

ADHD, a Food-Induced Hypersensitivity Syndrome: in Quest of a Cause

**The effects of a restricted elimination diet (RED) on ADHD,
ODD and comorbid somatic complaints,
and a preliminary survey of the mechanisms of an RED**

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Liduina Maria Josephina Pelsser

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Lidy M.J. Pelsser

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Chapter 8

Summary



8.1. General introduction

Chapter 1 of this thesis is a general introduction that provides an overview of the history, diagnosis and aetiology of ADHD. Furthermore, the current assessment and therapy of ADHD is described and food as a specific environmental factor is discussed, considering the results of additive studies, supplement studies and restricted elimination diet (RED) studies in children with ADHD. No relevant effects have been found of additive free diets on ADHD, and the results of studies supplementing omega-3 (fish oil) and/or omega-6 fatty acids are commensurable to the results of additive studies, i.e. no relevant beneficial effects of fatty acids on ADHD have been found. Conversely, there is convincing evidence for the statistically significant and clinically relevant effects of an RED on ADHD. In a meta-analysis including all double-blind placebo controlled RED studies conducted preceding the studies discussed in this thesis, an average effect size of 0.8 was calculated, which is impressive. For comparison, the effect size of methylphenidate, the most used drug in children with ADHD, may vary from 0.6-0.9. Subsequently, in 2001 an RED was included in a UK algorithm for treatment of ADHD. Still, despite the results of the RED studies and the recommendation for application, an RED is not part of the current ADHD assessment or therapy yet.

8.2. Part 1

The overall aim of *Part 1* of this thesis was to investigate the effects of an RED on ADHD in heterogeneous groups of children with ADHD, in order to determine whether the RED results are applicable to the general population of children with ADHD, and to investigate the RED effects on comorbid ODD, physical complaints and sleep problems.

In *Chapter 2* an exploratory pilot study is described in which a group of young children with ADHD, of whom 84% also suffered from comorbid ODD, followed a 2-week RED. Children were not selected for atopic constitution or diet affinity and all children with ADHD whose parents were motivated to follow an RED were included. Conversely, children whose parents reported unfavourable environmental factors associated with ADHD were excluded from participation.

According to parents' and teacher's ADHD measurements 62% of children showed behavioural improvements of at least 50% following the RED. According to the ODD measurements an ODD symptom decrease of 50% or more was shown in 81% of children with comorbid ODD. The diet response did not differ between children with or without an atopic constitution. Physical and sleep complaints were reported in the majority of children, which diminished significantly following the RED.

Chapter 3 reports the results of a randomised controlled trial (RCT) in which children with ADHD were randomised either to an RED group or to a control group. In accordance with the previous study, the children included in this study were not preselected, but children with potentially predisposing environmental factors were excluded. The results shown in Chapter 2 were confirmed in this randomised controlled design: following the RED impressive effect sizes of 2.1 (ADHD) and 1.1 (ODD) were established, according to both parents' and teacher's measurements. The ADHD behaviour improved with an average of 70% in 85% of children. ODD improvements, with an average of 55%, were shown in 73% of children with comorbid ODD. No significant ADHD or ODD improvements were established in the control group.

In *Chapter 6* the INCA study is described, which comprises two parts. Based on the immunological assessments chapter 6 has been incorporated in part 2 of this thesis. Conversely, the first and behavioural part of Chapter 6 is a follow-up study of the RCT discussed in Chapter 3, consequently, this part of the INCA study will be discussed here. The INCA study was an RCT including an unselected and heterogeneous group of children with ADHD; no children were excluded. According to parent, teacher and blinded paediatrician ADHD measurements the majority of children showed striking behavioural improvements following an RED. Sixty-four per cent of children in the diet group showed behavioural improvements of an average of 60%; the average improvements in responders were 89% (see chapter 9.1, figure 1). The average ODD improvements in diet group children with comorbid ODD were 65%, and were found in 70% of children; the average improvements in the ODD responders also amounted to 89% (see chapter 9.2, figure 2). In the control group no significant improvements of ADHD as well as ODD were found.

The responders did not meet the criteria of ADHD and ODD anymore, neither at home nor at school, thus confirming the results of previous studies (see chapter

2 and chapter 3). Considering that the children participating in the INCA study were representative of the general population of children with ADHD, the INCA results are applicable to all young children with ADHD whose parents are motivated to follow a 5-week RED.

