Kawasaki disease: Studies on etiology, treatment and long-term follow-up
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Since the first report of patients with Kawasaki disease (KD) by Dr. Tomisaku Kawasaki in 1967\(^1\), many studies have been performed to unravel numerous different aspects of the disease. However, there is still a lot to discover about this mysterious pediatric disease. This thesis comprises several studies on different aspects of KD with a focus on the epidemiology, etiology, treatment and long-term (psychological) consequences of this rare disease.

**PART I - EPIDEMIOLOGY**

There were no systemic reports of Dutch patients when we initiated this study. To determine the incidence of KD in The Netherlands and to study the demographic characteristics, treatment regimen and cardiac outcome of Dutch patients with KD, we initiated a national survey using the Dutch Pediatric Surveillance System (DPSU). This prospective epidemiological study is described in chapter 2. Based on the results, we calculated a mean annual incidence of KD in The Netherlands of 5.8 per 100,000 children under the age of 5 years. Although this incidence falls within the range from 3.6 to 15.2 observed in other European countries, we believe that it should be taken as a minimum estimate of the true incidence of KD in The Netherlands because cases may have been missed or may not have been reported by the pediatricians. An interesting observation of the study is that the incidence of KD per province seemed to be related to the varying population density throughout the country. This finding supports the general hypothesis that KD is triggered by an infectious agent in genetically susceptible individuals. Epidemiological features of the Dutch patients like age at the onset of disease, treatment regimen and rate of coronary artery aneurysms (CAAs) were comparable to other countries. Male gender, IVIG non-responsiveness and delay of treatment were identified as risk factors for the development of CAAs.

**PART II - TREATMENT**

In part II we focused on treatment of patients with KD. Chapter 3 reviewed treatment for acute patients with KD and treatment options for IVIG non-responsive patients. The initial treatment has been well established and consists of a single infusion of high-dose IVIG (2 g/kg). Aspirin is also administered, although the optimal dose regimen is still unproven and there is limited evidence for its true efficacy in preventing coronary artery lesions in acute KD.

The optimal therapy for the IVIG non-responsive patients remains controversial. Different therapies have been described in these patients, including high-dose intravenous pulse methylprednisolone, TNF-α blockade, and IL-1 blockade, but controlled clinical trial data are currently lacking regarding the safety and efficacy of these treatments. To date we recommend a second dose of IVIG (2 g/kg) in patients who do not respond to the initial IVIG infusion because this has been shown to be safe and effective in controlling disease activity.
in the majority (up to 80%) of these patients. In our view, other treatment options should be reserved for the small number of patients non-responsive to repeated IVIG infusions.

Based on the positive outcome of the severe KD case described in chapter 4, we believe that anti-IL-1 treatment may provide a promising treatment option for patients who are non-responsive to IVIG. Evidence to date about anti-IL-1-treatment in patients with KD is still at the level of this single case report, but a European multicenter trial will be launched this year (phase II-III). Large, randomized multicenter clinical trials are warranted to identify the best treatment regimen for IVIG non-responders, but numbers of patients to be included will be a serious issue. Such studies may not be feasible.

Major developments in the genetic field, resulting in the identification of genes influencing disease susceptibility and treatment efficacy in patients with KD, may also lead to the improvement of therapy and treatment outcome in patients with KD. At this moment it is not possible to predict at start of the standard treatment which patient will not be responding to IVIG treatment. Several scoring systems have been developed, mostly in Japan, but they have not yet been proven to be sensitive in different ethnic groups. To be able to optimize the treatment options for these patients it would be ideal to have reliable prediction models – independent of ethnicity.

PART III – IGG-RELATED IMMUNITY

Part III of this thesis discussed two studies about IgG-related immunity in relation to KD. In chapter 5 we compared the serological response to measles, mumps, and rubella (MMR) vaccination in patients treated with IVIG for KD with healthy age- and gender-matched controls. Results showed that patients vaccinated before the IVIG administration had comparable MMR IgG concentrations and seroprotection rates as controls. However, patients who were vaccinated after the IVIG administration had significantly lower IgG concentrations and seroprotection rates. MMR IgG concentrations appeared to be correlated with the interval from IVIG administration to vaccination. Evaluations based on the time interval between IVIG administration and vaccination indicated that we should adhere to an interval of at least 9 months after IVIG administration for an optimal serological response to vaccination. Current national guidelines in The Netherlands recommend a shorter interval of 6 months and should therefore be revised. Our study results suggest that medical personnel carrying out the immunization program are generally unaware of the recommendation to defer live vaccinations after administration of IVIG. We aim at an increased awareness of the guidelines to optimize serological response to vaccination in patients treated with IVIG.

