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Rouhani-N, Mary M

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SLEEP PATTERNS IN PAEDIATRIC PATIENTS WITH ATOPIC DERMATITIS AT CHRIS HANI BARAGWANATH HOSPITAL, JOHANNESBURG, SOUTH AFRICA

MARY M ROUHANI-N

Student Number: 9513058P

Faculty of Health Sciences, WITS University, as partial fulfilment for the requirements of the degree of Master of Medicine in Dermatology

Johannesburg 2017

DECLARATION

I, Mary M Rouhani-N declare that this research report has been my own work. It is submitted for the degree of Master of Medicine in Dermatology to the University of the Witwatersrand, Johannesburg. It has not been submitted before for any degree or examination at this or any other university.

_____

Mary M Rouhani-N

14 June 2017

DEDICATION

This research report is dedicated to my dear parents Ata and Aghdas Rouhani, my wonderful husband Behzad Naraghi and my beautiful children: Nadia Lua, Ryan, Juliet Ella and Kamal Thomas, and to my siblings Suha, Suhayl and Sepi.

It is especially offered with the utmost gratitude to my dear mother, Aghdas Rahimpour-Rouhani, who passed away during the completion of this study and who was a great source of support during the Dermatology registrar programme.

ABSTRACT

Introduction: Atopic Dermatitis (AD) is a chronic relapsing inflammatory skin condition affecting 5-20% of children under 11 years of age, characterised by intense pruritus, redness and discomfort. Research suggests that AD has been shown in quality of life assessments to be rated among the worst in term of its effect on sleep. There is no research on the effects of sleep loss on the natural history and time course of skin disorders either, especially in South Africa.

Aims: The objectives of this study were:

1. to describe the various sleep disturbances associated with AD in children up to and including 12 years of age and
2. to compare the characteristics of children with sleep problems to those without sleep problems in AD

Patients and Methods: This was a prospective observational / descriptive hospital based study conducted at the paediatric dermatology outpatient department at Chris Hani Baragwanath Academic Hospital (CHBAH). Questionnaire technique was used consisting of the children's sleep habits questionnaire (CSHQ), a useful parent-reported instrument validated to identify both behaviourally based and medically based sleep problems in 4-12 years old school age children.

Results: The prevalence of sleep problems in paediatric patients with AD was found to be 61.3%.

There was no significant difference between males and females.

Snoring as well as apnoea and snorting were significantly different in the rhinitis versus non-rhinitis group. The overall sleep disturbance rate was significantly different in those with rhinitis versus those without.

Conclusions: While Atopic Dermatitis is often regarded by health professionals as a minor problem, in this study, 61.3% of children with AD have disturbed sleep.

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ABBREVIATIONS

AAEDS	Allergic Atopic Eczema Dermatitis Syndrome
AAD	American Academy of Dermatology
AASM	American Academy of Sleep Medicine
AEDS	Atopic Eczema Dermatitis Syndrome
AC	Allergic Conjunctivitis
AD	Allergic Dermatitis
AMPs	Antimicrobial Peptides
AR	Allergic Rhinitis
BAI	Beck Anxiety Inventory
BDI	Beck Depression Inventory
BSA	Body Surface Area
CHBAH	Chris Hani Baragwanath Academic Hospital
CI	Confidence Interval
CCS	Corticosteroids
CRSWD	Circadian Rhythm Sleep Wake Disorders
CSHQ	Children's Sleep Habit Questionnaire
CNI	Calcineurin Inhibiter
CXCL	Chemokine (C-X-C motif) Ligand
ECG	Electrocardiogram
EDC	Epidermal Differentiation Complex
EEG	Electroencephalogram
EMG	Electromyogram
EOG	Electrooculogram
FcεR1	Fc epsilon Receptor (high-affinity receptor for the Fc region of IgE)
FLG	Filaggrin
GM-CSF	Granulocyte Macrophage – Colony Stimulation Factor
H&E	Haematoxylin and Eosin
HOME	Harmonised core Outcome Measures for atopic Eczema
HPA	Hypothalamic Pituitary Axis

HSV	Herpes Simplex Virus
ICSD	International Classification of Sleep Disorders
IFN-γ	Interferon γ
Ig	Immunoglobulin
ISAAC	International Study of Asthma and Allergies in Childhood
IL	Interleukin
LSC	Lichen Simplex Chronicus
MHC	Major Histocompatibility Complex
NAAEDS	Non Allergic Atopic Eczema Dermatitis Syndrome
NRS	Non Restorative Sleep
OCST	Out of Centre Sleep Testing
OPD	Out Patient Department
OR	Odds Ratio
OSA	Obstructive Sleep Apnoea
OSAAD	Objective Severity assessment of Atopic Dermatitis
PGE_2	Prostaglandin E_2
PSG	Polysomnography
PSQI	Pittsburgh Sleep Quality Index
RAST	Radioallergosorbent Test
RBD	REM sleep Behaviour Disorder
RCT	Randomised Controlled Trials
REM	Rapid Eye Movement
SA	South African
SCORAD	SCORing Atopic Dermatitis (severity score)
SD	Standard Deviation
SPTs	Skin Prick Tests
TEWL	Trans Epidermal Water Loss
Th	T helper cells
TISS	Three Item Severity Score
TLR	Toll-Like Receptor
TNF	Tumour Necrosis Factor

TPE	Therapeutic Patient Education
TS	Topical Steroids
TV	Television
UE	Ung Emulsificans
UK	United Kingdom
USA	United States of America

PREFACE

Atopic Dermatitis (AD) is a common relapsing inflammatory skin condition seen in primary care that typically starts during early childhood / infancy affecting between 5%-20% of children under 11 years of age at any time.[1,2] It is characterised by intense pruritus and a chronic or chronically relapsing course [2,3] although in infants, acute inflammation of the cheeks, scalp and extensor extremities predominate. In children, adolescents and adults, chronic inflammation and lichenification with a predilection for flexural areas are seen.[2]

It is well known that a proactive approach including trigger avoidance, daily emollients and anti-inflammatory treatments e.g. topical corticosteroids, can control subclinical inflammation and prevent overt flares. Thus, Atopic Dermatitis is often regarded by health professionals as a minor problem, often overshadowed by other allergy/atopy related health conditions e.g., asthma. Research suggests that it may actually cause considerable disruption to the lives of the affected children as well as their caregivers having major public health and economic implications.[3,4,5] One of these areas of disruption is that of sleep.

Paradoxically, an extensive Pubmed and Scopus literature search reveals a dearth of studies on sleep problems in skin disorders and very few Randomised Controlled Trials (RCTs) of treatment for chronic dermatitis that measure sleep as an outcome.[3] In the few studies published, up to 60% of children with AD have disturbed sleep with an increase in frequency to 83% during exacerbations of AD.[3,4,5]

This study was a prospective observational / descriptive study carried out at the Paediatric Dermatology OPD at Chris Hani Baragwanath Academic Hospital run on a

Monday and Thursday morning. It was a questionnaire based study using the Chidren's Sleep Habits Questionnaire (CSHQ), a useful parent report screening instrument validated to identify both behaviourally based and medically based sleep problems in 4 - 12 years old school aged children.[6,7,8]

In creating more information and awareness regarding the crucial importance of the sleep disorders associated with AD in our local South African Dermatology clinics, it is hoped that the results of this study will influence the better care and management of chronic dermatological conditions.

CHAPTER 1 – LITERATURE REVIEW

1.1 Atopic Dermatitis

1.1.1 Introduction

Atopic Dermatitis (AD) is an acute, subacute or chronic relapsing inflammatory skin disorder, usually beginning in infancy or early childhood, often associated with other "atopic" disorders such as asthma or allergic rhinoconjunctivitis, characterised principally by dry skin and intense pruritus. [2,9] Consequent rubbing leads to increased inflammation and lichenification and further itching and scratching, creating an itch-scratch cycle.[9] AD is often associated with a personal or family history of atopic dermatitis, asthma, allergic rhinitis, skin barrier dysfunction and IgE reactivity, and there appears to be a common genetic predisposition, influenced by environmental factors, that predisposes patients to the development of AD, asthma and allergic rhinoconjunctivitis – known as the "atopic disorders".[2,9,10] There are also alterations in the immunologic responses in the T cells, antigen processing, inflammatory cytokine release and infection and allergen sensitivity.[9,11] In many texts, the terms "eczema", atopic eczema, atopic dermatitis and IgE dermatitis are used interchangeably[9] and as synonyms. In this literature, all these terms are included under AD.

1.1.2 Definition and History

Eczema is derived from the Greek word 'Ekzein'[12] meaning "to boil out" as eczema periodically flares up (boils out). Flares are precipitated by irritation of the skin, various infections and stress. Atopy is derived from the Greek word 'Atopos', meaning out of

place[12,13] and refers to one's predisposition to developing asthma, dermatitis or allergic rhinoconjunctivitis.[2,10-13] Surfaces located between the body and the external environment are 'over reactive' (in asthma it is the lower airways, in allergic rhinitis it is the upper airways, in allergic conjunctivitis it is the conjunctivae and in atopic dermatitis it is the skin).

'Dermatitis' and 'eczema' are regarded as synonymous. However, as shown in figure 1.1, the term dermatitis is a broader term and includes eczema. Internationally there appears to be no consensus on the use of these terms.[12,14] The term 'dermatitis' refers to the condition of the skin being inflamed analogous to 'appendicitis',[12] inflammation of the appendix. It was reported by Jon Hanifin at the Dermatology Foundation Clinical Symposia in 2007[13] that 'atopic dermatitis is not an allergic disease, but a skin disease with allergies'. Interestingly, in this regard it is noted that atopic dermatitis typically improves in spring whilst allergic rhinitis is at a peak.[13] Atopic dermatitis, therefore, is one of the types of dermatitis with an atopic component (figure 1.1).

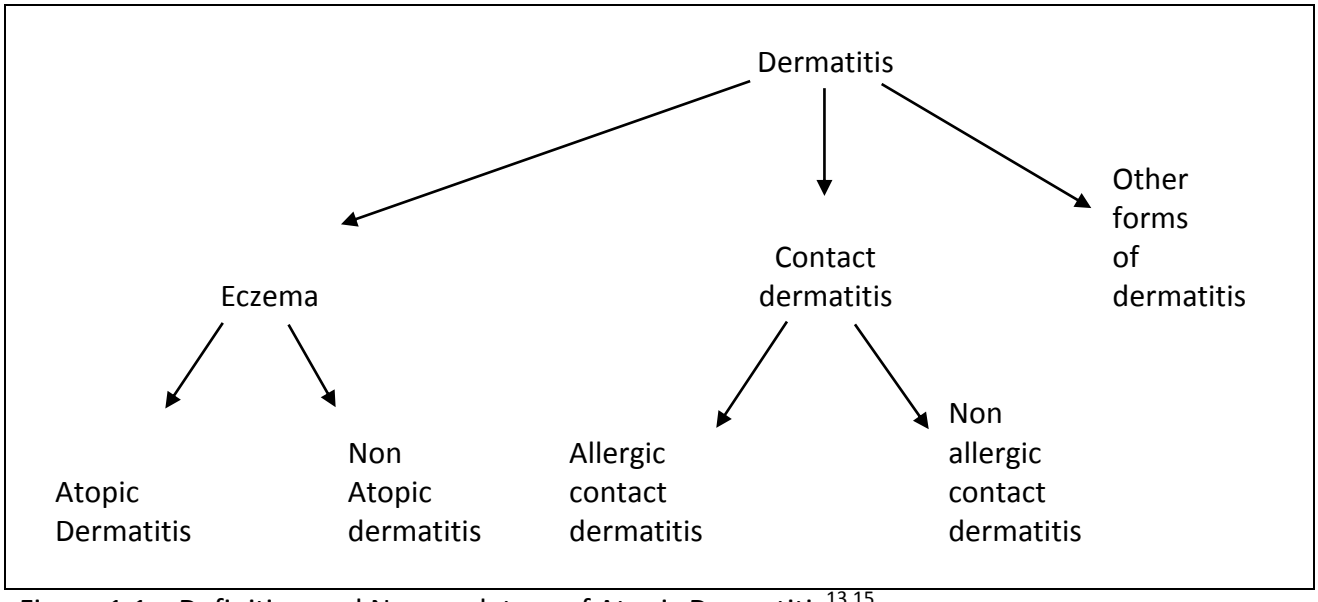


Figure 1.1 – Definition and Nomenclature of Atopic Dermatitis[13,15]

1.1.3 Nomenclature and Classification

According to the position paper by the Nomenclature Review Committee of the World Allergy Association,[12] the term atopic eczema dermatitis syndrome (AEDS) is an umbrella term including different subtypes of AD. This new nomenclature (AEDS) underlines the important fact that AD is not just a single disease entity but an aggregation of several disease entities that have certain common clinical characteristics. The two main subtypes included in AEDS are intrinsic and extrinsic AD.