In *Chapter 4* the effects of an RED on comorbid physical and sleep complaints in children with ADHD were investigated following an RED. Significant symptom reduction was shown in three domains: headaches or bellyaches, unusual thirst or unusual perspiration, and sleep complaints. The total number of complaints was significantly reduced in the RED group (a reduction of 77%, effect size 2.0) but not in the control group (a reduction of 17%, effect size 0.2). The symptom reduction did not differ between children with or without an atopic constitution and did not differ between children who did or did not show behavioural improvements following the RED. The results of this RCT confirm the findings of the pilot study described in Chapter 2.

Conclusions part 1: An RED may have considerable effects on ADHD and comorbid ODD, physical complaints and sleep problems, thus confirming and strengthening the results of the previous RED studies. The double-blind placebo controlled RED studies have shown that the beneficial effects of an RED on ADHD are not moderated by parental expectations, and all studies investigating the relationship between an RED and ADHD resulted in statistically significant and clinically relevant improvements of behaviour. Therefore, in accordance with the recommendations mentioned in *Chapter 6*, the conclusion is warranted that an RED is beneficial to the majority of young children with ADHD, with an overall effect size of 1.2, and that it is timely for an RED to be implemented. In responders the behavioural problems may diminish to such an extent that they do not meet the ADHD and ODD criteria anymore and show normal behaviour. Considering that children with comorbid ODD have a worse prognosis, interventions that may reduce ODD have great clinical potential. The INCA study, as discussed in *Chapter 6*, used the most pragmatic design including a heterogeneous group of children. Consequently, the results of this study are applicable to all young children with ADHD provided that parents are motivated and able in terms of parenting skills and time resources to follow a 5-week diet.

8.3. Part 2

The overall aim of *Part 2* of this thesis was to investigate the occurrence of an underlying immunological mechanism of food in children with ADHD by means of IgE and IgG blood tests. Furthermore, the effect of an RED on family structure and environment was considered in order to define whether behavioural improvements during an RED were instigated by improvements of parental capabilities.

In *Chapter 5* it is hypothesised that ADHD may be a (non-)allergic hypersensitivity disorder. According to the terminology of allergy the manifestation of ADHD when eating normal amounts of foods which are usually tolerated by the general population, implies that the criteria of a hypersensitivity reaction are met. The hypersensitivity hypothesis in ADHD is in accordance with other hypersensitivity disorders, e.g. the manifestation of asthma when exposed to dust mite or the manifestation of eczema when eating strawberries. The hypersensitivity triggering ADHD may be allergic or non-allergic, depending on whether or not an immunological mechanism will be established.

The occurrence of an immunological mechanism was investigated in the second part of *Chapter 6*. In all children participating in the INCA study immunological parameters (IgE and IgG blood levels) were determined at the start of the trial and following an RED or control period. At the start of the trial only a minority of children showed increased IgE-levels (14%), and no association was found between a behavioural response to the RED and increased IgE blood levels, thus confirming previous findings that IgE or an atopic constitution is not related to a hypersensitivity reaction to foods in children with ADHD. Chapter 6 also focussed on IgG, investigating whether a relationship might exist between IgG blood levels against specific foods and ADHD behaviour. It was shown that IgG blood levels did not predict behavioural changes in RED responders; no differences in behavioural relapses were established after challenges with either high-IgG foods or low-IgG foods. These results suggest that the underlying mechanism of food hypersensitivity in ADHD is non-allergic, although the involvement of a cell-mediated allergic response cannot be ruled out.

The main aim of *Chapter 7* was to investigate whether the children's behavioural improvements following an RED were due to improvement of family structure and environment as a consequence of the strict structure of the diet. The results indicated that family abilities in families motivated to enter an RED trial were

equivalent or even better than those of families without ADHD, and that an RED did not affect family structure or family environment. It is conceivable that only parents confident of their parenting capacities decided to participate in the RED trial, consequently the results of this study are applicable to those families motivated to follow a 5-week RED.

Conclusions part 2: ADHD may, in the majority of children, be considered a hypersensitivity disorder triggered by food. The underlying mechanism of food hypersensitivity in children with ADHD appears not to be IgE or IgG mediated, consequently a non-allergic mechanism or a cell-mediated allergic response may be involved. Furthermore, families motivated to follow an RED have shown excellent parenting capabilities and an RED does not affect family structure or family environment.

8.4. General discussion

Chapter 9 of this thesis is a general discussion in which the results of this thesis are elucidated in coherence with all previous RED results and in light of the current opinions of ADHD. The general discussion concludes with recommendations for further research into this intriguing subject (see chapter 9.6), with a proposal for an Algorithm for Multimodal Diagnosis and Treatment of ADHD in which the results of this thesis are incorporated (see chapter 9.7, figure 4), and with suggestions for the DSM-V which may lead to improvement of our child mental health (see chapter 9.8).