In chapter 6 we focused on the genetic variation of the genes coding for the IgG receptors (FcγRs). We hypothesized that both CNV and SNPs in and around the FCGR2/3 locus,
regulating gene transcription and expression of the activating and inhibitory FcγRs, are associated with KD susceptibility. To study this homologous and complex gene cluster we used a Multiplex Ligation-dependent Probe Amplification (MLPA) assay. Genetic variation in the FCGR2/3 gene cluster has been studied before in patients with KD, but not in such detail as became possible with this MLPA assay. Two independent studies were carried out in a total of 3050 samples; a case-control study in patients and controls of European descent, as well as a family-based replication study in about 600 families of variable and or mixed ethnic origin. In comparison with healthy controls, patients with KD more often carried a classical open-reading frame (ORF) in exon 3 of FCGR2C, coding for the activating FcγRIIc. In addition, we confirmed our recent GWAS finding that a variant in FCGR2A (131H>R) is also associated with susceptibility to KD.

PART IV - CARDIOVASCULAR LONG-TERM FOLLOW-UP

In part IV of this thesis we focused on the long-term cardiovascular consequences of KD. Chapter 7 and 8 described two studies that applied cardiac magnetic resonance imaging (CMRI) during the long-term follow-up of patients with KD. We showed in chapter 7 that the current recommendations of the American Heart Association for follow-up of patients with persisting CAA are not routinely implemented in daily practice in The Netherlands. We considered invasiveness, the potentially hazardous radiation exposure, and the complication rate of nuclear perfusions scans and conventional invasive coronary angiography (CAG) the main reasons for lack of adherence to the guidelines. Another drawback of the current guidelines is that echocardiography is routinely used to screen patients for lesions of the coronary arteries. CAA may be missed by echocardiography because of a more peripheral localization or poor echocardiographic windows, leading to an underestimation of disease severity. CMRI is a noninvasive and radiation-free imaging method that overcomes these disadvantages. In 63 patients with history of KD, we applied a comprehensive CMRI protocol including magnetic resonance angiography (MRA), myocardial wall motion analysis, first-pass perfusion during adenosine stress and in rest, as well as late gadolinium enhancement studies. We showed that this comprehensive protocol is feasible without the use of any form of anesthesia in young patient. We confirmed that in a considerable number of patients (~10%) CAA were identified on CMRI that had not been detected by recent echocardiography. First-pass myocardial perfusion defects and delayed hyperenhancement were identified in 5 of 15 patients with CAA and were not detected in any of the patients without coronary artery pathology.

CMRI has become the standard for evaluation of biventricular dimensions and function. In chapter 8 we reported on functional evaluation during the long-term follow-up of 60 patients with KD in comparison with 30 healthy controls. Although left ventricular dysfunction
is a well-known feature of the acute KD phase, we showed that biventricular function is not impaired during the follow-up of patients with KD. Late enhancement imaging detected no signs of prior myocarditis. Myocardial fibrosis was only detected in patients with severe coronary artery pathology and prior myocardial infarction.

Although we found encouraging results of biventricular evaluation in patients with history of KD, we do recommend periodic monitoring of cardiac function because of the possibility of deterioration over time and the relatively short follow-up interval in our study (mean interval from KD onset, 12.0 years [range 0.6-20.7 years]).

Based on our experience with CMRI in patients with KD, we have recently introduced a 2-step CMRI protocol in the AMC. Step 1 of this protocol (MRA and functional evaluation) can be considered from 8 years of age, but is routinely offered at the age of 12 to every child with history of KD. If CAA are unexpectedly identified on CMRI the second step of the CMRI protocol is also performed, involving the administration of intravenous contrast and adenosine to detect (reversible) myocardial perfusion deficits and myocardial infarction. If CAAs have been observed in the past on echocardiography, both steps are performed at the same time.

The major disadvantage of CMRI is that it cannot be implemented without anesthesia at young age. An alternative in these patients is CT angiography (CTA). A study by Carbone showed that CTA allowed accurate detection of all CAAs, stenosis and occlusions previously diagnosed with conventional coronary angiography in 12 patients with history of KD (mean age 17.6±2.9 years). Another study by Xing et al showed in 48 children with KD that CTA detected two dilatations in the left anterior descending branch and three CAAs with stenosis and/or calcification that had not been detected by 2-dimensional echocardiography.