Intrinsic AD (Non-Allergic AEDS (NAAEDS) or Atopiform Dermatitis) is a term fulfilling the diagnostic criteria most commonly used for AD and comprises 20% of cases. [10,12]

Extrinsic AD (Allergic AEDS (AAEDS)) is, on the other hand, commonly associated with upper and lower respiratory allergies, e.g. rhinitis and asthma, the presence of high levels of serum IgE, specific IgE to various allergens and positive Skin Prick Tests (SPTs) to aeroallergens or foods and comprises 80% of patients.[12]

Furthermore the risk of an 'Atopic March' (described later) is significantly lower in children with NAAEDS than in those with AAEDS.[12,15] It is noteworthy, however, that the distinction between NAAEDS and AAEDS is controversial and that some cases may actually transform from one type to another and the division may not be pertinent to adults. Therefore, until the exact genetic and causative agents are known, it is best to consider AD as one condition.[12,15]

1.1.4 Epidemiology of Atopic Dermatitis

As very few studies are actually based on community samples, the prevalence of atopic eczema is not clear.[14,16-18] Studies use various ways to define the disease, various age ranges of children are studied and various study methods are used in the literature creating problems in comparing studies. There are large scale longitudinal studies, especially from the United Kingdom (UK), from which we can gain insight,[14,18] showing a cumulative prevalence of 5% - 20% by age 11 years.[14,18]

Globally over the past three decades, in keeping with the findings of the International Study of Asthma and Allergies in Childhood (ISAAC) phase 1 and phase 3 studies there is a decline in AD prevalence in developed countries and an increasing AD prevalence found in the developing world.[14,18] Longitudinal studies of Scottish school children 8-13 years show increasing prevalence of AD of 5.3% in 1964 to 12% in 1989.[18] Studies on British children have shown an increase from 5.1% in 1946 to 12.2% in 1970.[18] In the developed countries of UK, Denmark and Finland[18] prevalence rates for AD reflect that it is the commonest skin disease seen in the general population[14,18,19] (5-20% of children) associated with several major comorbidities namely infection, food allergy, increased osteoporosis and even bone fractures. Associated sleep disturbance is a factor in the poor quality of life for the patients and their families.[3,18,19,20,21]

Overall the following studies summarise our South African data on AD prevalence and explain the wide range of prevalence found (1-13%):[14]

1. Phase one ISAAC (International Study of Asthma and Allergies in Childhood) study – 13-14 years old Cape Town school children included
    - 8.3% one year prevalence rate for AD

- 2.3% severe AD (evidenced by sleep disturbance > 1 night per week)

2. Phase three follow up ISAAC study on the same group (13-14 years old) recorded an increased prevalence rate of 13.3%. No reasons were found for the increase.
3. Normal 3 – 11 years old AmaXhosa children had a 1% – 2.5%, one-year prevalence, depending on the methodology of defining AD and whether the population studied was urban versus rural.

Studies from Ethiopia and Nigeria show that 40% - 60% of AD patients are children ≤ 19 years of age. The prevalence of AD has increased more than two fold[18] over the past fifty years with increased urbanisation and increased socioeconomic status playing a part.[10,12,17]

There are few incidence studies on AD so far in the world. These are on cohorts of European children and the incidence varies by age. The National Child Development Study from the UK suggests incident rates of 50 cases per 1000 in the first year of life, but decreasing to 5 new cases per 1000 per year throughout the rest of childhood.[18]

Studies show that AD affects 5% - 20% of children under 11 years of Western Europe, Australia,[1,2,17,18] or most industrialised countries[4,5] quoted to be affecting up to 30% of children[21,22] with a prevalence that is continuously increasing, and adult prevalence of 2% - 3%.[4] Females seem to be affected more severely than males.[18]

1.1.5 Aetiopathogenesis and Genetics of Atopic Dermatitis

The aetiopathogenesis of AD is rather complex and has two components: i) genetic predisposition (including immunoaberration) and ii) environmental influences. There is

an inherited stratum corneum (top layer of the skin) barrier defect, transepidermal loss of water, early cutaneous exposure to antigens and the over-hygienic handling of young infants (known as the hygiene hypothesis) as the major drivers of AD, together with exogenous, endogenous (table 1.1)[13] and various environmental factors (table 1.2)[17]. As described below, a genetic predisposition to the development of AD interacts with several environmental factors (table 1.2)[17] thus influencing clinical manifestation.[2,10,12,15]

Endogenous factors	**Exogenous factors**
Perspiration	Warm environments
Xerosis	Wool fibres
Physical exertion	Soaps, detergents
Emotional stress	Hot water Atopic dermatitis flare Contact with allergens

Table 1.1 - Factors leading to development of pruritus in Atopic Dermatitis[13]

The Hygiene Hypothesis[2,10,12,17] is a theory which suggests an increased risk for atopic dermatitis in a hygienic environment in early life without pathogenic exposure, i.e., an extra sterile environment which may increase the risk for the development of AD. Other risk/triggering factors leading to the development are shown in table 1.2.

↑ Risk	↓ Risk	Unknown Risk
↑ socioeconomic status ↑ education of parents ↓ family size ↑ urbanisation ↑ pollution ↑ personal hygiene (hygiene hypothesis) Early life antibiotic use (hygiene hypothesis) Cooler climates ↑ maternal age Maternal history of AD Tobacco smoke Emotional stress Irritant exposure • Hard water – disease aggravation • Clothing – disease aggravation by fibre, roughness and heavy textiles	Animal exposure in early life / early pet exposure (hygiene hypothesis) Day care attendance (hygiene hypothesis) Early endotoxin exposure (hygiene hypothesis) Maternal diet probiotics Probiotics (hygiene hypothesis) Breastfeeding - ↓ risk of AD in those who are breastfed and have a positive family history of AD Partially hydrolysed formulae Diet exclusion – disease control in children < 2 years of age with known diet allergy only	Maternal diet / probiotics Parasitic infection Diet restriction; organic food – therefore routine food allergy testing is not recommended. Diet supplementation • Antioxidants (vit. E, zinc, selenium – no effect • Essential fatty acids (borage, fish, evening primrose oils – no effect) House dust mite exposure – no effect Superantigen – staphylo-coccal control – no effect

Table 1.2 - Environmental influences on Atopic Dermatitis as per the South African Atopic Dermatitis Guidelines[17]

Atopic Eczema is related to three key factors which interact and potentiate each other: stratum corneum impaired barrier function (genetic and environmental), a Th2 pro-inflammatory atopic response mounted to antigens (genetic), and decreased cutaneous antimicrobial peptides (AMPs) and activity (genetic and environmental).[12,23] Any treatment strategy would thus need to address all 3 factors in order to prove efficacious.

In terms of the genetics of AD, studies have shown a 77% concordance rate of AD in monozygotic twins but only a 15% concordance rate in dizygotic twins (i.e., genetic factors are very important in AD).[2,12] Parental history of AD is a stronger risk factor for AD

than is the presence of asthma or allergic rhinitis in the child concerned, thus suggesting specific AD genes exist. There are two major sets of genes that have been described in AD pathogenesis:

1. Epidermal Protein Genes (1q21, 5q31-q32, 11q13.5, 19q13)
2. Immunologic Function Protein Genes (1q23, 4q32, 4q34, 5q31, 8p23, 11q13, 11q22, 14q11, 16p12, 17q11)

An imbalance in the adaptive immune system which is mediated by various T cells is part of the pathogenesis of AD. Specialised T helper cells are involved in acute and chronic AD. Th2 helper cells are mostly involved in acute AD and Th1 mostly in chronic AD. Despite the involvement of the genes associated with the EDC, the majority of AD patients do not actually have EDC mutations but have an increased Th2 cytokine activation e.g. IL-4, IL-5, IL-13, IL-25, IL-33, IL-22 which may inhibit skin barrier function through interference with the complex epidermal differentiation process, i.e., an acquired filaggrin deficiency.[19,24]

The reduced epidermal barrier function explains why AD patients are more prone to bacterial (Staphylococcus) and Viral (Herpes Simplex and Molluscum Contagiosum pox virus) infections.[13] In addition, there are other contributing factors in AD such as reduced Toll-like receptor (TLR) activity of the innate immune response versus the increased infection susceptibility.

AD patients experience increased neuronal sensitization and have increased epidermal innervation thus explaining why they are more prone to itching and discomfort.[25] The question arises as to whether there may be a molecular link between itch, emotional stress and the autonomic nervous system,[23,25] due to the fact that heart rate changes

have been shown to demonstrate an excessive sympathetic response to scratching and itch in AD patients versus patients with normal skin.[23,25]

It should be noted that IgE hyper-responsiveness, although it defines the term atopy, does not necessarily imply atopic dermatitis, even if present in the AD phenotype.[12] Although it is rare that diet would trigger AD[12] about 60% of AD patients are sensitized to various food allergens (increased IgE RAST values or a positive Skin-Prick Test) but this does not equate causality.[14]

The theory of 'atopic march', historically understood as atopic eczema in children evolving into other mucosal forms of AD, e.g., asthma and rhinoconjunctivitis, has been challenged by cohort studies (see Comorbidities of AD).[2]

Thus, AD is multi-factorial, related to skin barrier dysfunction, cytokine and neurogenic mediated inflammation, decreased innate and adaptive immune responses, decreased antimicrobial function and chronic scratching, causing a vicious itch-scratch-itch cycle, resulting in tremendous inflammation and discomfort, with its resultant sequelae, importantly including various sleep problems.[23]

1.1.6 Clinical Features of Atopic Eczema

Symptoms range from small mildly irritating patches (figure 1.2), to more widespread painful rashes which are physically distressing (figure 1.3), painful and can persist for years with chronic changes (figure 1.4) and flare ups (figure 1.5). There may be oozing, scaling, crusting, fissuring and lichenification which frequently accompany the observed primary lesions.[2,9-11,26] (figure 1.6)



Figure 1.2 – Eczematous papulovesicles coalescing to form eczematous patches periorbitally, on cheeks as well as P.Alba, hypopigmented scaly macules on cheeks (top). Dennie-Morgan prominent infraorbital lines and orbital darkening, associated with Atopy (bottom)

Atopic dermatitis may be mild, moderate or severe according to the South African Guidelines (table 1.3, figures 1.3 - 1.6). Several other scoring systems exist namely the SCORAD (Scoring Atopic Dermatitis), OSAAD (Objective Severity Assessment of AD), and the TISS (Three Item Severity Score) .[12,17]

Mild	
	Less than 5% body surface involved
	No acute changes
	No significant impact on quality of life
Moderate	
	5-30% body surface involved
	Mild dermatitis with acute changes
	Mild dermatitis with significant impact on quality of life
Severe	
	More than 30% body surface involved
	Moderate dermatitis with acute changes
	Moderate dermatitis with significant impact on quality of life

