# THIRD ATAXIA-TELANGIECTASIA CLINICAL RESEARCH CONFERENCE 2016

# WARSAW, POLAND

My name is Natalie Elkheir. Five years ago, my then 3 year old daughter was diagnosed with Ataxia Telangiectasia. Overnight, I found myself thrust into a journey of research and self-education, spending countless hours reading medical journals, scientific papers and health and nutrition books in an attempt to better understand the intricate complexities of our biology. Alas, I have not discovered a cure for A-T hidden amongst the millions of words I've read. However, I have gained an extraordinary appreciation for the many doctors and researchers who have dedicated themselves to our cause from around the world. Their efforts fuel my hope that, one day, we will discover the elusive cure for A-T.

I am a strong believer in being pro-active towards my ultimate hopes of a cure being discovered. To this end, I am actively involved with BrAshA-T Ataxia Telangiectasia Limited, and participate in regular fundraising initiatives. It was a pleasure and a privilege to recently attend the 2016 Ataxia Telangiectasia Clinical Research Conference in Warsaw, Poland, on behalf of BrAshA-T. My notes from some of the standout presentations at that conference follow.

**Role of Oxidative Stress in Pulmonary Disease in Ataxia Telangiectasia – Professor Martin Lavin, Brisbane, Australia**

Professor Martin Lavin outlined his upcoming BrAshA-T funded project investigating lung disease in A-T patients, with sample collection due to commence at the November 2016 clinic in Brisbane. Prof Lavin discussed how diseases of the respiratory system such as recurrent sinopulmonary (nasal sinus passages and airways of the lungs, form part of the upper respiratory tract) infections, bronchiectasis (permanent enlargement of parts of the airways of the lung, increasing risk of infection) and interstitial lung disease (occurs when the tissue between the air sacs of the lungs is affected by inflammation or scarring) account for up 40% of deaths in A-T patients. He pointed out that the involvement of oxidative stress has long been established to play a role in the A-T phenotype, and hypothesised that oxidative stress due to recurrent sinopulmonary infections contributes to the development of lung disease in A-T patients. It is believed that micro-organisms such as *Streptococcus pneumoniae* found in the upper respiratory tract of A-T patients secrete hydrogen peroxide ($H_2O_2$), which is known to cause oxidative damage. The project aims to identify the micro-organism composition of the upper respiratory tract of A-T patients, collect and culture nasal epithelial cells from A-T patients, characterise the cells for their response to $H_2O_2$, and to investigate the effect of *S. pneumoniae* on them. It is hoped the information obtained will allow us to better understand the role of oxidative stress in pulmonary disease and improve the therapies available and outcomes for lung disease in A-T.

**A Multi-centre, randomised, double blind, placebo controlled trial to evaluate the effects of Intra-Erythrocyte Dexamethasone Sodium Phosphate on Neurological Symptoms in Patients with Ataxia Telangiectasia (ATTeST)**

That's a mouthful! We've all been waiting for this. Finally we can confirm that Australia will be involved. Our centre will be based in Melbourne under the care of Pediatric Neurologist Dr Victoria Rodriguez-Casero.

Key inclusion criteria/ those eligible as follows:

- Patient with neurological signs of A-T
- Patient is in autonomous gait or is helped by periodic use of a support
- Genetic diagnosis must be confirmed – either prior or during the study
- Age criteria – I think over 6?
- Body weight must be greater than 15kg
- Consent

Key exclusion criteria/ those ineligible as follows:

- Females that are of childbearing potential, pregnant or breastfeeding – those using adequate birth control, as determined by their health care provider, will be eligible. Not sure if abstinence is considered "adequate birth control"?
- A disability that may prevent the patient from completing all study requirements.
- CD4+ lymphocyte count as reported in the protocol (can't find this in my notes)
- Current or previous (remission less than 2 years) neoplastic disease
- Severe or unstable pulmonary disease
- Uncontrolled diabetes
- Renal and/or hepatic impairment
- Use of any drug that is a strong inducer/inhibitor of CYP3A4within 4 weeks before baseline e.g. ketoconazole, midazolam

They expect to satisfy all of FDAs requests by the end of October, with first patient screenings to commence before year end.

