procedures involve surgery on the Central Nervous System tissues of the brain and posterior eye. All but one medium infectivity procedure involved lymphoid tissues of the gut
2. Excludes 6 individuals for whom date of death is not known
3. Two individuals classified as "at increased risk" at the time of the surgical incident later developed clinical symptoms
4. According to the assumptions made about the factors influencing the risk of surgical transmission, the level of risk is presented in decreasing order



Neurological conditions	Cause of Death	Contributing condition
Glioblastoma	7	3
Oligodendroglioma	2	
stroke	2	
sub arachnoid haemorrhage	2	1
Alzheimer's Disease	1	2
cerebral tumour unspecified	1	
Epilepsy (SUDEP)	1	
head injury	1	
meningioma	1	
Ependymoma (u/l)	0	1

Figure 2. Summary cause of death including neurological conditions identified

DISCUSSION

Long term monitoring of exposed patients following CJD surgical incidents is designed to detect the development of clinical CJD amongst surgical contacts, even if this occurs many years later or is diagnosed in a different part of the country. This approach would have detected the documented historic instances of CJD attributed to contaminated surgical instruments in the UK, should such circumstances arise today [3].

The likelihood of surgical transmission has decreased following awareness of the dangers and introduction and strengthening of specific CJD infection control measures. However, inadvertent surgical exposure has been reported from several countries [4-6], and will likely continue to occur although perhaps infrequently.

Meanwhile, scrutiny of potential iatrogenic transmission has increased and despite these known incidents, no new transmission via surgical instruments has been recognised for several decades. While this is reassuring, that the frequency and risk of such transmission may be low, there are several factors to consider before ruling out the possibility that surgical transmission has occurred in the UK or elsewhere.

It is difficult to quantify and scale the actual exposure, if any, for CJD surgical contacts. The potential infectious dose and the site of inoculation vary. The longest follow-up time in our cohort is in excess of 20 years but is much shorter for more recent incidents. Since the main reliance on detecting transmission is the observation of clinical cases the development of symptoms following peripheral exposures or a low dose inoculum may take much longer than the current follow-up times. The role of host genetic factors and CJD strain type is not accounted for.

In addition, those presumed as having the highest risks of transmission, following exposure to high infectivity neural tissues, are also those with shortened survival times from the underlying condition which required the surgery. Our approach is limited in being able to detect pre-symptomatic infection. Post-mortem review information is incomplete and no tissues which could be investigated for preclinical signs of infection have been available.

CONCLUSIONS

- CJD surgical incidents are rare but have continued to occur.
- Systematic follow-up of surgical contacts in the UK since 2000 has not identified any associated development of CJD to date.
- Public Health follow-up will continue long term to add to the body of evidence informing the transmission risks of CJD through modern surgery.

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