Table 1.3 – Severity Scoring of Atopic Dermatitis – South African Guidelines[12,17]

These are used mostly in research as they are not practical to be used in daily clinical practice.[12,14,17] According to the South African AD Guidelines, assessment of the severity of AD is more practical and useful in terms of management strategies.[17]



Figure 1.3 – Chronic Eczema Changes – Follicular Eczema (top left), Lichenification (right), Chronic AD (bottom left)



Figure 1.4 – Chronic infant atopic dermatitis

The morphology of AD depends on whether it is acute, subacute or chronic. Acute eczema is defined by erythema, oedema, papulovesicles, crusts and exudation. Chronic eczema is characterized by thickening of the skin (lichenification) with exaggerated skin markings. Subacute eczema is characterized by overlap of features of acute and chronic eczema, i.e., elevated, red purplish / brownish patches with scaling and is the most common presentation.[10] The morphological distribution pattern of AD varies depending on whether it is in infants (birth to 2 years), childhood (2 to 12 years) or in adolescence / adulthood (>12 years) (table 1.4).[9]

Infant (birth - 2 years): cheeks (sparing perioral and perinasal area), chin, cheilitis (corners of the mouth), extensor areas ±whole body and scalp, sparing napkin area.
Childhood (2 – 12 years): flexural (cubital and popliteal), neck, wrists, ankles
Adulthood / adolescents (>12 years): flexural, neck, wrist, ankles, hands, periorbital, anogenital, nipple, may be follicular pattern

Table 1.4 - Distribution Pattern of AD by Age[9]

Thus, there can be various presentations with acute inflammation involving the cheeks, scalp and extensor aspects of the extremities predominating in infants, shifting to chronic inflammation with lichenification and later, a predilection for the flexural areas in children, adolescents and adults.[2,9-12,27] Clinical features are generally highly variable with regard to morphology (acute, subacute, chronic), time of presentation (infantile, childhood, adolescent, adult), body site and severity (mild, moderate, severe).[14]



Fig 1.5 – Childhood AD flare up – generalised eruption, confluent inflammatory patches



Figure 1.6 – Acute infant AD – oozing, serous crusting and secondary infection of acute lesions in this age group

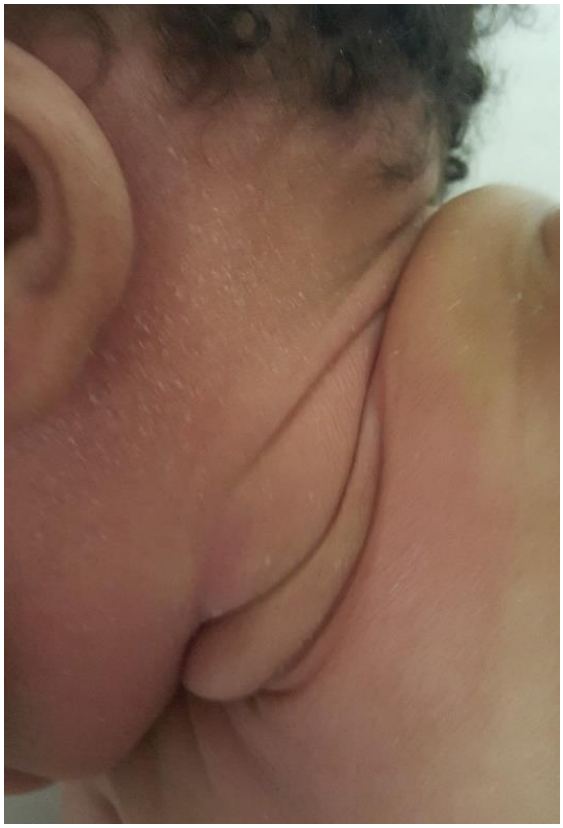


Figure 1.7 – Subacute eczema: scaly elevated red / purplish / brownish patches





Figure 1.8 Childhood AD – lichenification in the flexural region – a hallmark of chronic atopic dermatitis – skin thickening, linear excoriations exaggerated skin lines and fissures[9]

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1.1.7 Diagnosis and Differential Diagnosis[12,15,17,27]

The diagnosis of Atopic Dermatitis is unfortunately not easy. When young babies present with the typical dry pruritic skin inflammation, in a classically described distribution for AD in accordance with the age of the child, the diagnosis may be somewhat straight forward.[12,17,27] However, before the diagnosis of AD can be made, other conditions often need to be excluded in the differential diagnosis, i.e., a differential diagnosis may need to be considered before the diagnosis (Table 1.5).

Seborrhoeic dermatitis
Discoid (nummular) dermatitis
Irritant contact dermatitis (especially of the hands)
Allergic contact dermatitis and airborne contact dermatitis
Photo-allergic and photo-irritant dermatitis
'HIV dermatitis'
Drug-induced dermatitis
Psoriasis, especially the erythrodermic type
Scabies
Insect bites

Table 1.5 – List of the Differential Diagnosis of Atopic Dermatitis[12,17]

Certain patients may present with atypical morphology or localisation e.g., nummular eczema (coin shaped or discoid lesions), prurigo-like, seborrheic lesions (exfoliative dermatitis involving ≥ 90% body surface area) or follicular type lesions, or even rarely as Erythroderma.

There have been a number of diagnostic criteria ranging from Hanifin and Rajka Criteria which are less commonly used to the American Academy of Dermatology guidelines. In South Africa, the UK Working Party criteria are used in the South African Guidelines[14,17] (Table 1.6).

a. Must have
    Pruritus
b. Plus 3 or more of the following
    History of involvement of skin diseases (front of elbows, back of knees, front of ankles, neck, around the eyes)
    History of a generally dry skin in the past year
    Personal history of asthma or hay fever
    Onset under the age of 2 years
    Visible flexural dermatitis

The diagnosis of atopic dermatitis in adults is primarily clinical; special investigations only contribute in identifying external aggravating factors

Table 1.6 – Revised criteria for the diagnosis of atopic dermatitis – SA guidelines[12,17]

Special investigation for Atopic Dermatitis that may be needed as an adjunct in the diagnosis. These special investigations are rarely if ever necessary in the diagnosis of AD, which is mainly a clinical diagnosis, but maybe useful in identifying trigger factors and aggravators that need to be avoided (mostly in children).[12,17,27]

Patch tests are formal tests for the diagnosis of allergic contact dermatitis superimposed on AD, especially in adults with hand dermatitis. They are used to diagnose a type IV hypersensitivity reaction and help in determining food and aeroallergen triggers of AD and the test has a high specificity but low sensitivity.[27]

The Skin Prick Test (SPT) maybe used to investigate inhaled (mites, pollens, animal dander, moulds) or food (cow's milk, wheat, fish, soy, peanuts, hen's egg) allergen sensitisation.[12,14,17,27]

The total serum IgE or specific IgE RAST Test maybe raised in 50% of cases and normal in the rest and has thus reduced value in the diagnosis of AD.[12,17,27] It does not correlate with severity. It should be noted that 15% of nonatopic patients may have raised IgE levels.[12,17]

For cases of suspected immunodeficiency, HIV, HTLV1, immunoglobulin subtypes, peripheral blood smears and flow cytometry may need to be done. Pus swabs may be helpful for secondary infections and a Tzanck smear (to diagnose HSV) may help in suspected herpes infections.[14,27]

The histological features for AD on skin biopsy may aid in the diagnosis but cannot be relied on for a definitive diagnosis which is mainly clinical.

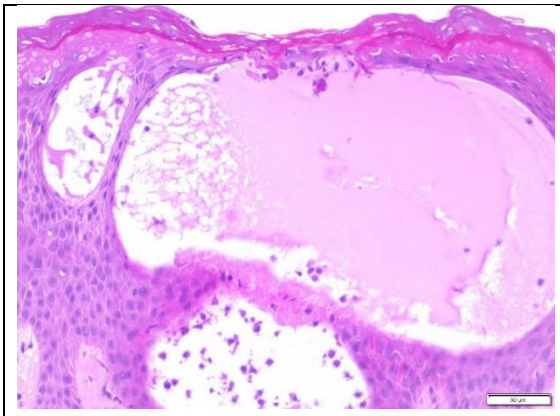
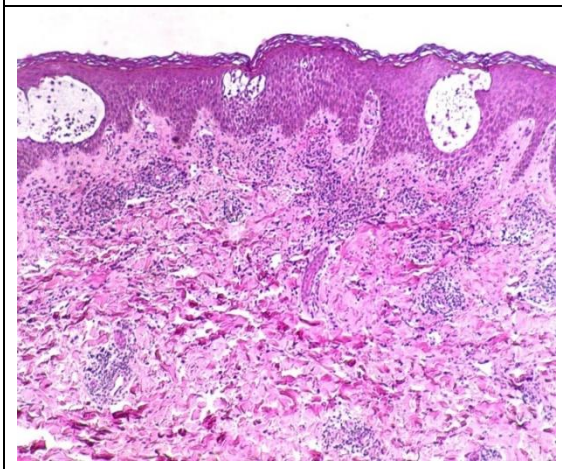
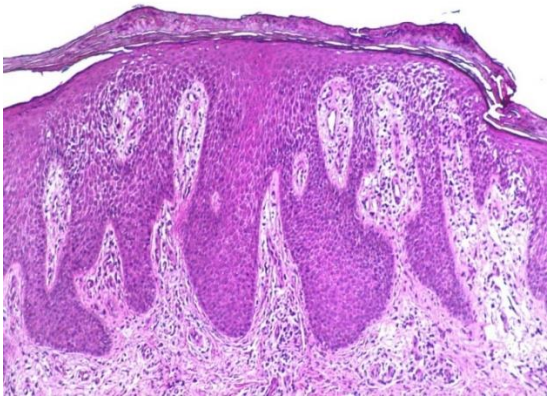
	Acute lesion of AD • Intraepidermal vesicles • Spongiosis • Exocytosis of lymphocytes
	Subacute lesion of AD • Parakeratosis • Less spongiosis
	Chronic lesion of AD • Acanthosis • Hyperkeratosis • Epidermal hyperplasia

Figure 1.9 – Histology of AD on skin biopsy (H&E)

1.1.8 Prognosis, course and the Atopic March

Most studies on the natural history of AD show a 60% spontaneous resolution by puberty but there is a risk of possible recurrence in adults, as determined by family history, severity and early onset, mucosal atopy and persistent AD.[14]

AD is often accompanied by other disorders associated with atopy e.g., asthma / allergic rhinoconjunctivitis, which may appear simultaneously or successively.[2,12,15] AD affects infants and young children mainly, asthma more likely in older children and allergic rhinoconjunctivitis predominantly occurs in adolescents, with this age-dependant sequence characteristically called the 'Atopic March'.[2,12,15] It is postulated that maintenance treatment aimed at managing the epidermal barrier dysfunction in AD, preventing the active dermatitis, could well block the potential sensitization and inflammatory pathways that propel the progression of this Atopic March.[2,12,15]

Around 60% of infants / young children suffering with AD have remission at age 12 years, and up to 40% present for the first time in adulthood.[14]

In terms of the course and prognosis, at any stage of AD, a generalized exfoliative dermatitis (Erythroderma) may develop in the most severely affected patients. All types of lesions seen in AD may resolve with post inflammatory hyper / hypopigmentation / depigmentation.[2,11] Long term habitual scratching and rubbing may result in chronic papular lesions, thick lichenified plaques of Lichen Simplex Chronicus (LSC) or Nodular Prurigo. Intense pruritus may result in sleep disturbances, social isolation and psychological disturbances, negatively affected and stressed family dynamics, impaired school / work function.[2,4,5,20,28-32]