Timeline of the trial:

O months – baseline ICARS (International Cooperative Ataxia Rating Scale) scores established for all participants

0-6 months – participants will be blindly administered a high dose, low dose or placebo

6-9 months – 1/3 of the placebo group will be shifted off placebo

9-12 months – 1/3 of the remaining placebo group will be shifted off placebo

Some interesting findings with respect to the application of the Erydex system (EDS) in patients with A-T following the previous phase II 6 month study:

ICARS scores were recorded in 4 A-T patients (group A) who received EDS treatment for an additional 24 months. They were compared with ICARS scores of 7 A-T patients (group B) who stopped the treatment after completion of the phase II 6 month study, but who continued to be monitored according to the same protocol. After 24 months, Group A improved 10.7 points vs baseline, while Group B worsened 6.7 points vs baseline. No treatment related adverse events, or steroid dependent adverse reactions were observed during the entire period of treatment in group A. To date, 7 patients with A-T continue to receive EDS treatment under compassionate grounds, some for more than 3 years, with no adverse side effects. EryDel advised that it would be reasonable to expect a 10-20% improvement in ICARS scores. However, whilst the treatment had positive effects on cerebellar ataxia and oculomotor apraxia, it had no effects on extrapyramidal symptoms such as parkinsonism and hyperkinetic movements, or on peripheral neuropathy. It was suggested that in the future, treatment might involve both steroids and dopaminergic/NMDA antagonists to improve all physical symptoms.

It was put forth that Dexamethasone induces in A-T cells the expression of a truncated (mini) ATM form that maintains kinase activity in vitro. miniATM was also found in the lymphocytes of A-T patients receiving EDS treatment, but not in wild type controls, or in A-T patients not receiving dexamethasone. The expression of miniATM appears to be dose-dependent, and correlates with ICARS variations. The higher the dose, the better the ICARS scores.

As you know, most A-T patients do not produce ATM, which is fundamental to cell integrity, viability and repair in the face of oxidative stress. Other presentations during the conference suggested that slow progression and late onset of A-T in some patients may be due to the fact that they express some ATM protein – even 4% of normal expression would make a difference. If dexamethasone can in fact enable the expression of this miniATM, it would be an amazing development to say the least.

I will say that the clinicians were predominantly excited about this upcoming trial. Howard Lederman from the US congratulated Erydel on bringing this seemingly impossible international trial so far. I felt that his excitement was almost an

endorsement, while the consensus of those I spoke with was that there really isn't any promising alternative at the moment, and they would support it.

Hoping, praying, crossing all my fingers and toes that this results in improvement, or at least cessation of degeneration, without any side effects.

**Applying big data approaches to A-T – Brad Margus, A-T Children's Project, US**

Presented information on the Global A-T Family Data Platform which is now live at **atfamilies.org.**

Information will be entered by families, with consent for information to be shared with researchers. One of the consents is for whole genome sequencing. If the patient agrees, a saliva test will be sent to the patient and returned for analysis. Unfortunately, the results of the sequencing will not be available to the patient due to legal restrictions, however, there was some discussion that if the analysis indicated some further abnormalities, then the patients physician may be contacted for further local investigation. Despite not having access to this information, Brad revealed that 99 out of 100 patients still elected to have the genome sequencing done – this alone would be an invaluable dataset! In addition to genome sequencing, it is envisaged that information from patient questionnaires, microbiome analysis of lungs and intestines, and neuroimaging results will be collated, providing an amazing opportunity for researchers to access fundamental information on disease progression with the view to identify novel drug targets.