8.5. Conclusions and recommendations

Taking the results of all previous and recent RED studies into account, there is conclusive evidence for the statistically significant and clinically relevant effects of an RED on ADHD and ODD. The RED studies discussed in this thesis have shown that an RED has a beneficial effect on ADHD and comorbid ODD in 60% of children with ADHD, to such an extent that in children responding to an RED the behavioural problems, ADHD as well as comorbid ODD, disappear completely (see chapter 9.1, figure 1 and chapter 9.2, figure 2).

The impact of an RED appears not to be limited to ADHD and ODD, but is also manifest in the frequently occurring comorbid physical and sleep complaints in children. Consequently, an important environmental cause of ADHD, ODD, comorbid physical complaints and sleep problems has now been established; this recognition may lead to a paradigm shift with regard to our knowledge and opinions on the aetiology of ADHD and may have considerable consequences for the current diagnostic procedure and therapy of ADHD.

8.5.1. Implementation of RED research

The most important recommendation is implementation of RED research in young children with ADHD. Right now, the main therapy of children with ADHD is medication, eliminating symptoms during 3-12 hours (the duration depending on the drug), with an effect size of 0.6-0.9 and with disappointing long-term effects. This dissertation has shown that in the majority of young children ADHD may be caused by food and that an RED is an effective treatment of ADHD in children diagnosed FI-ADHD, preventing symptoms 24/7, with an effect size of 1.2 and with promising long-term prospects. The pros of an RED are to such an extent that RED research should be implemented especially in young children with ADHD, consequently, all young children with ADHD should be offered the opportunity to participate in RED research, provided that expert supervision is available. Children with ADHD responding favourably to an RED should be diagnosed with food-induced ADHD (FI-ADHD), considering that in these children food appears to be the predominant cause of ADHD and that elimination of specific foods results in normal, typical behaviour. Children not responding to an RED should be diagnosed with Classic ADHD (C-ADHD); in these children the cause of the disorders remains, for the time being, unknown. These children, just like children of parents not motivated to start or to comply with an RED, should start treatment as usual.

Children diagnosed with FI-ADHD are advised to start a challenge period, as described in the Algorithm for Treatment in chapter 9.7, in order to establish the incriminated foods, at the end of which the therapy consists of dietary advice to avoid a limited number of foods. Offering children with ADHD the opportunity to start RED research may consequently result in prevention of ADHD and in improvement of the children's prospects.

Finally, the concurrent economical effects of every child completing the RED research may be impressive. According to a Dutch report, making a rough inventory of some of the costs of ADHD by comparing the costs including RED research with the current costs of ADHD, implementation of RED research may yield savings of 7.000 euros per year per child starting RED research.

8.5.2. alleviation of the challenge period

Facilitation of the challenge period is another important recommendation. This part of the RED research is the most poignant part for parents, child and school, due to the recurrent behavioural relapses during this period. All efforts should be made to facilitate this period by means of expert coaching and by means of follow-up research in order to define the mechanisms of food in children with FI-ADHD. It must be noted that, until an easier method is available to define the incriminated foods, the current challenge period is crucial to determine the incriminated foods and thereby to compose a feasible diet. At the end of the challenge period the child's diet will be practically normal and the child will have to avoid the incriminated foods only, which may differ per child. Thus, compared to the RED and the challenge period the final dietary restrictions will be easy to adhere to, and relapses will only occur if the child does not stick to the diet. Concluding, additional expert coaching during the challenge period will increase the compliance and further research should focus on facilitating the challenge period and on defining the mechanisms of food in children with FI-ADHD.

8.5.3. Follow-up research

Some RED studies have already shown that the beneficial effects continue unabated during a follow-up period of one year. Also, the preliminary results of the INCA 10-month follow-up study show that the behavioural effects, in children who adhere to their diet, persist. Still, it is important to investigate the effects of an RED during a longer period of time, and to investigate whether children may overgrow the sensitivity to specific foods when avoiding the incriminated foods.

8.6. Acknowledgement and consensus

In 2001 RED research was already advised to be applied in subgroups of children with ADHD. Unfortunately, this advice has been confronted with a striking deficit of attention and has, just like all previous RED research and despite convincing evidence, generally been ignored. Now, in 2011, RED research has repeatedly been conducted in heterogeneous groups of children, thus confirming the results of the previous RED trials in groups of children representative of the general population of children with ADHD. Consequently, this thesis results in the advice to implement RED research in all young children with ADHD. Acknowledgement of the impact of food on ADHD is needed in order to achieve consensus. It would be deplorable, especially for all children suffering from ADHD, if the advices resulting from this thesis would sink into oblivion, commensurable to the 2001 advices.