The radiation dose, an inherent problem of CT, should be noted because of the potential long-term risks. Due to recent developments low-radiation dose CT with prospective ECG gating has become available and is increasingly being used. With low-dose CTA the radiation burden is reduced from an average of 12-14 down to 0.8-2.0 mSv.

We believe that the current guidelines of the American Heart Association for follow-up of patients with KD are outdated and need to be revised to incorporate newer imaging methods like CMRI and CTA (S.M. Dietz, C.E. Tacke, in preparation). This should lead to a better detection of coronary artery pathology, while reducing the radiation burden, costs and potential complications in patients with KD. Future studies are needed to define the exact risks and benefits of the different imaging methods.

In chapter 9 of this thesis we applied B-mode ultrasound to measure carotid intima-media thickness (cIMT) for premature atherosclerosis in a large cohort of 176 patients with KD and 82 controls. The cIMT measures are assumed to be a valid surrogate marker of premature
atherosclerosis\textsuperscript{7,8}. Since the first case of KD was only reported 50 years ago, the follow-up of KD patients has not been long enough to define the natural history of the disease. A surrogate marker is therefore needed.

Prior cIMT studies in patients with KD are limited and have produced conflicting results. We showed that cIMT is increased in patients with history of KD, in comparison with healthy controls. Plotting the mean difference in cIMT between patients and controls against age at the cIMT measurement, demonstrated that the difference in cIMT decreased with age. In adulthood, the mean cIMT of patients without CAA (CAA-negative) is comparable to the mean cIMT of healthy controls. We suggest that the increased cIMT in these KD patients is merely a result of the acute vessel wall inflammation rather than a process of atherosclerosis. However, in CAA-positive patients the difference in cIMT between patients and controls persisted. It is unknown if these stably increased cIMT findings represent an atherosclerotic process and what it exactly means for the prognosis of these patients. Future studies are underway to correlate longitudinal cIMT data to cardiovascular outcome in patients with KD (S.M. Dietz & C.E, Tacke; unpublished). Based on such and other results, more evidence-based decisions can hopefully be made about the long-term follow-up, both of patients with and without CAA.

**PART V – PSYCHOSOCIAL CONSEQUENCES**

The two chapters of **part V** focused on the health related quality of life (HRQOL) and psychosocial functioning of families of a child with KD. These reports contribute to the scarce literature about the long-term impact of the acute KD phase on patients and their parents.

In **chapter 10** we reported on the HRQOL and behavioral functioning of 280 former KD patients (mean age 8.6 years). HRQOL was significantly worse for patients aged 0-5 years, but was comparable with their peers at older age. We believe that this could partly be explained by the increased interval from disease onset to study participation in the older patients. However, we also think that the impact of KD on parents might also contribute to the reported difference in HRQOL of young (proxy report) and older patients (self-report). This was supported by the results of the questionnaire about behavioral problems. Parents reported hyperactivity and emotional problems compared with the norm population, while the patients themselves reported no such differences. We hypothesized that the difference between children and their parents could possibly reflect the parent's own anxiety and concerns. However, a pathological substrate cannot completely be excluded.

In **Chapter 11** of this thesis we showed results about HRQOL and perception of child vulnerability (PPCV) among parents of children with history of KD. We observed no difference in HRQOL of parents of KD patients compared to the HRQOL of parents of healthy children. However, an interesting finding of the study was that the KD parents perceived their child
as more vulnerable than healthy children, while the vast majority of the patients with KD had fully recovered and did not face daily cardiovascular consequences of their disease. We believe this is an important finding because it has been shown that parents who perceive their child as more vulnerable are more likely to overprotect their child, and that higher PPCV scores are associated with worse developmental outcome of the child.

A suggestion for future research is to study medical traumatic stress symptoms in parents of a child with history of KD, both shortly after the disease onset and during long-term follow-up. We know from our clinical experience that KD can be considered as a traumatic event for parents, but symptoms or pediatric medical traumatic stress were not measured in this study. Future studies should identify the potential burden for parents, as well as their stress levels and reactions to the uncontrollable aspects of the disease. More insight in the psychosocial consequences of this rare pediatric disease is needed to provide comprehensive care for families of children with history of KD.

In summary, the studies described in this thesis contribute to the total of approximately 5000 publications on the subject of KD since 1967. Although this thesis provides new insights in many different aspects of the disease, future research is warranted to unravel the remaining questions.
REFERENCES


