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

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

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

Reason to worry?

Transmission of BSE by blood transfusion in sheep

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

Clinical consequence: Prevalence of agent in blood donors × Infectivity/ transmissibility × Probability that recipient lives long enough.

**Alzheimer’s disease**

<table>
<thead>
<tr>
<th>Disease</th>
<th>20 yr cumulative incidence</th>
<th>Expected 10 yr survival</th>
<th>Expected cases per 100,000 transfusions (5% infect.)</th>
<th>Expected cases per 100,000 patients (5% infect.)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Alzheimer’s disease</td>
<td>0.03%</td>
<td>0.3</td>
<td>0.5</td>
<td>2.1</td>
</tr>
<tr>
<td>Parkinson’s disease</td>
<td>0.03%</td>
<td>0.3</td>
<td>0.4</td>
<td>1.0</td>
</tr>
<tr>
<td>Amyotrophic lateral sclerosis</td>
<td>0.02%</td>
<td>0.3</td>
<td>0.3</td>
<td>1.7</td>
</tr>
<tr>
<td>Dementia, unspecified</td>
<td>0.08%</td>
<td>0.3</td>
<td>1.2</td>
<td>4.7</td>
</tr>
</tbody>
</table>

**Example: Cancer as a TTD?**

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 at increased risk if their donors develop disease?
- **Approach 2:** Do all recipients of blood from one specific donor have a shared increased risk?

**Transmission analyses (2)**

- “Healthy” donor
- Donor with later dementia dx

Are patients 3&4 at increased risk compared to patients 1&2?
Transmission analyses (3)

"Healthy" donor

Also infected?

Develops dementia

Develops dementia

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

SCANDAT 2

DONORS

DONATIONS

TRANSFUSIONS

RECIPIENTS

- 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)

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)

<table>
<thead>
<tr>
<th>Number of patients with later dementia donor has donated blood to</th>
<th>Relative risk of dementia in &quot;next&quot; recipient</th>
</tr>
</thead>
<tbody>
<tr>
<td>No prior recipients</td>
<td>1.00 (ref)</td>
</tr>
<tr>
<td>1-4 recipients</td>
<td>1.01 (0.99-1.03)</td>
</tr>
<tr>
<td>5-9 recipients</td>
<td>1.03 (0.98-1.07)</td>
</tr>
<tr>
<td>≥10 recipients</td>
<td>1.06 (0.87-1.30)</td>
</tr>
</tbody>
</table>

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)

<table>
<thead>
<tr>
<th>Number of patients with later AD donor has donated blood to</th>
<th>Relative risk of AD in &quot;next&quot; recipient</th>
</tr>
</thead>
<tbody>
<tr>
<td>No prior recipients</td>
<td>1.00 (ref)</td>
</tr>
<tr>
<td>1-3 recipients</td>
<td>1.01 (0.98-1.04)</td>
</tr>
<tr>
<td>≥44 recipients</td>
<td>1.14 (0.83-1.56)</td>
</tr>
</tbody>
</table>
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)

<table>
<thead>
<tr>
<th>Number of patients with later PD who the donor has donated blood to</th>
<th>Relative risk of PD in “next” recipient</th>
</tr>
</thead>
<tbody>
<tr>
<td>No prior recipients</td>
<td>1.00 (ref)</td>
</tr>
<tr>
<td>1-2 recipients</td>
<td>1.01 (0.98-1.04)</td>
</tr>
<tr>
<td>≥3 recipients</td>
<td>1.14 (0.81-1.60)</td>
</tr>
</tbody>
</table>

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)

<table>
<thead>
<tr>
<th>Number of patients with later ALS who the donor has donated blood to</th>
<th>Relative risk of ALS in “next” recipient</th>
</tr>
</thead>
<tbody>
<tr>
<td>No prior recipients</td>
<td>1.00 (ref)</td>
</tr>
<tr>
<td>1 recipient</td>
<td>0.95 (0.69-1.31)</td>
</tr>
<tr>
<td>2 recipients</td>
<td>0.00 (n.e.)</td>
</tr>
</tbody>
</table>

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

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