1.1.9 Treatment of AD

As can be seen thus far, AD is a rather challenging skin condition for both clinicians and patients. Recent advances documented,[23] describing the key points and evidence based therapy of AD with an updated review of immunopathology, were presented at the latest

South African Dermatology Congress[23] and not only highlighted the latest AD evidence-based treatments, but also suggested practical tips for the families and patients and clinicians involved.[23] A proactive management approach including trigger avoidance, daily emollient use and anti-inflammatory treatment is recommended in order to control subclinical inflammation as well as overt flares.[2,10,11,23]

It appears that successful AD treatment takes various factors into account including the patients' age, needs, morphology of the AD, extent and distribution of the AD at presentation, the disease course, specific previous treatment responses, the disease severity and persistence, as well as the number and frequency of flares and infection susceptibility. Management goals, on the whole include education of patients and caregivers regarding the disease, proper skin care (soaps and emollients), reducing the frequency and degree of flares, carefully monitoring the quality, type and quantity of the medication used and thus modifying the overall course of the disease and the development of the Atopic March (table 1.7).[2,17,23,30,33]

The management and education of AD are the cornerstone of a Dermatologists training and practice. Physicians, General Practitioners and Allergologists / Immunologists may also be involved in this paramount management.[10,12,17]

Management of Atopic Dermatitis		
	Nonpharmacological treatment of AD	Emollients, wet wraps, soaps, salt baths, ↓bathing frequency, ↓triggers &exacerbating factors, food elimination[17]
	Treatment of AD	**Level of evidence**
	Education of patient/caregivers	B
	Acute treatment of inflammation & pruritus	
1st Line Therapy	1. Education 2. Emollients 3. Wet wraps 4. Topical steroids	A B C A
	Maintenance & prevent disease recurrence	
2nd Line Therapy	5. Topical immunomodulators 6. Antibacterials 7. Anxiolytics / antihistamines 8. Trigger avoidance 9. Barrier repair products	A C C A B
	Severe refractory cases	
3rd Line Therapy	10. House dust mite reduction 11. Solid food introduction 12. Phototherapy 13. Cyclosporine 14. Azathioprine 15. Mycophenolate mofetil 16. Methotrexate 17. Interferon – γ 18. Systemic corticosteroids 19. Efaluzimab	A A A A A C B A B E
Adjunct Therapy	Avoid triggers Antivirals therapy Antimicrobials (bleach baths) Psychological interventions (stress relief)	

Table 1.7 – Evidence based management of AD – adapted from the South African Guidelines[2,17,23,30,33]

Results of recent studies have shown that diagnosis of AD has positive outcomes on progression of the AD as well as for the future development of related important comorbidities viz secondary skin infections, the Atopic March and IgE mediated allergies, mental health disorders and sleep.[23,34] The main cause of known diagnostic failure appears to be the non-use of prescribed treatments.[35]

Family and patient education programs for AD, established in the last ten years are very important in providing the appropriate education as well as the much needed psychological support in AD (Table 1.8). [35,36,37,38] These can also address new documented observations that there is an increasing presence of psychosomatic AD comorbidities.

Regarding patient educational programmes, when parents of 1628 children with a mean age of 1.7 years were studied through a questionnaire, they were found to have a significantly increased rate of self-confidence to manage their AD child with 90% rating their consultation with the educational nurse as being highly supportive.[39] The authors suggested that therapeutic patient education (TPE) programmes, especially individually tailored consultations, ought to be part of the treatment of AD in addition to our usual medical care.[39]

It is important to stress that there are no “quick fixes” in AD patients and that treatment is effective so far as alleviating and managing the symptoms is concerned, but cannot cure it and that the dermatologists / clinicians should be aware of several interventions including antimicrobial, allergen and behavioural and / or educational modalities and these may greatly improve the AD severity and wellbeing of AD patients[15,17,23,35,36,39,40] and prevent significant comorbidities and complications e.g., infection, behavioural problems, sleep disturbances and growth impairment.[23,41] (see section 1.1.11.2)

Sleep disruption 1. Optimisation of sleep hygiene a. Consistent schedule of sleeps and naps b. Relaxing, consistent bedtime routine c. Avoidance of screen time and/or electronics before bed d. Attention to sleep associations after skin improved (phasing out the need for parental presence at bedtime) 2. Use of relaxation strategies for sleep onset and focusing of attention away from itch (downloadable recordings and CDs available for adults and children) 3. Covering of skin to reduce skin damage due to nightime scratching a. Wet dressings as necessary b. Cotton pyjamas with long pants and sleeves c. Eczema “sleepsuits” available for purchase online d. Coverings for hands and feet (or modified pyjamas with socks or gloves sewn or taped to pyjamas) 4. Consideration of sedating antihistamines 5. Consultation with sleep specialist or psychologist (psychological support) for persistent sleep problems
Itching and scratching 1. Nonblaming approach to itch (focus on what patients can do when itchy) 2. Use of elements of skin care plan (baths, moisturizer, medication, wraps) 3. Covering of skin (long clothing, gloves, tights, wraps) 4. Distraction and redirection to hands-on activities a. Handheld electronics, blocks, crayons, stress balls, knitting b. Special toys for baths (bath crayons) 5. Use of competing sensory sensations (cool pack, cool washcloth) 6. Use of psychological interventions to reduce stress and focus attention away from itch a. Relaxation strategies (guided imagery, relaxed breathing, muscle relaxation, biofeedback) b. Psychological support - Cognitive behavioural therapy to address stress and anxiety

Table 1.8 - Practical strategies for managing itch and sleep disruption[23]

1.1.10 Complications and Comorbidities of AD

1.1.10.1 Complications of AD

In AD there is a large burden caused by this chronic relapsing inflammatory disorder,[36] viz

1. The insatiable itching, scratching, dryness, excoriated skin and secondary infection,

2. The impaired quality of life of not only the affected paediatric patients but the families,

3. The recurrent course of this skin disease, and one may find that patients and caregivers often lose confidence in the management and may fear side effects of medication used especially steroids – “steroid phobia”.[35,37,38]

Infections[2,9,11]

These may be due to the impaired epidermal skin barrier as well as the modified immune milieu in AD. Infections include various bacterial and viral infections:

- Staphylococcus aureus / Streptococcus Impetiginisation
- Staphylococcal exotoxins may act as superantigens and stimulate the inflammatory cascade and worsen AD. Superantigens are a class of antigens that cause nonspecific T cell activation resulting in polyclonal T cell populations and massive cytokine release.
- Eczema Herpeticum
    - Rapid HSV dissemination over eczematous skin in AD patients. (monomorphic scalloped-edged, punched out erosions with haemorrhagic crusting, maybe widespread, involve any site of the body but most commonly on the head, neck, trunk and associated with pyrexia, lymphadenopathy and malaise ± superinfection with staphylococcus / streptococcus, may include eye involvement with herpetic keratoconjunctivitis and cerebral meningoencephalitis)
- Molluscum Contagiosum
    - Widespread poxvirus lesions may be seen with skin coloured umbilicated papules

Ocular complications (allergic conjunctivitis, keratoconus, herpetic keratoconjunctivitis needing ophthalmology consultation)

Erythroderma – This is defined as a generalised > 90% BSA exfoliative dermatitis (red, scaly, itchy skin) seen in very severe AD and often needing inpatient management.

1.1.10.2 Comorbidities of AD

The list of comorbid conditions that may be associated with AD includes various atopic and nonatopic conditions and include the Atopic March (see below), increased risk of obesity, headaches, high blood pressure, anaemia and speech disorders as well as vitiligo and alopecia areata.[2,10,11,23]

In the subset of AD with raised IgE levels, i.e., extrinsic Allergic Atopic Eczema Dermatitis Syndrome (AAEDS), the typical itchy lesions often herald the early stages of the Atopic March[10,42,43] (Figure 1.10 and 1.11 describing the possible progression of mucosal atopy)[2], a well described comorbidity.

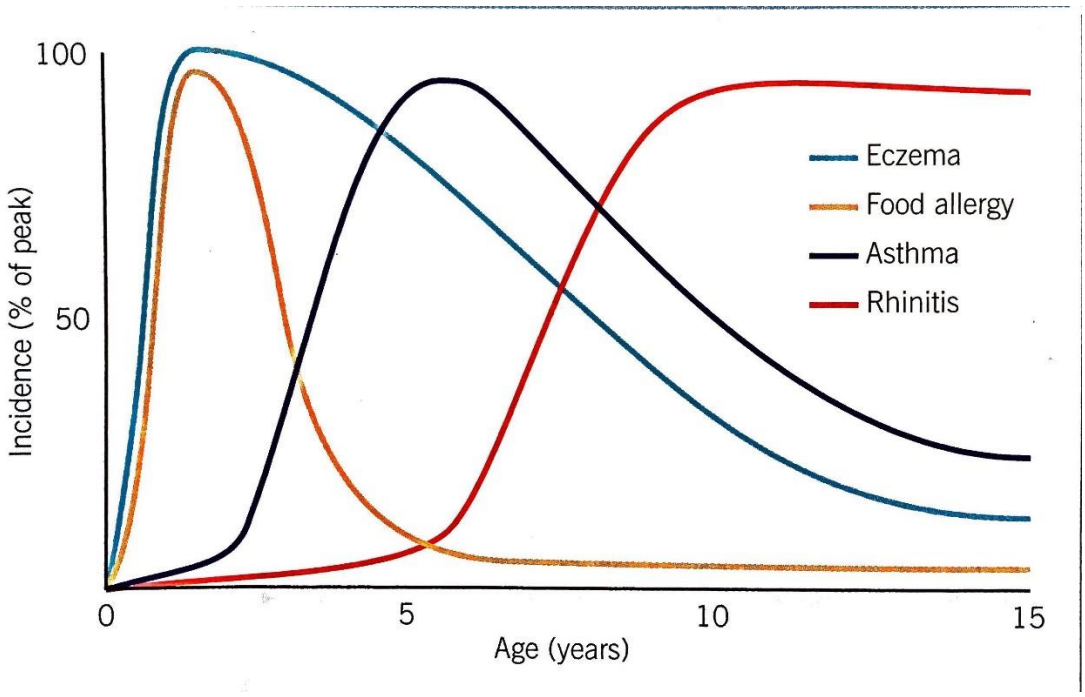


Figure 1.10 – Prevalence rates and progression of the Atopic March[2]

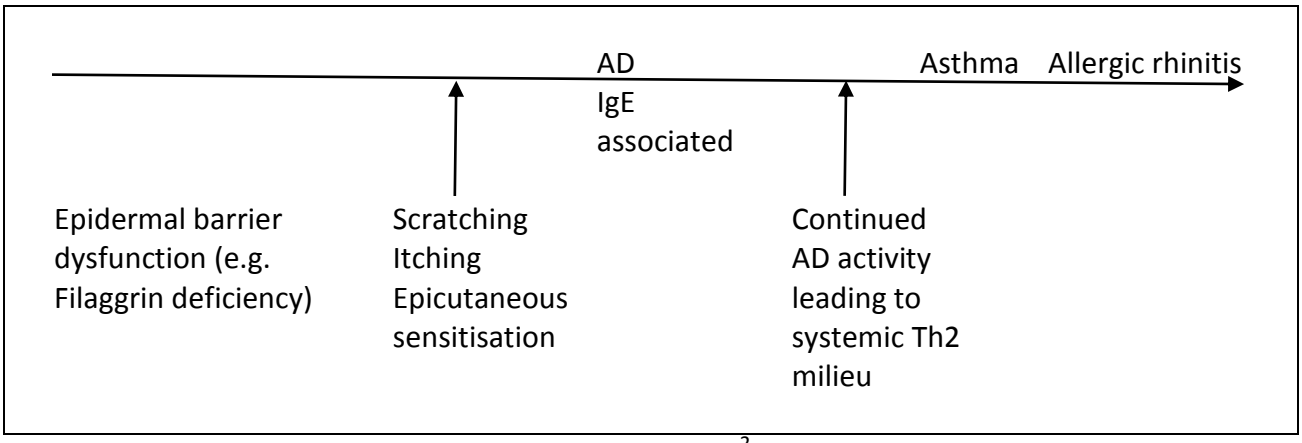


Figure 1.11 – General progression of the 'Atopic March'[2]

In approximately 30% - 50% of children with AD, asthma develops,[42,43] allergic rhinitis may develop in 35% - 70% of AD sufferers,[43] food allergy in 40% of infants with severe AD and allergic conjunctivitis may also be an associated comorbidity.[43] Other associated conditions, as mentioned previously, may include an increased predisposition to bacterial infections e.g. staphylococcal or streptococcal Impetigo or to various viral infections e.g. Molluscum Contagiosum or HSV induced eczema herpeticum (Figure 1.9).

