A-T
Clinical Research Conference 2014

Nijmegen, The Netherlands
13-15 november 2014

Radboudumc

Mild phenotypes

Bart van de Warrenburg

- Variant phenotypes: spectrum from complex to isolated tremor at 30 yrs
- MRI can be normal in rare cases (without cerebellar atrophy)
- Attention to: dystonia-predominant AT (incl. myoclonus-dystonia like)
- Dystonia may be remarkably L-dopa responsive

Altered corticomotor-cerebellar integrity in young A-T patients

Ishani Sahama

- Paper in Cerebellum 2014 en Mov Dis 2014
- Diffusion MRI: tractography shows neuronal degeneration

Immunodeficiency in A-T

Mirjam van de Burg

- Most patients lack B and T cells
- IvIg replacement necessary in different phenotypes (ATM protein +/-)
- Immune deficiency is stable over time, although Ig levels may vary over time
- Decreased BM output and increased proliferation of naïve mature B-cells
- Class switching: less switching to downstream elements in AT (IgG1 dominates)
- Papers: Driessen JACI 2013, Khair J Immunol 2014

Oncology: retrospective study of treatment

Jan Loeffen

- Many problems, few answers
- Need for international registry
- Succesful treatment of German patient with Hodgkins disease with brentuximab (see also poster)

Growth, immunocompetence and lung disease in AT

Stefan Zielen

- Multiple factors cause airway disease
- Growth homone – IGF axis is disturbed in many patients
- Body weight and BMI are often low and linked to shortened survival
- Lymphopenia and IgA deficiency are linked
- IgA: prognostic marker in classical AT?
- Loss of lung function
- Progressive impaired gas exchange
- Patients with AT versus asthma (during 2 yrs): cough, runny nose, fever in AT >> asthma → mild symptoms occur OFTEN while severe infections don't
- Paper: Pietzner in HMG 2013 (BMT in AT mice)
- **First BMT in AT in Frankfurt: boy born 5/2007, diagn 8/2010, BMT 12/2012), restoration of immunology, neurology?**

Steroid therapy

Luciana Chessa

- Dexamethasone sodium phosphate in autologous erythrocytes (EryDel)
- Paper: Chessa, Orphanet J Rare Dis, Jan 2014
- Steroids improve ataxia and OMA, not EP mov dis and neuropathy
- Study: n=180; 60 placebo, 60 low dose, 60 high dose; 1x/month infusion; 12 months

Introduction WS-1A (BMT)

Marek Ussowicz

- Case: 3 yr old boy with AT and ALL (originallly misdiagnosed as atactic CP)
- Follow-up 66 months: immuno / hematology good; neurology stable (?, no good follow-up, ‘able to walk’)
- During steroid therapy for ALL: neurology better
- Literature plus unpublished: BMT in AT, n=5 (incl Frankfurt case), 3/5 died
- Gatti: there are 4 or 5 more unpublished cases (unpublished, failures)

Introduction WS-1B (Respiratory management)

Jayesh Bhatt

- Consensus statement will be published (Bhatt, Merkus for ERS Task Force)
- Lung disease (data from AT society, 1982-2014): cause of many deaths in AT
- Progression accelerates after diagnosis of bronchiectasis
- Surveillance microbiology: often positive (viral and bacterial) cultures, comparable to CF
- Aspiration is often silent and common; ATM mice are more sensitive for gastric acid than controls
- Interstitial lung disease 97/437 resp symptoms or caues of death*
- Task force: many Q's left
- Management: Mcshane AJRCCM 2014, Felix Ped Pulm 2014, Leifton Graff 2011 (on PEG); *Schroefer Ped Pulm 2005

Introduction WS-2A (ATM carriership)

Nienke van Os

- Increased cancer risk!
- Risks beyond malignancies?
  - Cardiovascular disease: diabetes type 2, atherosclerosis, …
  - Radiosensitivity: ‘intermediate’ (experimental); ? (observational studies)
  - Neurodegenerative disease: Parkinson, Alzheimer
  - Others: schizofrenia, altered response to (chemoth) drugs, fertility, telangiectasia
- Carriers may have lower ATM protein and kinase levels
- Plan: cohort study in NL
- Goal: guideline for carriers (discussion in workshop)
- Mitral valve prolapse occurs more often (suggestion by Chessa)

