Risk of transmission of neurodegenerative disorders through blood transfusions: a retrospective cohort study

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Background

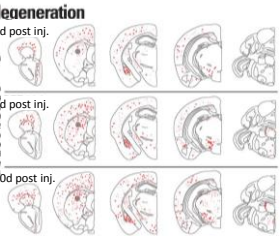
- Since the 1980's, the transfusion medicine community has maintained a strong track record for dealing with new threats to the blood supply
- However, the current approach for detecting and managing emerging TTIs may not be able to manage
  - Diseases with long induction times
  - Poorly understood/recognized diseases
  - Unexpected / unconventional pathogens
  - Common diseases
- Recent data indicates a possible prion-related (and hence possibly transfusion transmitted) etiology for several neurodegenerative diseases – potentially very large consequences

Science 338, 949 (2012);

Pathological α-Synuclein Transmission Initiates Parkinson-like Neurodegeneration in Nontransgenic Mice

Kelvin C. Luk, Victoria Kehm, Jenna Carroll, Bin Zhang, Patrick O'B
John Q. Trojanowski, Virginia M.-Y. Lee*

Parkinson's disease is characterized by abundant α-synuclein (α-Syn) neu as Lewy bodies and Lewy neurites, and the massive loss of midbrain dop cause-and-effect relationship between Lewy inclusion formation and unclear. Here, we found that in wild-type nontransgenic mice, a single in synthetic α-Syn fibrils led to the cell-to-cell transmission of pathologic α- Lewy pathology in anatomically interconnected regions. Lewy pathology a progressive loss of dopamine neurons in the substantia nigra pars compa ventral tegmental area, and was accompanied by reduced dopamine level deficits. This recapitulation of a neurodegenerative cascade thus establishe transmission of pathologic α-Syn and the cardinal features of Parkinso



Intracerebral inoculation of α-Syn fibrils → Cell-cell transmission of α-Syn fibrils → Loss of dopamin neurons (Lewy pathology) → Gradual development of motor deficits

Science 330, 980 (2010)

Peripherally Applied Aβ-Containing Inoculates Induce Cerebral β-Amyloid

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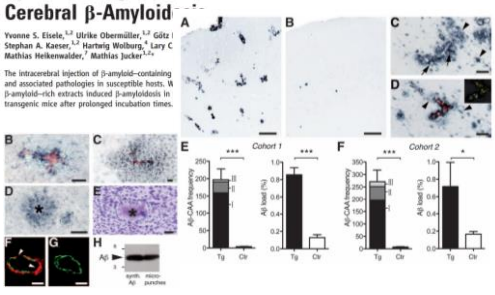
Stephan A. Kaeser,[1,2] Hartwig Wolburg,[4] Lary C
Mathias Heikenwalder,[1] Mathias Jucker[1,2]*

The intracerebral injection of β-amyloid–containing and associated pathologies in susceptible hosts. W β-amyloid–rich extracts induced β-amyloidosis in transgenic mice after prolonged incubation times.



CELL BIOLOGY

22 JUNE 2012 VOL 336 SCIENCE

A Unifying Role for Prions in Neurodegenerative Diseases

Stanley B. Prusiner

A profound change in thinking about the etiologies of many neurodegenerative diseases has far-reaching implications for developing therapeutics.

Prion diseases	Precursor proteins	Prion forms	Protein deposits	Self-propagation in mammals	Self-propagation in cultured cells	References
CJDiscrapie	PrP^C	PrP^{Sc}	PrP plaques	inoc apes, monkeys, wt mice & Tg mice	N2a, GT1	(1–13)
Alzheimer's	APP	Aβ	Aβ plaques	inoc marmosets & Tg(ΔAPP) mice		(14–24)
Tauopathies (FTD, PSP, Pick's, CTE)	tau	tau aggregates	NFTs, Pick bodies	inoc Tg(HuTau), inoc Tg(HuTau,P301S) & inducible Tg(HuTau, ΔK280) mice	C17.2, HEK293	(25–32)
Parkinson's	α-synuclein	α-synuclein aggregates	Lewy bodies	Lewy bodies in grafts & inoc Tg(HuSNCA,H53T) mice	Primary mouse hippocampal neurons	(33–39)
fALS	ΔSOD1, ΔTDP43	ΔSOD1 aggregates	Bunina bodies		N2a, HEK	(40–43)
Huntington's	ΔHtt	ΔHtt aggregates	Nuclear inclusions		Cos7	(44–47)

Abbreviations: CJD, Creutzfeldt-Jakob disease; PrP, prion protein; inoc, intracerebral inoculation; wt, wild-type; Tg, transgenic; APP, amyloid precursor protein; Aβ, amyloid beta; FTD, frontotemporal dementia; PSP, progressive supranuclear palsy; CTE, chronic traumatic encephalopathy; NFTs, neurofibrillary tangles; fALS, familial amyotrophic lateral sclerosis; ΔSOD1, mutant superoxide dismutase; ΔHtt, mutant huntingtin.