Several other comorbidities associated with AD include various psychosocial issues. Most studies have shown prevalence rates of psychiatric and psychological and behavioural comorbid conditions to be approximately 30% in skin disorders.[5,44-47] Picardi and colleagues reported an overall psychiatric morbidity prevalence of 25,2% at dermatology clinics in Italy.[44] While other studies have reported mood problems (depression and anxiety) of 56.25%, much higher than the usual 30% generally reported.[5,45,46,47]

Sleep, a vital human function, has not been studied much in dermatological conditions but the current theory of sleep problems in patients with AD relates to the night time pruritus and scratching behaviour.[44]

1.2 Sleep and Sleep Disturbances in the Normal Paediatric Population

1.2.1 Introduction

Sleep is described as an active process occupying 1/3 of our human life.[3,5] There is an increasing body of evidence of the crucial importance of sleep on children's general health and optimum functioning.[7,48,49,50]

Sleep consists of various cycles of light to deeper sleep within a certain periodicity throughout the night and children who are considered to be 'good sleepers', are those who although they wake regularly during light sleep through the night, settle back to sleep with no disturbance to the parents.[51]

Sleep arousals may be spontaneous or follow various pathophysiological alterations, e.g., pruritus, pain or obstructive sleep apnoea (OSA). Pruritic skin disorders, e.g., atopic dermatitis may be a major factor in sleep disturbance.[3]

Several studies have previously attempted to establish a prevalence for sleep problems.[6,49,50,51] However, due to the wide variations in sampling, study measuring instruments or scales used, disagreement on the definition of sleep disorders versus sleep problems versus sleep behaviours, there has been great variability or lack of necessary compatibility in many of the above.[6,51] Nonetheless, it is widely accepted that paediatric sleep problems are wide spread.[6,49,50,51]

The estimated prevalence of sleep problems in school aged children is up to 40%.[6,49,50,51] Furthermore, there is a reported 25% prevalence for bedtime struggles combined with night waking and an overall prevalence of 43% is reported for "sleep difficulties".[6]

The most common sleep problems may be broadly divided into two main categories:[51,52]

1. Those children with difficulty falling asleep
2. Those children who wake frequently and cry for parental attention
3. A coexistence of the above problems

Later research over the ensuing years[5-8] have included a whole host of other sleep parameters (which are discussed in detail under 1.2.2).

Various authors have studied different age groups of the paediatric population regarding sleep habits and sleep disturbances[49-51,53,54] and overall it appears that the prevalence of sleep problems is relatively higher in younger children (infants, pre-schoolers, first and second graders) than in older children. It is estimated that 13%-20% of normal 1-2 year olds wake regularly with 6%-10% having severe sleep disruptions[52] and that 14% of three year olds wake regularly.[52] There is a wide range in the reported prevalence of sleep

problems and this may be due to the fact that most of the few studies surveying sleep and sleep problems are parent report based and may not be very accurate.

There are no reported significant gender differences in younger children regarding sleep disturbances.[49,50,52] In older children there may be gender differences. In a study on 5-20 year olds from community schools in the Midwest USA, it was found that males were more likely to snore and have enuresis while females were found to be more likely to report dreams and have prolonged bedtime grooming rituals.[55]

The lower socioeconomic group subjects were found to be more likely to have night waking, snore, have restless sleep, have sleep anxiety and daytime sleepiness.[55]

There is a wide range in the prevalence of sleep problems ranging from 10% to 40% depending on the age group studied and the sleep problem considered. Overall in the normal paediatric population of ≤ 4 years of age common sleep problems including bedtime struggles and night waking maybe seen in about 1/3 of children.[49] Other studies have reported an overall sleep disturbance prevalence of 10%-29%[54] in normal preschool aged children and 40% in school aged children.[6]

During infancy, normal maturation may lead to progressively longer bouts of sleep at night, and up to 20% of a normal 1-2 year old London population and 14% of the a normal 3 year old London population were reported to wake regularly.[52] In other references, older normal children in a New York based study, unlike younger children, are described to have a significantly longer bedtime routine, may insist on sleeping with the light on and request more attention before falling sleep and are normally more likely to report nightmares and 29% had once per night waking. This is similar to the 31% prevalence rate reported in an Oxford study.[52,54] The similarity of sleep problems in normal paediatric

populations of around 30% in different geographic areas and various social circumstances across different publications, may have various reason including a neurophysiologic developmental basis.[52] Thus it can be summarised that around 1/3 of normal children may have general sleep problems. However, it is noted that this prevalence rises to 60%-83% of children suffering with AD who may have disturbed sleep with the higher prevalence being related to periods of an exacerbation of their AD.[3,4,5]

Regarding specific sleep problems, bedtime conflicts and night waking are described as quantifiable and easily ascertainable in any clinical dealing with the paediatric population and may alert health professionals to more pervasive child and family disturbances that need attention.[49,56]

Sleep wake behaviour maybe objectively evaluated with overnight polysomnography (PSG) studies or actigraphy. PSG measures simultaneous recording of electroencephalogram (EEG), electrooculogram, submental electromyogram ± respiratory effort, oximetry, heart rate, electromyography of the tibialis anterior muscle.[3] Actigraphy measures limb movements, monitored by wrist actigraphs and is based on the premise that movement is minimal or absent during sleep and recordable during wakefulness and may be used to record the presence of scratching during sleep and thus give some insight into the severity of both the skin condition and the associated sleep problem.[3,57]

It is a widely accepted fact that the correct amount of normal sleep is essential for the optimum health and proper development of the paediatric population, with a child spending up to 40% of his or her childhood sleep.[7,48,49,50] It is especially important for children to sleep as the latter has a direct impact on their mental and physical

development.[49,50] However, there is a dearth of data about specific biologic function of sleep regarding normal development.[48]

Factors that may affect sleep and contribute to sleep problems include prematurity, chronic illness (renal failure, cardiac disease), being physically or mentally challenged, perinatal aberrations, temperament, certain allergic conditions, e.g., atopic dermatitis, financial difficulties, overcrowding, maternal abuse, poor housing conditions, mother's mental health status, cultural factors and separation anxiety.[51,53]

Sleep disturbances can have significant effects on children and adults resulting in considerable daytime deficits, e.g., mood disorder, fatigue, poor behavioural functioning and especially in children, developmental disorders.[58]

1.2.2 Classification of Sleep Disorders

The International Classification of Sleep Disorders (ICSD) is a revised version of sleep disorders by the American Academy of Sleep Medicine and is published in association with International Sleep Societies.[59] The ICSD-3 forms the key reference for sleep disorder diagnoses and identifies seven major categories of sleep disorders, namely:

1. Insomnia disorders
2. Sleep related breathing disorders (obstructive sleep apnoea, OSA)
3. Central disorders of hypersomnolence (narcolepsy type I & II, Idiopathic hypersomnia)
4. Circadian rhythm sleep-wake disorders (CRSWD)
5. Parasomnias

6. Sleep related movement disorders
7. Other sleep disorders

Paediatric diagnosis differs only with regards to paediatric OSA (obstructive Sleep Apnoea) and will be discussed under OSA.

The literature review will be focused on the main sleep disturbances affecting children, viz. insomnia, obstructive sleep apnoea and parasomnias.

1.2.3 Insomnia (definition and causes)

Insomnia[3,59] has been defined as 'a repeated difficulty in sleep initiation, sleep duration, consolidation, or sleep quality occurring despite age appropriate opportunity and time for sleep, resulting in functional impairment during the day for the child and / or family'. Insomnia among the paediatric population may be reported by their caretakers as bed time resistance, being unable to sleep independently or the presence of both. It may be due to normal developmental changes, a sleep disorder, psychosocial duress, a medical condition known to disrupt sleep, a psychiatric disorder, substance misuse, or side effects of various medications. It may include a very wide range of dermatology patients, especially as pruritus, a cardinal symptom in many dermatological diseases, is worse during the night.[1,3,29] However, it should be noted that many pruritic skin conditions may be associated with a significant psychological comorbidity and the contribution of the comorbid psychiatric condition needs to be considered when dealing with insomnia.[3]

Careful insomnia assessment in children needs to include a symptom rating scale (e.g., the CSHQ), various laboratory tests, and full medical examinations.

The ICSD-3 has consolidated all types of insomnia under an umbrella term of chronic insomnia disorder (includes 'primary' and 'comorbid').[59] The criteria include:

1. Sleep initiation / maintenance abnormalities,
2. The presence of an adequate circumstance / opportunity to sleep,
3. The daytime consequences / daytime impairment. [3,59]

Insomnia is a common problem in both children and parents.[56] Parent reports show a prevalence of 41% for insomnia in their children aged 2-14 year olds. 31% of school aged children in the normal population of 6-13 year olds had reported disorders of initiating and maintaining sleep, while 16% of 4-11 year olds 'sometimes' had, and 5% 'usually' had difficulty falling aleep.[56] Differences in prevalence rates seem to be based on different methods, the samples used and the ages of the children. Unfortunately longitudinal data are underrepresented.[3,29,34,56]

The consequences of insomnia in the paediatric population may lead to significant stress in the entire family and lead to dysfunctional family dynamics.[23,29] It may also result in significant daytime fatigue, poor performance at school / work, mood disorder and even attention deficit hypersensitivity disorder.[3,60]

1.2.4 Obstructive Sleep Apnoea (OSA)

OSA is the commonest type in a group called sleep disordered breathing disorders which may be described by disordered sleep respiration and snoring as a key symptom.[3] In OSA, obstruction in the airway results in an ongoing breathing effort but inadequate ventilation.[3,59]

The diagnosis of OSA requires the presence of signs or symptoms such as daytime sleepiness, insomnia, snoring, fatigue, reported respiratory disturbances at night (snorts & gasps) or observed apnoea (stops breathing). In terms of paediatric OSA, the criteria are simplified in the ICSD-3 and there is a single subjective criterion consisting of all the signs and symptoms consolidated together as laboured snoring or obstructed breathing, or daytime consequences of sleepiness, e.g., hyperactivity need to be present. Objective measurement of paediatric OSA include polysomnograms (PSG) criterion of either,

1. ≥ 1 obstructive event per hour of sleep or
2. Obstructive hypoventilation ($PaCO_2$ > 50 mm Hg for > 25% of sleep time)

together with snoring, flattening of the nasal airway pressure waveform, or paradoxical thoracoabdominal movement.[59]

Sleep disordered breathing, e.g., OSA is a associated with multiple and frequent arousals from sleep, resulting in sympathetic activation, altering immune neuroendocrine pathways and networks in the skin,[1,3,24] precipitating inflammatory skin conditions e.g., AD due to the secretion of various proinflammatory neuropeptides.[24,61] OSA may be associated with sleep-related sweating, probably due to the sympathetic activation, and acting as an added risk factor in the development of pruritus in AD (table 1.1).[3,17]

It is postulated that successful treatment of OSA using nasal CPAP masks (continuous positive airway pressure) may improve skin treatment and prolong the disease-free period in dermatology patients.[3,62]

Snoring and OSA found in children with AD[3,62-65] may also be related to the presence of asthma or allergic rhinitis, as a comorbidity or as part of the Atopic March.[62] Allergic

rhinitis (AR) is characterised by the presence of pruritus, sneezing, nasal congestion and rhinorrhoea.[62] These or OSA caused by these symptoms may lead to impaired sleep, as objectively recorded on polysomnography (PSG),[62] resulting in daytime deficits, and reducing efficiency at work/school and affecting the quality of life. AR has various mediators, e.g., histamine, proallergic cytokines (IL-1B, IL-4, IL-10), leukotrienes, prostaglandin D_2 (the major cyclooxygenase metabolite from degranulating mast cells), and Bradykinins which affect sleep regulation and cause impaired sleep independent of the nasal obstruction.[62] Clinicians need to be aware of these various comorbidities in the management of AD patients.