I have partially completed my daughter's profile, it's not difficult to work through. For those living in Australia, it lists the Brisbane clinic as our local centre from which they can request medical records. I would strongly encourage our local families to participate in this exciting initiative.

**CATNAP study – Dr Robert Dineen, UK**

The aim of the study is to identify and develop imaging markers through MRI which would measure the underlying disease process and also help to assess whether future new treatments work. The study involves neurometabolic profiling of several compounds including NAA, chromium, Cho, Glu, and Ins.

Preliminary results indicate that there may be a correlation between glutathione reduction in the cerebellum and ataxia. This piqued my interest because glutathione is a master antioxidant – I wonder if supplementation would benefit?

Neuromelanin of the substantia nigra increases with age – possible relationship with bradykinesia (slowness of movement).

Nigrostriatal (pathway that connects the substantia nigra with the dorsal striatum in the brain) degeneration may contribute to extrapyramidal features of A-T. (Extrapyramidal symptoms include dystonia (continuous spasms and muscle contractions), akathisia (motor restlessness), parkinsonism (characteristic symptoms such as rigidity), bradykinesia (slowness of movement), and tremor, and tardive dyskinesia (irregular, jerky movements).

**Role of ATM in brain functionality – Dr Ari Barzilai – Israel**

Tested the hypothesis that A-T is at least partially a glial disease. Glial cells are non-neuronal cells that maintain homeostasis (balance), form myelin, and provide support and protection for neurons in the central and peripheral nervous systems. In vitro testing revealed a significantly less complex cell branching in ATM deficient circuits versus wild type (typical/normal) circuits. ATM deficient astroglial cells replaced with wild type astrocytes fully restored the dynamics of neural networks in ATM deficient mice, whilst, in contrast, replacing wild type neurons with ATM deficient astrocytes failed to support the survival and functionality of the wild type neurons. This supports the notion that neuronal network failures in genetic brain degenerative diseases such as A-T are correlated to the impairment of astroglial cell functionality.

In laymen's terms, my understanding from the presentation was that this suggests that the impaired functioning of the astroglial cells resulted in impaired vascularization (formation of blood vessels/connections) in the cerebella of ATM deficient mice, but was able to be fully restored when replaced with wild type astrocytes. Would be great to be able to replicate this in our kids! (very long way away, if ever).

**Immunodeficiency and survival in A-T – Prof Corry Weemaes, Netherlands**

Conducted a retrospective study of the immunodeficiency of 61 A-T patients.

Found that those with normal and deficient levels of IgA had the same survival outcomes. Classical A-T patients, especially those that developed malignancies, had a shorter life expectancy than those with variant/late onset A-T – no surprises here.

Patients with Hyper IgM (HIGM), as well as those with IgG2 deficiency, showed decreased survival compared to those with normal IgG and normal IgG2 respectively. Reduced survival for those with IgG2 deficiency was due to increased malignancies.

HIGM occurs when there is decreased levels of IgG and IgA but normal or elevated levels of IgM in their blood. Typically, patients with other HIGM syndromes are susceptible to recurrent and severe infections and in some types of HIGM syndromes, opportunistic infections and an increased risk of cancer as well – not dissimilar to A-T.

Out of the cohort of 61 patients, 7 had HIGM, and all died before the age of 15 – 3 from malignancies and 4 from respiratory failure. The study looked at 15 other patients with A-T and HIGM outside of the cohort, and found that 13 of them had died between the ages of 2-15. HIGM phenotype = lowest survival ☹️

Clinical application – may be beneficial to test all the Ig subsets to determine those with HIGM and provide even greater observation/intervention.