Reason to worry?

Lancet 356, 999-1000 (2000)

RESEARCH LETTERS

Research letters

Transmission of BSE by blood transfusion in sheep

F Houston, J D Foster, Angela Chong, N Hunter, C J Bostock

See Commentary page 955

Lancet 363, 417-421 (2004)

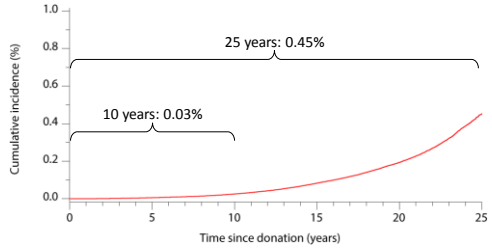
Clinical presentation and pre-mortem diagnosis of variant Creutzfeldt-Jakob disease associated with blood transfusion: a case report

Stephen J Wroe, Suvankar Pal, Dominique Siddique, Harpreet Hyare, Rebecca Macfarlane, Susan Joiner, Jacqueline M Linehan, Sebastian Brandner, Jonathan D F Wadsworth, Patricia Hewitt, John Collinge

Conceptual TTI risk model

Clinical consequence ≡ [Prevalence of agent in blood donors] × [Infectivity/ transmissibility] × [Probability that recipient lives long enough]

Alzheimer's disease



Results

Clinical consequence ≡ [Prevalence of agent in blood donors] × [Infectivity/ transmissibility] × [Probability that recipient lives long enough]

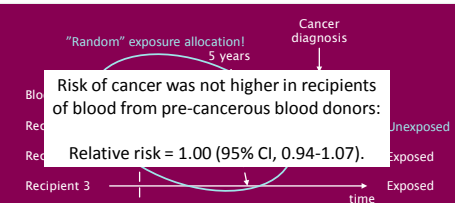
Disease	10 yr. cumulative incidence	Expected 10 yr. survival	Expected cases per 100,000 transfusions (5% infect.)	Expected cases per 100,000 patients (5% infect.)
Alzheimer's disease	0.03%	0.3	0.5	2.2
Parkinson's disease	0.03%	0.3	0.4	1.9
Amyotrphic lateral sclerosis	0.02%	0.3	0.3	1.7
Dementia, unspecified	0.08%	0.3	1.2	4.7

Example: Cancer as a TTD?

The Lancet 2007; 369:1724-30

Risk of cancer after blood transfusion from donors with subclinical cancer: a retrospective cohort study

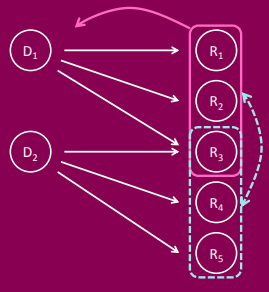
Gustaf Edgren*, Henrik Hjalgrim*, Marie Reilly*, Trung Nam Tran, Klaus Rostgaard, Agneta Shanwell, Kjell Tillestad, Johanna Adami, Agneta Wikman, Casper Jersild, Gloria Gridley, Louise Wideroff, Olaf Nyrén, Mads Melbye



Risk of cancer was not higher in recipients of blood from pre-cancerous blood donors:

Relative risk = 1.00 (95% CI, 0.94-1.07).

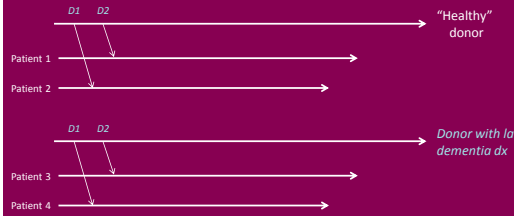
Transmission analyses (1)



Approach 1:
Are recipients risk increased if their donors develop disease?