It is important to note that OSA is a multifactorial disorder and although allergic rhinitis (AR) may be just one of these factors, its management may nonetheless contribute to enhancing the associated sleep quality.[62] The major cause of OSA in children is adenotonsillar hypertrophy related to the Atopic March.[66]

1.2.5 Parasomnias

The parasomnias include

1. Sleep enuresis, sleep talking and restlessness
2. Sleep walking, grinding of teeth during sleep
3. Confusional arousals
4. Sleep terrors / alarmed by scary dream[6,59]

The parasomnias may be divided into 3 clusters according to the ICSD-3:[59]

1. Non rapid eye movement (NREM) related

2. Rapid eye movement (REM) related
3. Other

The Non REM related parasomnias (NREM) include confusional arousals, sleep walking and sleep terrors and the criteria include:

1. Recurrent incomplete awakenings
2. The absence of responsiveness or inappropriate responsiveness
3. Limited / no cognition or dream report
4. Partial / complete amnesia of episode

REM related parasomnias occur due to state disassociation occurring between REM sleep and wake or disturbed cognitive – emotional regulation occurring from REM. The non-REM related parasomnias generally occur in otherwise healthy individuals,[59] whilst REM related parasomnias (REM sleep behaviour disorder (RBD), nightmare disorder and recurrent isolated sleep paralysis) actually arise from serious neuropathology (RBD) or psychopathology (nightmare disorder)[59] and require appropriate referral.

The reported prevalence of parasomnias in normal preadolescent school aged children is 20.4% as compared to 42.4% in the AD population. The prevalence in the studies appears to be higher in the 9 and 10 years age group with no gender difference. There is an association with past physical illness and neurobehavioural abnormalities.[59,63]

1.2.6 Sleep Behaviour Measurement

Sleep behaviour measurement tools include questionnaires (parent or child reported), polysomnography and actigraphy.

Data has revealed that in a recent survey performed on 500 paediatric clinicians, sleep problems were inadequately screened for by the practising physicians especially in school aged children.[6] Various studies examining sleep behaviour have used a variety of different brief questionnaires, interviews or sleep survey instruments, which according to Owens has low reported reliability or validity in many of these;[6] as a result, study results have not been comparable.

One of the better questionnaires is the CSHQ – Children's Sleep Habit Questionnaire, designed primarily as a reliable and valid parent report questionnaire screening tool.[6] It reflects the most common and key sleep disorders of note in school aged children.

The CSHQ is formulated according to a standardized system for clinical sleep disorder categorisation such as contained and listed in the International Classification of Sleep Disorders (ICSD) manual,[6,7,12] and is based on the most prevalent clinical symptom presentations in the paediatric ICSD diagnoses.

The CSHQ is not a diagnostic tool regarding the definitive diagnosis of the cause of a sleep disorder[6] but is useful in highlighting sleep areas warranting further clinical information and evaluation.[6,7] The CSHQ is particularly useful in identifying sleep disturbances complicating medical or mental health issues in children, especially with chronic illnesses.[6]

Polysomnography (PSG) is an objective test used to diagnose sleep disorders, recording many body functions including brain (EEG), skeletal muscle activity (EMG), eye movements (EOG) and heart rhythm (ECG) during sleep. It also includes respiratory indicators and peripheral pulse oximetry. It requires the expertise of a sleep medicine physician and is regarded as the gold standard for sleep assessment.[3,7]

Actigraphy is an objective, non-invasive measure of monitoring sleep / activity cycles. An actimetry sensor / actigraph unit, a wrist watch like package, may be worn for a week or more and measures gross motor activity which is recorded and linked to a computer and analysed. This method is increasingly used since the 1990's with the advantage that the patient can move and perform normal routines, is more affordable and more useful for large field studies. It has good accuracy comparable to the PSG (studies show more than 90% accuracy).[3,7] Actigraphy is especially useful in the objective evaluation of insomnia especially in the evaluation of night time scratching secondary to pruritic dermatological conditions resulting in insomnia.

1.2.7 Sleep Disorders in AD

Atopic eczema / dermatitis affects up to 17% of children[12], associated with dry, easily irritated skin and can range from mild disease to almost total body involvement. Disturbed sleep is commonly reported by the parents of these paediatric patients as well as by older patients themselves.[32] These subjective reports of prevalent sleep disturbances are corroborated by observational studies which show that AD children awaken far more often and actually sleep less throughout the night. [30,48,63]

One of the main symptoms of AD is itch with this pruritus increasing during the night[1] and results in itch related loss of sleep / sleep disturbance. Sleep disruption or loss associated with AD or other dermatologic disorders, may significantly impact the quality of life as well as the mental health of the individual and may lead to exacerbations of the skin condition.[3]

In a pilot study done at the University of Wisconsin, Madison, using four self-assessment questionnaires, very high prevalence rates of 93.75% poor sleep quality were found in adult outpatients with chronic skin disease at the Dermatology Department. The presence of mood problems was found to worsen the quality of sleep.[44]

1.3 Sleep Loss in AD

1.3.1 Aetiology of Sleep Loss in AD

The Aetiology of sleep loss cited in various studies in AD has been postulated to be due to various reasons:

1. Skin temperature – Skin temperature increases at night and is lowest in the morning, resulting in an increase in transepidermal water loss (TEWL) at night, which in turn is associated with increased itch intensity in AD patients,[2] damage to the stratum corneum (outer most layer of the skin) compromising the skin's epidermal barrier function and thus allowing irritants to get much closer to the itch sensitive areas[1]. Ambient heat increases the sensation of pruritus possibly due to sensitised dermal nerve endings and a lowered itch threshold.[1,3,12] Sweating which may occur at night or secondary to exercise, stress and ambient heat, may increase pruritus and nocturnal itching, thus leading to sleep loss.[1,3]
2. The Hypothalamic-Pituitary-Adrenal axis (HPA axis) secretes corticosteroids in an orderly circadian rhythm. After sleep commencement, the endogenous cortisol levels are at their lowest and it has been shown that at this stage of sleep there is a corticosteroid trough thus allowing for mini-exacerbations of inflammatory skin disorders e.g. AD, thus increasing nocturnal itch[1]. Furthermore, it should be noted

that subnormal levels of cyclic AMP (CAMP), allow for greater cytokine secretion (IL-2, IL-8, IL-31) and it has been postulated that circadian CAMP reductions maybe associated with nocturnal histamine release and pruritus.[1]

3. Psychological components – It is thought that nocturnal awakenings are generally associated with itch and have a medical rather than a psychological aetiology[1]. Nonetheless one must be aware of the possible psychogenic causes of sleep disturbances in patients with pruritic dermatological conditions such as AD. Itch is a subjective symptom[2] and as such, the perception of itch maybe enhanced by stress, anxiety and increased depression, which may themselves be the result of poor sleep quality and quantity.[1,3,5,45,64]

   In a study in the UK, twice the rate of psychological disturbance was found in children in the AD group versus the control group and this was statistically significant[45]. The psychosomatic link of AD is further corroborated in an article from Germany[64] where psychophysiological and psychoneuroimmunological mechanisms influencing AD were proposed. Another psychological mechanism may be due to boredom and reduced psychological stimulation in the evenings which may increase pain perception. Since pain and pruritus have a complex neuroimmunological interaction, it is possible that boredom may increase itch[1].

4. The itch scratch cycle – It has been shown that scratching an itch, releases more pruritic mediators within the skin[1,2,3,10]. The stratum corneum mechanical damage allows for pruritogenic antigens to be in closer association with the skin, resulting in a self-perpetuating and very debilitating routine – the ITCH– SCRATCH cycle[1,3]. Scratching can become habitual in AD i.e. a subconscious or automatic behaviour which is acquired yet reinforced through repetition causing patients to

scratch even without the presence of a pruritic stimulus[1,2] and thus anything that promotes nocturnal itching, such as the various aetiological factors described above, are likely to both initiate and perpetuate this itch-scratch cycle[1,2,9,10,11].

5. Sleep deprivation, immune function and dermatologic disorders and the role of melatonin

   Sleep disturbance is a major factor which may lead to an impaired quality of life in AD patients and may have negative effects on both the neurocognitive function and the behaviour of AD children.[3,21,22,23]

   Reduced levels of night time melatonin have been found to be associated with sleep disturbances in children with AD.[21,22] Melatonin, known to have sleep inducing as well as anti-inflammatory properties, has been shown to be useful in the management of sleep disturbances in patients with AD. In a recent study by Chang in 2016, it was shown that melatonin supplementation is safe and maybe effective in improving the sleep onset latency as well as improving the disease severity in children with AD. [22] Melatonin may also be involved in sleep problems due to various 'other' effects on sleep, anti-oxidant ability and immunomodulation.[21,22]

1.3.2 Effects of Sleep Disturbance / Sleep Loss

Sleep deprivation is known to have detrimental effects on the physiological, behavioural and psychological functioning of an individual.[1,17,48,55,63] AD is one of the leading causes of sleep loss in children[5,13,43] and adults, making patients desperate for relief. Children with

eczema have been noted to experience sleep with poor initiation, prolonged nocturnal wakefulness and frequent night wakings.[5]

Skin disorders such as atopic dermatitis are variably associated with sleep disturbance, with some having an increased risk for sleep disordered breathing.[1,66,67] This is discussed under the section on obstructive sleep apnoea (OSA).

