Risk Factors for Nerve Impairment

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Outline

- About risk factors
- Literature review
- Classified risk factors
- Validation using the INFIR data
- Illustration
Identifying risk factors

- **Logistic Regression**
  - How outcome relates to predictive variables
    - Death/survival, positive/negative
  - **Odds ratios**
    - The increased risk attached to one value of a predictor variable as compared to another

- **Proportional Hazard Regression**
  - Includes time adjustment
  - **Hazard Ratios**

- **Examples:**
  - Death rates associated with smoking or drinking

What are the risk factors for nerve impairment in leprosy?

- Search relevant publications
- Indexed by keyword in title or abstract.
  - “Leprosy” plus (“risk” or “factor” or “predict”)
- Focus on clinical rather than genetic or immunological
- At least 32 relevant papers
Risk factors classified into four groups

- Personal and demographic
- Visible signs
- Advanced stage of nerve involvement
- Others

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Personal and demographic

- Sex
- Age, age >40
- Mode of case finding, passive case finding or self-reporting
- Pregnancy, lactation
- Duration of symptoms, delay > 12 months
- Stress
Visible signs

- Leprosy group
- Leprosy classification - borderline leprosy
- Smear BI - positive smear
- Number of body areas - >= 3 body areas
- Number of skin lesions - >= 6 skin lesions
- Number of enlarged/palpable nerves - >= 2
  - ulnar or lateral popliteal enlargement
- Lesions overlying nerves
  - Specifically facial involvement

Advanced stage

- WHO Grade 1 and/or WHO Grade 2
- EHF score
- Pre-existing sensory loss
  - By nerve, or in total
- Pre-existing motor loss
  - By nerve or in total
Other

- Clinical/physical state
  - BCG
  - Tuberculosis
  - Trauma
  - Inter-current infection
  - Time since start of MDT
- Anti PGL1_IgM seropositivity

Are these risk factors relevant?

- What population was studied?
  - MB alone, mix of MB and PB
  - Variety of study designs and sample sizes
- What definitions were used?
  - MB/BP leprosy?
  - Which sensory or motor functions assessed and how?
  - What constituted a (treatable) change?
- What coding system and relative frequencies?
- What outcome variable was used in the analysis?
  - RR, NFI within RR, NFI alone (SN), NFI with ENL?
Are any of them applicable?

- Possibly
  - Could re-analyse BANDS, AMFES, Schreuder/Thailand, INFIR and other data sets

- Following reports risk factors for nerve impairment using the INFIR Cohort Study data set

The INFIR data set

- 303 cases
- Up to 24 months follow-up – 4,767 visits
- MB leprosy only
- For this analysis:
  - Excluded individuals with baseline reaction
  - 188 individuals, 74 had incident events, 52 included incident changes detected by MF or VMT
Analysis Methodology

- Cox Proportional Hazard regression using STATA
- Outcome:
  - Incident, treatable change in nerve function detected by MF or VMT
- Univariate analysis of listed predictor variables
  - Stepwise analysis to obtain a simplified predictive model

Health warnings
- Prefer a larger N.

Demographic and personal predictors in INFIR

- Age – Increasing age carries greater risk (p<0.001)
  - Age groupings above 30 years or 40 yrs also p<0.001
- Sex, delay beyond 12 months, stress – Not sig.
- Variables not available or very small numbers:
  - Mode of case finding, passive or self-reporting
  - Pregnancy, puerperium, lactation
Visible signs in INFIR

- Count of enlarged nerves (p<0.001)
- But none of the following:
  - R Jclassification (BT, BL or LL)
  - Positive smear,
  - >=3 body areas, >=10 skin lesions, >=2 enlarged nerves, lesions overlying nerves
  - Facial involvement
- Not available:
  - Leprosy group - no PB cases

Advanced stage in INFIR

- WHO Grade
  - Grade 1 – p<0.05
  - Grade 2 – p<0.01
- EHF score – not statistically significant
- Any pre-existing sensory loss – p<0.001
- Any pre-existing motor loss – not statistically significant
- Any nerve tenderness – p<0.05
Others in INFIR

- Inter-current infection – not statistically significant
- Anti PGL1_IgM seropositivity – not statistically significant
- Not available
  - BCG
  - Tuberculosis – excluded from INFIR study
  - Trauma

Summary of simple (univariate) predictors in INFIR

- Age
- Pre-existing sensory loss
- Count of enlarged nerves
- WHO Grade 2

- Stepwise analysis produces best predictive model
Predictive model

- Primary risk factors:
  - Pre-existing sensory loss, HR 4.93 (2.24 – 10.86), p<0.001
  - Age > 30 year, HR 3.25 (1.82 – 5.81), p<0.001

- Secondary risk factors:
  - More than 5 enlarged nerves, HR 2.11 (1.09 – 4.08), p<0.05
  - WHO Grade 1 has a protective effect, HR 0.44 (0.21 – 0.89), p<0.05

- Approaching statistical significance:
  - Delay less than 12 months
  - More than 10 lesions
  - BT or BL classification
  - High levels of PGL1_IgM

Application of the primary model

<table>
<thead>
<tr>
<th>Number of predictive factors present</th>
<th>Cases with new nerve impairment</th>
<th>Cases with no new nerve impairment</th>
<th>Total (N)</th>
</tr>
</thead>
<tbody>
<tr>
<td>None</td>
<td>6.5%</td>
<td>93.5%</td>
<td>92</td>
</tr>
<tr>
<td>One</td>
<td>43.3%</td>
<td>56.7%</td>
<td>67</td>
</tr>
<tr>
<td>Two</td>
<td>58.6%</td>
<td>41.4%</td>
<td>29</td>
</tr>
</tbody>
</table>

- Identify low and high risk groups
Additional risk factors identified in the INFIR Cohort Study

- Deterioration in:
  - Ulnar above elbow (proximal) motor nerve conduction amplitude or latency
  - Ulnar, median, radial or sural sensory nerve conduction amplitude or latency
  - Posterior tibial or sural cold or warm sensation
High risk individual: Male/40/BL

Sensory loss by MF in ulnar at 18 months.
Impaired SNC Amp in 4 nerves

Normal ulnar and median and impaired lateral popliteal MNC proximal and distal amplitude
Conclusions

- Yes! We have risk factors for new nerve impairment in MB leprosy:
  - Will vary according to the patient group and definitions
  - For MB, age over 30 years and history of sensory loss at diagnosis are important

- BUT, more to this than meets the eye.
  - What measures of nerve status are really important?
  - What implications for detecting, treating and preventing impairment?

Oral Sessions on INFIR Study, Sunday, from 3pm.

References - 1

References - 2


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