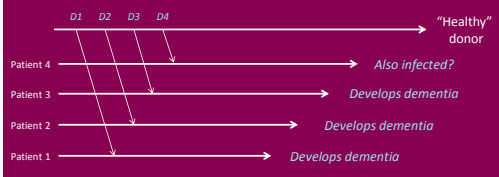
Approach 2:
Do all recipients of blood from one specific donor have a shared increased risk?

Transmission analyses (2)



Are patients 3&4 at inreased risk compared to patients 1&2?

Transmission analyses (3)



Do patients 1-4 have a "shared" increased risk?

SCANDAT 2

- Data on 1.7 million donors and 2.1 million patients in Sweden and Denmark since 1960's and 1980's, respectively
- Ability to track transfusions between donors and their respective recipients
- Linkages with a range of health outcome registers providing follow-up for various health outcomes through 2012

Methods

- Retrospective cohort analysis based on SCANDAT2 database
- All patients followed from first transfusion until death or diagnosis of neurodegenerative disease (Dementia, Alzheimer's, Parkinson's, or ALS)
- Two sets of analyses:
  - →Transmission analyses, assessing effect of receiving blood from diseased donor
  - →Cluster analyses, assessing if certain donors' blood increases risk (without donor necessarily becoming ill)
- Methods validated using chronic hepatitis

Validation analyses: transmission of chronic hepatitis

- Relative risk before 1992 = 8.36 (95% CI, 7.25-9.63)
- Relative risk after 1992 = 1.19 (95% CI, 0.72-1.95)

Number of patients with a later hepatitis diagnosis the donor has donated blood to	RR of chronic hepatitis in "next" recipient (before 1992)	RR of chronic hepatitis in "next" recipient (after 1992)
No prior recipients	1.0 (ref)	1.00 (ref)
1-4 recipients	1.32 (1.19-1.46)	1.07 (0.97-1.20)
≥5 recipients	3.33 (2.55-4.36)	1.29 (0.76-2.22)

Overall dementia transmission

- Overall relative risk, relative risk = 1.04 (95% CI, 0.99-1.09)
- <5 year latency, relative risk = 1.05 (95% CI, 0.89-1.22)
- Young onset in donor (<65 yrs), relative risk = 1.05 (95% CI, 0.97-1.14)

Number of patients with later dementia the donor has donated blood to	Relative risk of dementia in "next" recipient
No prior recipients	1.00 (ref)
1-4 recipients	1.01 (0.99-1.03)
5-9 recipients	1.03 (0.98-1.07)
≥10 recipients	1.06 (0.87-1.30)

Alzheimer's disease transmission

- Overall relative risk, relative risk = 0.99 (95% CI, 0.85-1.15)
- <10 year latency, relative risk = 0.73 (95% CI, 0.38-1.41)
- Young onset in donor (<65 yrs), relative risk = 0.79 (95% CI, 0.56-1.11)

Number of patients with later AD the donor has donated blood to	Relative risk of AD in "next" recipient
No prior recipients	1.00 (ref)
1-3 recipients	1.01 (0.98-1.04)
≥4 recipients	1.14 (0.81-1.60)

Parkinson's disease transmission

- Overall relative risk, relative risk = 0.94 (95% CI, 0.78-1.13)
- <10 year latency, relative risk = 1.10 (95% CI, 0.83-1.47)
- Young onset in donor (<65 yrs), relative risk = 0.88 (95% CI, 0.66-1.16)

Number of patients with later PD the donor has donated blood to	Relative risk of PD in "next" recipient
No prior recipients	1.00 (ref)
1-2 recipients	1.01 (0.98-1.04)
≥3 recipients	1.14 (0.81-1.60)

ALS transmission

- Overall relative risk, relative risk = 1.83 (95% CI, 0.87-3.88)
- <10 year latency, relative risk = 2.25 (95% CI, 0.84-6.05)
- Young onset in donor (<65 yrs), relative risk = 1.21 (95% CI, 0.39-3.79)

Number of patients with later ALS the donor has donated blood to	Relative risk of ALS in "next" recipient
No prior recipients	1.00 (ref)
1 recipient	0.95 (0.69-1.31)
2 recipients	0.00 (n.e.)

Conclusions

- Analyses based on SCANDAT2 indicate that even with (speculatively) high transmission rates, possible consequences on transfusion safety are limited
- Although recent animal model data suggest a prion-related etiology behind a range of neurodegenerative diseases, we find no sign of such transmission

Acknowledgements

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