Inflammatory skin conditions viz. AD, Psoriasis, Lichen Planus and Chronic Idiopathic Urticaria (hives) have been reported to have interference with sleep at night.[1] It is noted that the subjective reporting of nocturnal pruritus and the loss of sleep rarely matches quantitative measurements of disease severity.[1]

1.3.3 AD, Sleep Loss and ADHD

Sleep is a fundamental biological regulation system associated with mental health and wellbeing.[31] Sleep problems or disturbances refer to non-clinical sleep parameters marked by reduced sleep amount and decreased sleep quality on a continuum[31] and in comparison to other children in the sample. In the context of sleep disturbances, less appropriate physiological regulation may have a negative effect on children's general emotional regulation, as well as on the availability of attentional and physiological resources, which may help children to cope with their environmental demands.[31] When physiological regulation is disrupted, the sleep problems may then make these children much more susceptible to dysregulated stress responses[31], which are then associated with externalizing (impulsivity, distractibility, disruptive behaviour, delinquency) and internalizing (depression, anxiety, self-esteem) problems.[5,31,44]

From several studies it has been reported[1,2,3,5,43,45,64] that itching and soreness cause sleeplessness in over 60% of children and adolescents with AD; that AD is one of the leading causes of sleep loss in childhood; that sleep efficiency decreases when the severity of AD increases; and that sleep deprivation leads to tiredness, mood changes and impaired psychosocial functioning[1,43] and may resemble and / or exacerbate ADHD. Increased discipline problems, ADHD, and behavioural problems including reduced family-and-child quality of life have been described in children with AD.[5] Most studies have a prevalence rate of 30% for psychiatric and psychological comorbidities in dermatological disorders. In a study of 77 children aged 6 to 16 years with eczema (in Adelaide Australia) examining daytime behaviour deficits, it was concluded that children with eczema had a greater number of sleep problems, lower quality of life, increased ADHD and increased oppositional behaviour compared to normal controls.[5] In a German epidemiological study of more than 13000 children aged 3 to 17 years, ADHD and AD were strongly related (odds ratio 2.67; 95% CI, 1.03-3.97) in children with sleeping problems but not in children without sleeping problems (odds ratio 1.24; 95% CI, 0.83-1.84).[43] According to a pilot study on adults done at the Psychocutaneous Medicine Clinic at the University of Wisconsin,[44] the relationship between chronic skin problems and mood and sleep disorders merits more attention.[44] The study, conducted at the Outpatient Dermatology Clinics in Wisconsin, used four self-assessment questionnaires on dermatology OPD patients with any skin problems of ≥ 6 months duration. Participants were asked to complete questionnaires including Current Life functioning, Pittsburgh Sleep Quality Index (PSQI), Beck Depression Inventory (BDI-II) and Beck Anxiety Inventory (BAI) with the results being that 15 of 16 participants had poor quality of sleep.[44] Mood problems worsened the quality of sleep and functioning: 56.25% reported mood

problems (depression or anxiety),[44] and the results showed very high prevalence of poor quality sleep. Considering the negative effects of comorbid psychiatric and sleep problems (in this small study) on both the prognosis and management of chronic skin diseases,[5] several authors have demonstrated the need for stressing the importance of screening all patients with chronic skin diseases for sleep problems and mood problems.[1,3,5,23,44]

Insufficient and poor quality sleep are associated with child adjustment problems including externalising problems of behaviour,[3] depression and anxiety[31,44] and reduced child and family quality of life.[5,31,44] Furthermore a small body of literature has linked sleep problems with lower self-esteem in children (especially linked with reduced sleep or less optimal sleep quality), increased discipline problems and ADHD.[5,31]

1.3.4 AD and Sleep

Skin disorders have variable associations with sleep disturbances and insomnia.[1] Sleep problems were also defined as decreased amount of sleep and efficiency of sleep, and increased number of wake minutes during the night based on Actigraphy Studies[31]. Sleep in children with AD has been reported to be characterised by poor initiation and maintenance of sleep (42% compared to 7% of controls),[5] disorders of excess daytime sleepiness (27% compared to 7% of controls) and total sleep problems (47% compared to 10% of controls).[5]

Poor sleep is known to be associated with a range of daytime deficits in healthy children[5]. Sleep disruption resulting from night time scratching is linked to daytime fatigue, mood disorder, and poor work and school performance[3,30].

Non-restorative sleep (NRS) is defined as a subjective unrefreshing experience upon waking.[56] Epidemiological studies suggest that NRS is common in the normal general population, with varying rates of 1.4% to 35% across different studies with various definitions and populations[56]. Unfortunately, there is lack of data on non-restorative sleep in non-western countries.[56]

In the normal paediatric population sleep disturbance rates are around 30% as previously cited. These rates are much higher in children with AD: In a study of 300 children with AD aged 6 years or younger, 60% of the patients reported that the skin condition affected the sleep of their child[29,43]. Co-sleeping due to the dermatological condition was reported in up to 30%, and as much as 66% of families affected were bothered by this co-sleeping.[29] Sleep disturbance and co-sleeping, which itself was a direct index of the child's sleep disturbance, were linked directly to the severity of the AD[29] and were also linked to the degree to which the parents reported the AD to affect the child and family's mental wellbeing.[29]

1.3.5 Pruritus and Sleep

In studies of insomnia using polysomnography, it was found that scratching was followed by a lighter sleep stage and that scratching was not the result, but the cause of a lighter

stage of sleep and fragmented sleep (with greater number of sleep stage changes and arousals on polysomnograms).[2]

It seems that in humans, the regulatory process of 1L-31 in skin inflammation and pruritus is very complex, with a correlation of 1L-31 serum levels with the SCORAD (severity of AD score), sleeplessness and Th2 cytokines including 1L-4 and 1L-13, in the children observed with extrinsic AD.[24,61] Thus 1L-31 represents an interesting cytokine with promising potential for the Rx of the inflammation in childhood AD. This corroborates earlier articles in the Journal of Allergy and Clinical Immunology,[32] which state that there is evidence from human and animal studies suggesting that sleep is affected in AD due to inflammatory mediators (several cytokines have been implicated in changes in sleep associated with AD), and that the circadian fluctuations in certain inflammatory mediators (the increase in inflammation during the night associated with the circadian drop in cortisol) may also account for the increased sensation of itching at night reported by many patients.[32]

1.3.6 The Role of Generalised Allergy on Sleep

Atopy associated with atopic dermatitis may be associated with allergic rhinitis (AR) (nasal congestion) which may itself result in sleep disturbances (including obstructive sleep apnoea).[10,43,34,62,66] Allergic Rhinitis (AR) is classically characterised by sneezing, pruritus, rhinorrhoea and nasal congestion. These symptoms may lead to impaired nocturnal sleep due to impaired breathing or associated obstructive sleep apnoea (OSA) with resultant daytime fatigue and somnolence, reducing children's learning and causing decreased quality of life.[62,65,66,67] The medications used to treat AR, addressing histamine,

leukotrienes, cytokines and prostaglandins may play a role in sleep regulation, being directly involved in this sleep impairment irrespective of - and independent of - nasal obstruction.[62,66] The role that rhinorrhoea has on sleep impaired breathing is another factor, as well as the annoyance of mucus drainage impairing sleep.[62,66]

In a three year prospective study looking at sleep disorders in childhood and adolescents in allergic disease, it was found that children with allergic diseases had more bedtime resistance and needed more time to fall asleep than controls, with AD children having greater problems falling asleep and lower number of nights of sound sleep.[34] Children having AD and food allergy were found to be most predisposed to sleep disruption. The authors concluded that allergic diseases viz AD, are accompanied by different sleep disorders, including dyssomnias and parasomnias, i.e., bedtime resistance, disrupted sleep or sleep-disordered breathing. They further stressed the importance of physicians paying attention to sleep quality in children with allergic diseases irrespective of whether allergy was related to the skin (AD), the respiratory tract (bronchial asthma) or the alimentary system (food allergy).[34]

1.4 Effects of Sleep Disturbance on Family

Although sleep problems may often be thought of as transitory, Richman et al[52] demonstrated that disturbance to a child's sleep pattern, e.g., due to AD, worsened by any chronic illness, may be long-lasting and even persist for years, causing major demands on his/her parents' coping abilities.[51,52]

Several studies have alluded to the consequences of poor sleep in children and on family life.[50,52,56] Families interviewed often felt desperate, needing outside support, with 30% of parents reporting chronic fatigue, and 70% reporting more serious consequences of poor sleep: 37% reported serious arguments as a result of the sleep problem, 8% admitted to resorting to serious abuse of their child,[52] and 2% reported that the breakup of their marriage was directly due to the sleep disturbance of their child.[52] Other issues reported by parents included difficulties with their other children and curtailment of their sexual activity and social life.[52] Sleep deprivation may result in symptoms like depression, anxiety, apathy, aggression and irritability, and necessitate specific treatment aimed at sleep restoration. It is further stressed in the literature that a child who sleeps poorly may be at risk for non-accidental injury,[52] although it is also stated that such parents may lack necessary 'safety valves', i.e. stress relieving mechanisms or adequate family support that would ensure that the parents described do not take their stress and anger out on the child. Thus, the presence of a sleep problem necessitates serious insight and action by the health professional.[52]

There is presently no data on AD and sleep in South Africa. Considering the importance of sleep disturbances as a comorbidity in AD and its far reaching implications for all health care workers involved in the care of AD patients, it was decided to undertake this study to determine our South African sleep patterns associated with AD, in order to compare these with overseas data and shed light on the importance of AD and its associated sleep disturbances in our local Dermatology Paediatric OPD setting.

The aims of this study were:

1. To describe the various sleep disturbances associated with AD in children up to and including 12 years of age, in a government hospital dermatology clinic in Johannesburg, South Africa.
2. To compare the characteristics of children with sleep problems to those without sleep problems in AD
3. To compare sleep symptoms between males and females
4. To determine a possible association between smoking in the household and symptoms of sleep disordered breathing
5. To determine a possible association between rhinitis and sleep disordered breathing
6. To explore the association between a family history of allergies and sleep disturbances

CHAPTER 2

METHODS

2.1 Study Design

The study design was that of a prospective observational / descriptive study.

2.2 Site of Study

The study was carried out at the Paediatric Dermatology Outpatient Department at Chris Hani Baragwanath Academic Hospital. The Dermatology clinic runs on a Monday and Thursday morning and is operated by Dermatology consultants and registrars for patients under 15 years presenting with general and chronic skin disorders. On average 120 paediatric dermatology patients are seen on each morning.

Chris Hani Baragwanath Academic Hospital is the third largest hospital in the world located in Soweto, Johannesburg, South Africa. It is situated on a 70 hectare property with 3400 beds and 6760 staff members. It is one of 40 Gauteng provincial hospitals, financed and managed by the Gauteng Provincial Department of Health. It is one of the teaching hospitals for the Faculty of Health Sciences of the University of the Witwatersrand.

The children seen are referred from the surrounding smaller government hospitals, local government clinics, general practitioners and the various other paediatric clinics within Baragwanath Hospital. The population served by the CHBAH is mainly black, lower to middle income, who cannot afford private care. Although openly available and accessible,

it is mainly attended by the surrounding geographical population of Soweto. Most children attending have chronic skin conditions and attend the clinic on a monthly, quarterly or biannual basis depending on the level of control of their skin condition.

2.3 Inclusion Criteria

All paediatric AD patients otherwise healthy ≤ 12 years who had attended the clinic at least once before and been diagnosed with AD by the attending doctor based on the Hannifin and Rajka,[16] the UK working party[12,27] or the American Academy of Dermatology Conference on Paediatric AD criteria.[9,28]

2.4 Exclusion Criteria

1. Paediatric patients ≤ 12 years, with a diagnosis other than AD and related atopic conditions (such as allergic rhinitis, allergic conjunctivitis and asthma). i.e., patients with an additional diagnosis such as HIV, diabetes, etc. were excluded as this may have been a confounding variable in the analysis.
2. Any patient with medical comorbidies, e.g., Diabetes, Hypertension, Cerebral Palsy or psychiatric condition (eg ADHD or depression) that could impact on the child's sleep onset, and/or night awakening.
3. Patients on medication with likely effects on sleep, eg
    a. Antihistamines
    b. Anticonvulsants
    c. Antipsychotics

d. Psychostimulants

2.5 Data Collection Procedure

Parents / Guardians of children aged 0-12 years seen at the Paediatric Dermatology OPD and diagnosed previously as Atopic Dermatitis by the clinician, were given the questionnaire together with information and consent letter (appendix A and B respectively) which were filled together with the parent / guardian by staff. Before completing the questionnaire, they were asked for informed consent and assent (appendix C and D respectively). As the questionnaire was in English, for parents / guardians who did not have adequate command of English, use was made of four nursing staff that could translate the information into one of the local languages widely spoken in the locality (isiZulu, Setswana).

The clinical paediatric population consists of the hospital based paediatric population of 130 consecutive patients diagnosed previously as AD at the same Paediatric Dermatology OPD clinic. The data was collected over a two-month period due to the high presentation rate and numbers of patients seen in the selected age group for the study.

2.6 Participants / Clinical Sample

The sample size was calculated based on the prevalence of sleep problems in AD being at 60% according to the literature search4,5,9. The statistician, Ms Enat Chirwa was consulted and based on the formula $n = z2\ p\ (1-p) / \delta 2$, where $z = 1.96$ for a 95% CI, $p =$

0.6 (known prevalence), δ = 0.10 (10% margin of error). Therefore n = 92. It was thus decided to interview at least 100 patients.