**Inflammatory Cytokines in A-T – Prof Howard Lederman, US**

Professor Lederman indicated that although A-T patients have an antibody deficiency, leading to recurrent infections and lung disease, there is more at play than just infections – he hypothesised that the lungs are experiencing constant inflammation. He conducted a study to evaluate the potential link between systemic inflammation and impaired lung function in A-T patients. Levels of proinflammatory markers IL-6 and IL-8 were tested in the patients' blood. Out of a cohort of 60 patients, approximately 80% (48 patients) had elevated IL-6 levels compared to normal - these patients had significantly lower forced vital capacity (FVC) rating compared with patients with normal IL-6 levels (FVC = is the amount of air which can be forcibly exhaled from the lungs after taking the deepest breath possible. FVC is used to help determine both the presence and severity of lung diseases. Our kids do this lung function test each year at clinic). This was the case even for those patients receiving gamma globulin therapy and supplemental nutrition. No association was found between elevated IL-6 and age. Elevated IL-8 levels were found in 23% (14) patients, and all patients with elevated IL-8 levels also had elevated IL-6 levels – these patients with both IL-6 and IL-8 had the lowest average lung function. Only 22% (13) patients did not have either elevated IL-6 or IL-8 levels, and therefore were not in a constant state of inflammation. These findings indicate that markers for systemic inflammation may be useful in identifying patients with A-T at increased risk of lower lung function and may help in assessing responses to therapy.

Clinical application – It may be beneficial to incorporate testing for serum IL-6 and IL-8 levels during clinic to identify those who require additional intervention with respect to lung care.

**Metabolic Syndrome and Liver Involvement in A-T – Dr Andreea Nissenkorn, Israel**

Conducted a retrospective review of 53 patients to investigate liver involvement, metabolic syndrome and growth patterns in A-T. Liver function tests and lipid profiles were conducted to determine liver health. 43% (23 patients) had consistently abnormal liver enzymes. Of those 23 patients, ultrasounds revealed fatty liver in 9 of them. 2 out of the 23 went on to develop advanced liver disease within 2-5 years. Dyslipidaemia (elevated cholesterol/triglycerides) was significantly associated with abnormal liver enzymes, despite low BMI. However, no association was found between abnormal liver function and diabetes, increased malignancies or gender. Ordinarily, non alcoholic fatty liver disease is associated with a high fat diet. There was a suggestion that increased calories should not come from fat, however, it was conceded that carbs also play a role. I believe the reference to fat was unsaturated fat, but I will have to read some of the articles referenced to clarify.

Another presenter, Prof Dr Stefan Zielen of Germany, observed an increase in abnormal liver enzymes around puberty in his cohort of A-T patients, leading to insulin resistance. This is becoming increasingly relevant in light of improved survival rates, with more adult patients. He recommended that patients older than 14 should be monitored for insulin resistance, metabolic syndrome and fatty liver disease.

Clinical application – I don't think it would be too difficult to perform liver function tests and lipid profiles. Would be beneficial to track these results year to year to keep a close eye on abnormalities.

**Respiratory Management of A-T - Dr Jayesh Bhatt, UK**

Dr. Bhatt is a clinician at the UK A-T clinic at Nottingham. He is a well-regarded consultant in respiratory pediatrics, his colleagues spoke very highly of him. He advised that in his opinion, children with A-T should be fitted with PEGs once they turn 8 as this is generally when their BMI starts to drop below average age levels. He believes that poor nutritional outcomes adversely affects lung health. This conversation took place in a social setting and I was unable to take notes!

However, there was a poster presented by a group from Israel who performed a review of the nutritional status (BMI) and lung function of A-T patients one year before and one year after PEG insertion. Lung function was measured using FEV1 (forced expiratory volume 1) which is the volume of air forcefully exhaled in 1 second, and FVC (forced vital capacity) which is the volume of air that can be maximally forcefully exhaled from the lungs after taking the deepest breath possible. They looked at 6 patients with PEGs and 6 patients of a similar age without PEGs. They found a statistically significant decrease in lung function in PEG-less patients, while patients with PEGs maintained their lung function.

Clinical application – in light of respiratory failure representing about 40% of deaths in A-T patients, should clinicians be recommending PEG insertion as a pro-active measure rather than delaying and risking not only reduced BMI, but also reduced lung function?