Childhood Leukemia and ELF Fields Progress Report

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Hematopoiesis

Prenatal
- Yolk sac
- Liver
- Bone marrow
- Spleen

Postnatal
- Vertebral and pelvis
- Sternum
- Rib
- Lymph nodes
- Femur

Cellularity (%)

Fetal months
0 1 2 3 4 5 6 7 8 9

Age in years
0 10 20 30 40 50 60 70

1st hit preleukemic clone
2nd hit(s)

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Leukemiaspecific chromosomal translocations as 1st hits


Mori et al. PNAS 2002

Olsen et al. JPHO 2011
Lausten-Thomsen et al. Blood 2011
Childhood leukemia and ELF

IARC 2002: "Possibly carcinogenic to humans" (Group 2B)

Pooled analysis of Kheifets et al. 2010:
- 7 case control studies
- 10 865 cases, 12 853 controls
- 24h measurements or calculated fields

since 2010:
new studies in France, Italy, UK, Denmark and California,…
IF..... the association is causal

- it is more likely, that magnetic fields are second hits

- depending on the exposure-response model, up to 2% of the annual number of CL cases is attributable to magnetic fields in EU (27 countries) – appr. 50 to 60 cases

Grellier et al. Environ Int 2014
Why ..... is progress so slow?

- CL is a rare disease (~5 per 100,000) and only ~0.5% of the kids are exposed > 0.3µT
- CL is a complex disease – different risk factors might exist at different time windows
- All we know is coming from case-control-studies facing methodological limitations (confounding, exposure misclassification, selection and recall bias)
- Origin and development of the disease cannot be elucidated retrospectively by studying cases
- Only few suitable animal models available
- Current research activities focus on therapy
2008 ICNIRP/WHO/BfS Workshop
….. other environmental and genetic risk factors are not more risky than ELF - new ways are needed

2010 Strategic Research Agenda
Initiation of 5 pilot studies

2012 BfS/IRSN/MELODI Workshop
From unexplained findings to recommendations for future research
Laurier et al. J Radiol Prot 2014

2014 BfS Workshop
Pilot studies under discussion

Nov 2016 - 5th Workshop
Status report and how to go on
Development of a new tool to detect the most common chromosomal translocations

Fueller et al. PLoS ONE 2014

- 1 µg DNA needed
- sensitivity between 24% and 83%
- 100% specific (no false positive)
- ready to be used in prospective studies
  e.g. in a (German) birth cohort

**objectives:**
- collaborative studies
- identify causes
- information exchange
Deep sequencing of 10 B-cell ALL cases
(TCF3-HLF with poor prognosis versus TCF3-PBX1)

- next generation sequencing (genome, exome, transcriptome, epigenome and miRNome): comparing subgroups revealed similar patterns within subgroup

- findings allowed drug design, „individualized medicine“

Published in final edited form as:


Genomics and drug profiling of fatal TCF3-HLF-positive acute lymphoblastic leukemia identifies recurrent mutation patterns and therapeutic options

Fischer et al. *Nat Genet* 2015
Review on animal models

Recapitulate human pathology... in the mouse

regarding
- origin
- progression
- therapy
- relapse

Hauer et al. Cell Cycle 2014
Engineering of a transgenic mouse model that mimics the most common translocation

- predisposed animal model (Sca1-ETV6-RUNX1) showed reduction of cytotoxic CD8+ T-cells under ELF exposure

- similar results in CD1-rats

- one out of 30 Sca1-ETV6-RUNX1-mice developed pB-ALL (1.5 mT), none of 65 controls
Old data/hypotheses get new support: immune system is involved….

- epidemiological data on daycare,…
- experimental studies
Latest risk assessment in 2015 following the IARC evaluation scheme

Cancer in humans
- Limited evidence

Cancer in experimental animals
- Inadequate evidence

Mechanistic and other relevant data
- Weak

Overall evaluation
Group 2B  Possibly carcinogenic to humans

Schüz et al. Bioelectromagnetics 2016

new data are consistent with the IARC classification of „possibly carcinogenic to humans“ (Group 2B)

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Summary and the way forward

- Prospective study designs become feasible with the newly developed tool to detect the most common translocations.

- With the use of a birth cohort (cord blood samples) the frequency of the preleukemic clone can now be determined – newborns with the preleukemic clone can be intensively monitored (e.g. immune status) – goal: prevention measures.

- The new transgenic mouse model (Sca1-ETV6-RUNX1) is ready to be used in exposure experiments (ELF and other risk factors).

- ELF exposure reduced CD8\(^+\) T-cells – their role in carcinogenesis has to be clarified.

- The established international network GALnet allows new comparative study designs.

- Deep sequencing of CL cases exposed > 0.3µT is a „must“, special focus on epigenetic changes.
Next time.....

.....we are 1 step further!

Thanks for your attention!  Gunde Ziegelberger