Introduction WS-2B (Immunology)

Asgeir Haraldsson

- IvIg for prevention of infections and for immunomodulation
- Immunomodulation, indications for IvIg: …., Haraldsson, J All Clin Immunol 2013;131(6); review in NEJM nov 2012
- AT with high IgM: bad prognosis (n=7, all died < 14 yr); relation with development of granulomas

Summary of workshop 1A

MALCOLM TAYLOR / TATJANA STANKOVIC

Malignancies
. Spectrum of tumours (adults vs childhood), generally with poor outcome
. Particular AT patient has risk for particular tumour? E.g. IgA defic and lymphoma?
. Screening for malignancies? Maybe in particular mutations? In monoclonal T-cell development? Hyper-IgM in NBS and lymphoma
. New: brentuximab for Hodgkin lymphoma (Frankfurt)
. PLAN: small meeting summer 2015 to decide on detail required

BMT
. Discussion on indication: high risk tumours (+), immunodefic (maybe), classical AT without ATM activity (??). No consensus.
. Reduced conditioning and low chimerism are desirable.
. Predictors of success?
. Long term benefits vs consequences?
. No consensus on “profylactic” BMT

Summary of workshop 1B

HOWARD LEDERMAN

Respiratory management / swallowing / gastrostomy
. Need better communication among professionals
. Need more pro-active approach
. Issues: inadequate caloric intake, aspiration etc
. Start early therapy to improve lung function: exercise, breathing, muscle training
. Start early cardiovascular exercise
. Early PEG? No consensus
. Discussion: scoliosis surgery very dangerous!
. Adequate pre-operative management is important
. PLAN: sharing e-mail addresses of all participants of this meeting

Summary of workshop 2A

NIENKE VAN OS

Cancer risks for carriers (focus: breast cancer)
. Life time risk to develop breast cancer: 28-49%
. Screening via regular national programs? No, start earlier namely at 40 (instead of 50) yrs; discussion about intervals (every 1 or 1.5 or 2 yrs?)
. MRI instead of mammograms? No, insufficient evidence for deviating from standard
. Particular mutations may necessitate particular screening programs
. IMPORTANT: prospective studies
. PLAN: submit review and guideline

Summary of workshop 2B

MARCEL VAN DEUREN

Immunology (AB profylaxis and IvIg)
. Generally accepted: conservative approach, i.e. ‘first do no harm’
. However, beware of: under-reported infections, subclinical infections, undetected infections may warrant a more ‘aggressive’ approach
. Need for clinical trials
. PLAN: task force (via sharing e-mail addresses)

William Davis: AT society will help building a registry for AT patients, coupled to the ESID registry for immunodeficiences; e-mail addresses will be shared and messages will be send around; a meeting will be organized in Paris in spring 2015

Telangiectasia

Jolanda Schieving

- Introduction to neurocutaneous disorders and the definition of telangiectasia
- Differential diagnosis of telangiectasia, with and without neurologic disease, e.g. hereditary haemorrhagic telangiectasia (Rendu-Osler-Weber) and Bloom syndrome
- Hypothesis on pathophysiology of telangiectasia: TGF-beta pathway, incl ALK1, ALK5 and endoglin genes, triggered by DNA-damage?
- Discussion: microbleeds in the brain do occur in AT, due to CNS telangiectasia; Loeys-Dietz syndrome is linked to TGF-beta

AT beyond 30

Marcel van Deuren

- Lessons from two patients:
  - male, classical AT, born 1970, died 2010 (low Ig's yet no infections, osteoporosis)
  - male, classical AT, born 1960, died 2014 (watermelon stomach, prostate carcinoma)
- Dutch population: 17 patients lived > 30 yrs; two mutations (at c.8147 and c.331) were typically found in these (older) patients
- Literature: thesis Mijke Verhagen 2012; J Neurol Sciences, Marie Y Davis, dec 2013

Posters and orals: prices

Best abstract, presentation:

HG Gregorek (from Poland) on immune system in AT and NBS

Best abstract, poster:

TJ Jackson (from UK) on long-term course of neurological features of AT

Next meeting

- ATW 2015: Beijing, Oct 11-14, 2015; www.ddrhd.org
- AT CRC 2016: ?