Translational studies in X-linked adrenoleukodystrophy
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Chapter

Summary, general discussion, future research and implications for clinical practice
Summary of the thesis
X-linked adrenoleukodystrophy (X-ALD) is a relatively common metabolic disorder (Moser et al 2007). It causes severe disability in the majority of affected men and women. For most patients there is currently no curative treatment. We review current recommendations for management in Chapter 1.

The biochemistry of X-ALD has been studied extensively. Although there are still unresolved issues, there is a reasonable understanding of the molecular mechanisms of this disease at the cellular level, as reviewed by Kemp and Wanders (Kemp and Wanders 2010). This, and an excellent in vitro model system available for research (i.e. cultured primary skin fibroblasts) offers possibilities to screen for compounds that might be of therapeutic use in this disorder. In Chapters 2 and 3 we describe the use of this in vitro model to test potential very long-chain fatty acid (VLCFA) lowering compounds.

It is important to stress that the hypotheses generated by in vitro experiments always need to be validated in clinical trials, maybe first with biochemical endpoints, but eventually with relevant clinical endpoints. Patients with X-ALD are often desperate for a cure and willing to take medication based on pathophysiological theories or inconclusive and poorly designed clinical trials. If one claims a compound might be effective based on in vitro data there is a moral obligation to validate these claims in a clinical trial. We show that even if compounds or strategies seem promising in the laboratory (and even in laboratory animals), they can be totally ineffective in a clinical trial. We performed two clinical trials to test if lovastatin (Chapter 4) or bezafibrate (Chapter 5) can lower VLCFA in X-ALD. Lovastatin was widely believed to lower VLCFA, but we show that the VLCFA lowering in plasma by lovastatin is an artefact. Bezafibrate is also ineffective, probably because plasma concentrations required for a VLCFA lowering effect can not be reached even with the maximum tolerable dose. Because a biochemical effect was absent further studies with clinical endpoints seem unnecessary.

As with all disorders, the clinical spectrum often expands with time as more “atypical cases” are diagnosed and described. In Chapter 6 we describe a man with X-ALD presenting with signs and symptoms of a demyelinating peripheral neuropathy. Usually, the peripheral neuropathy in X-ALD is not prominent and classified as an axonal sensomotor peripheral neuropathy (van Geel et al 1997). We conclude that in demyelinating peripheral neuropathy without a specific cause X-ALD can be considered. In Chapter 7 we describe a large cohort of women with X-ALD. It is clear that women with X-ALD are not merely carriers but develop signs and symptoms of myelopathy and peripheral neuropathy. Symptomatic status correlates with age, after 60 years of age most women can be considered symptomatic. There is a striking phenotypic heterogeneity; we could not find an association between the X-inactivation pattern in fibroblasts and symptomatic status. As we discuss in the paper, however, it is possible that expression in other (neural) tissues does correlate. These tissues are not easily accessible and so have not been studied by us.

General discussion and future research
Research to find the cause and possibly a cure for rare diseases is sometimes considered less relevant on the basis of the relatively small amount of people that would benefit. However, studying these disorders can sometimes lead to new insights in human physiology that
might be applicable to other disorders. Also, even though the number of affected individuals is small, the burden of disease is not for those affected and their families. We will continue with our efforts to improve the outcome in this devastating disease.

Unfortunately, the compound we identified in vitro as a VLCFA lowering drug, is not effective in a clinical trial. The concept, however, of decreasing VLCFA synthesis pharmacologically remains a plausible strategy for future studies. Currently, we are trying to identify inhibitors of ELOVL1 (the rate limiting enzyme involved in VLCFA synthesis) in vitro. We hope this will yield new drugs to stabilize the disease in the future.

Clinical trials in X-ALD to test clinical efficacy are difficult. The disease course is highly variable, age of onset and progression differ enormously between patients. To determine if a new drug offers clinical benefit trials with large groups of patients are necessary. This is a considerable challenge in a rare disease. Furthermore, long follow-up of at least 3 years is necessary because the disease is usually gradually progressive. Effects on surrogate endpoints (like reduction of plasma VLCFA) should not be considered proof of clinical efficacy. Lorenzo’s oil normalizes VLCFA, but does not prevent progression of disease in X-ALD (Aubourg et al 1993; van Geel et al 1999). Still, clinical trials with biochemical endpoints can be useful as pilot studies. Because trials with clinical endpoint take enormous effort potential new drugs can first be evaluated in small clinical trials with biochemical endpoint. If there is an effect on the surrogate endpoints a follow-up trial with relevant clinical endpoints can be performed. It is important to stress that plasma VLCFA can be misleading. In Chapter 4 we show that if plasma LDL is reduced, plasma VLCFA are lower because of reduced VLCFA transport capacity of the blood. It is vital to also determine VLCFA in leukocytes and/or erythrocytes.

In a university hospital patient care and clinical research are sometimes intertwined. We are planning to create a large cohort of men and women with X-ALD and follow them prospectively according to a fixed protocol. Our new collaboration with the VUmc will allow us to implement new MRI techniques in the follow-up, that could lead to earlier detection of the onset of cerebral ALD. This will provide well documented information on the natural history of X-ALD and might also be useful in future therapeutic research.

Research into the pathophysiology of cerebral ALD has been seriously hampered by the lack of a suitable mouse model. The current “X-ALD mouse” develops an AMN-like phenotype. We hope that the new mouse currently developed by Dr. S. Kemp will develop full blown cerebral ALD. This would provide many new research opportunities to unravel the pathophysiology of cerebral ALD.

The clinical course in X-ALD is unpredictable, there is no genotype-phenotype correlation (Kemp et al 2012). The identification of genetic or environmental modifiers could help in identifying those patients at risk for cerebral ALD. This would improve management, because a “tailor made” follow-up program can then be offered. New genetic modifiers have been discovered in collaboration with Professor Aubourg that bring this goal a step closer. In the women with X-ALD we hoped to be able to predict symptomatic status by analyzing the X-inactivation pattern in fibroblasts. We were unable to show an association, as described in Chapter 7. We are planning to analyze the X-inactivation pattern in different tissues and to increase the number of patients in our analysis by collaborating with other research groups.
**Chapter 8**

**Implications for clinical practice**

X-linked adrenoleukodystrophy is a complex disorder. Patients with X-ALD benefit from careful follow-up, as described in Chapter 1. Timely identification of adrenocortical insufficiency and hormonal substitution therapy reduces morbidity and mortality. There is a narrow window of opportunity for bone marrow transplantation after the onset of cerebral ALD and follow-up with routine MRI scans is recommended. Furthermore, virtually all patients will gradually develop neurological deficits and symptomatic treatment of bladder- or bowel dysfunction and spasticity should be started. This follow-up should be offered in a large center by physicians with experience in this field. Ideally, this follow-up should be done according to a fixed protocol. This will most likely result in better patient care and allows us to systematically study the natural history of the disorder. We are currently working on improving the X-ALD outpatient clinic.

**References**