In this research, all patients received the standard topical AD treatment administered at the Paediatric Dermatology OPD at Baragwanath hospital. Viz.:

- UE as soap (Ung Emulsificans)
- Liquid paraffin and Vaseline 50:50 as emollient
- Betnovate ointment 1:4 PMA applied to the body daily
- Mylocort ointment (1% hydrocortisone to face daily)
- Advantan ointment (methylprednisolone aceponate to severely affected areas only)[39]

2.7 Measure

A validated brief parent report questionnaire was used consisting of questions on demographics and the Children's Sleep Habits Questionnaire (CSHQ) (appendix B); these were given to the parent / guardian to complete.

- The questionnaire was anonymous.
- The CSHQ – Children's Sleep Habits Questionnaire consists of a validated retrospective, 35 sleep item parent questionnaire which screens for a number of important sleep domains that are key in this age group and encompasses 8 major clinical presenting sleep complaints, viz.:
    1. Bedtime behaviour or bedtime resistance
    2. Sleep onset delay

3. Sleep duration
4. Anxiety around sleep / sleep anxiety
5. Night wakings
6. Parasomnias
7. Sleep disordered breathing
8. Daytime sleepiness

- Parents were asked to recall the child's sleep behaviours that occurred over a typical recent week.
- Items were rated using a three point scale:
    - "usually" / "often" (if it occurred ≥ 5-7 times / week)
    - "sometimes" (if it occurred 2-4 times / week)
    - "rarely" (if it occurred 0-1 time / week)
- The Total Sleep Disturbance Score was calculated using all items of the eight listed subscales.

The CSHQ has been validated as a screening instrument in sleep disorders in a clinical setting, with good sensitivity (0.80) and specificity (0.72) for analysis of sleep problems in school aged children.[6]

2.8 Ethics Approval

This research was approved prior to commencement by the Chris Hani Baragwanath Hospital Review Board, Hospital Superintendent, the Paediatric Dermatology OPD consultant, the acting Head of Department as well as the Head of the Department of Dermatology at the Faculty of Health Sciences, University of

the Witwatersrand, Johannesburg. Final ethics approval was given by the Human Research Ethics Committee (medical) of the University of the Witwatersrand. (appendix E).

2.9 Statistical Analysis

Descriptive statistics and comparative statistics were used depending on the variables measured. Mean and standard deviation was used for parametric data and medians for non-parametric data. Categorical data were described using percentages.

With night waking, for the purposes of comparative statistical analysis variable 1 ("rarely") is compared with the combined variables 2 and 3 ("sometimes" and "often").

With restless sleep, the statistical analysis combined 1 ("rarely" 0-1 times per week) and 2 ("sometimes" 2-4 times per week) together, i.e. "rarely" and "sometimes" were together as normal while 3 ("often" 5-7 times per week) was abnormal.

The presence of snoring is always abnormal, therefore, for all variables scored here, item 2 and 3 were combined as the presence of the disorder, compared to item 1, as not having the disorder. Selected parts of the questionnaire such as a history of smoking at home was considered in the comparative statistics as it is one of the known environmental risk factors increasing the risk for AD, according to the South African AD guidelines.[17]

The unpaired t-test, Fisher's Exact Test and Mann-Whitney Test were used to compare various sleep parameters between the various groups.

CHAPTER 3

RESULTS

3.1 Demographics

The mean (SD) age of the sample was 5.5 (3.4) years. There were 61 boys (47%) and 69 girls (53%). The majority (98%) used electricity as the source of heat and cooking at home and 15% used gas as the source of heat and cooking at home. 33.8% were exposed to smoking in the house and 17.7% reported allergies (18 were dietary and 5 to dust). The median age of onset of skin condition was 5 months with a range of 0 to 120 months.

3.2 Global Allergy Burden

History of having	Child %	Family %
Eczema	100	33
Asthma	9.2	26
Allergic Rhinitis	50	54
Allergic Conjunctivitis	58	40

Table 3.1 – Personal or Family history of allergic diathesis

There was a high rate of personal and family atopy.

3.3 General Sleep Disturbances

The general burden of sleep disturbances in this group of children with AD is shown in Table 3.2.

The Children's Sleep Habits Questionnaire				
		Occurrence times/week		
Category	*Habits*	*"Rarely" 0-1 times % (n)*	*"Sometimes" 2-4 times % (n)*	*"Often" 5-7 times % (n)*
		1	2	3
1. Bedtime Resistance	a. Goes to bed at same time	44 (57)	29 (38)	27 (34)
	b. Falls asleep in own bed	48 (62)	14 (18)	38 (50)
	c. Falls asleep in other's bed	23.8 (31)	28.5 (37)	47.7 (62)
	d. Needs parent in room to sleep (n=129)	47.3 (61)	17.8 (23)	34.9 (45)
	e. Struggles at bedtime	46.9 (61)	22.3 (29)	30.8 (40)
	f. Afraid of sleeping alone	57.7 (75)	13.9 (18)	28.4 (37)
2. Sleep Onset Delay	a. Falls asleep within 20 minutes	27.8 (36)	20.7 (27)	51.5 (67)
3. Sleep Duration	a. Sleeps too little (n=129)	71.3 (92)	19.4 (25)	9.3 (12)
	b. Sleep the right amount	6.9 (9)	13.1 (17)	80.0 (104)
	c. Sleep same amount each day (n=128)	19.5 (25)	25.0 (32)	55.5 (71)
4. Sleep Anxiety	a. Needs parent in room to sleep	47.7 (62)	16.2 (21)	36.2 (47)
	b. Afraid of sleeping in the dark (n=129)	62.8 (81)	5.4 (7)	31.8 (41)
	c. Afraid of sleeping alone (n=129)	50.4 (65)	18.6 (24)	31.0 (40)
	d. Trouble sleeping away from home (n=129)	65.1 (84)	14.7 (19)	20.2 (26)
5. Night Waking	a. Moves to other's bed in night	75.4 (98)	9.2 (12)	13.4 (20)
	b. Awakes once during night	32.3 (42)	50.8 (66)	16.9 (22)
	c. Awakes more than once (n=129)	58.9 (76)	27.1 (35)	14.0 (18)
6. Para-somnias	a. Wets the bed at night	63.1 (82)	19.2 (25)	17.7 (23)
	b. Talks during sleep (n=129)	45.7 (59)	32.6 (42)	21.7 (28)
	c. Restless and moves a lot	23.9 (31)	21.5 (28)	54.6 (71)
	d. Sleepwalks	92.3 (120)	6.2 (8)	1.5 (2)
	e. Grinds teeth during sleep	74.6 (97)	15.4 (20)	10.0 (13)
	f. Awakens screaming, sweating	58.5 (76)	32.3(42)	9.2 (12)
	g. Alarmed by scary dream	58.5 (76)	36.1 (47)	5.4 (7)
7. Sleep Disordered Breathing	a. Snores loudly	49.3 (64)	19.2 (25)	31.5 (41)
	b. Stops breathing	90.0 (117)	6.9 (9)	3.1 (4)
	c. Snorts and gasps (n=129)	70.5 (91)	21.7 (28)	7.8 (10)
8. Daytime Sleepiness	a. Wakes self \ Others wake child (n=123)	3\1	8\19	53\39
	b. Wakes up in negative mood	34.6 (45)	24.6 (32)	40.8 (53)
	c. Has a hard time getting out of bed	46.2 (60)	24.6 (32)	29.2 (38)
	d. Takes long time to become alert after waking	53.8 (70)	18.5 (24)	27.7 (36)
	e. Appears tired during the day	46.9 (61)	33.1 (43)	20.0 (26)
	f. Falls asleep while watching TV	28.5 (37)	30.0 (39)	41.5 (54)
	g. Falls asleep while riding in car	26.9 (35)	24.6 (32)	48.5 (63)
Total score	35 questions mean (SD)	61.3 (8.5)		

Table 3.2 – Results of Children's Sleep Habits Questionnaire (n=130, otherwise stated)

Only about 1/4 of the children studied go to bed at the same time, every night. Nearly half of the children fall asleep in another person's bed and a significant minority show bedtime resistance. Overall only half of the study population fell sleep within 20 minutes. About 1/3 of the children have symptoms of sleep anxiety. The majority of children were perceived to sleep the right amount. Very few children wake every night. The most common parasomnia is restlessness. 1/3 of children have symptoms of sleep disordered breathing (as evidenced by snoring loudly) and between 3 and 8% report symptoms of OSA, nearly half the children fall asleep while watching TV or riding in a car and are reported to wake up in a negative mood and a significant group battle to get up in the morning.

3.4 The Impact of Night Waking on Sleep Parameters

It was noted that very few children wake every night and the impact of night waking on the other parameters is indicated in Table 3.3.

	Waking > 1 (n=53) % (n)	*Don't wake (n=76) % (n)*	*P value*
Age years mean (SD)	4.2 (3.0)	6.5 (3.4)	0.0001
Gender F/M	28/25	40/36	1.0000
Age of onset, months (median – range)	4 (0-60)	6 (0-120)	0.2313
Sleeps the right amount	64.2/35.8 (34/19)	100/0 (76/0)	<0.0001
Sleeps too little	45.3/54.7 (24/29)	16/84 (12/63)	0.0006
Falls asleep within 20 minutes	71.7/28.3 (38/15)	72.4/27.6 (55/21)	1.000
Struggles at bedtime	64.2/35.8 (34/19)	44.7/55.3 (34/42)	0.0331
Needs parent in room to sleep	60.4/39.6 (32/21)	46/54 (35/41)	0.1517
Moves to other's bed in night	32.1/67.9 (17/36)	19.7/80.3 (15/61)	0.1468
Any parasomnias (N/Y)	18.9/81.1 (10/43)	27.6/72.4 (21/55)	0.2986
Daytime sleepiness			
b. Wakes up in negative mood	75.5/24.5 (40/13)	63.4/36.6 (45/31)	0.0616
c. Has a hard time getting out of bed	52.8/47.2 (28/25)	55.3/44.7 (42/34)	0.8581
d. Takes long time to become alert after waking	45.3/54.7 (24/29)	46.1/53.9 (35/41)	1.000
e. Appears tired during the day	49.1/50.9 (26/27)	56.6/43.4 (43/33)	0.4738
f. Falls asleep while watching TV	83.0/17.0 (44/9)	63.2/36.8 (48/28)	0.0175
g. Falls asleep while riding in car	84.9/15.1 (45/8)	64.5/35.5 (49/27)	0.0151
Overall sleep disturbance mean (SD)	64.2 (8.1)	59.3 (8.2)	0.001

Table 3.3 – The effect of Night Waking on other sleep parameters
All comparisons done using a Fischer's Exact test except for comparisons of age and overall sleep disturbance where an unpaired t-test was used.

The children who woke up were about 2 years younger than those who did not wake up. There was no significant difference between the genders or age of onset of the night waking sleep problem in our AD population. Children waking up more than once per night were significantly more likely to not have the right amount of sleep and to sleep too little. Night waking was positively associated with reduced duration of sleep. Night waking was not associated with sleep onset delay, needing a parent to fall asleep, or moving out of their own bed at night indicating no association with sleep anxiety.

There was no difference in the rate of parasomnias between those that wake more than once versus those that do not. There were also no significant differences with regards to negative mood, having a hard time getting out of bed, taking long to get alert, or being tired during the day. However, children who woke at night were significantly more likely

to fall asleep while watching TV and while in the car, indicating a significant daytime effect from the night waking.

Those children who woke regularly at night had a significantly higher total sleep disturbance score compared to those without reported night waking.

3.5 The Impact of Restless Sleep on Sleep Parameters

Restless sleep was the most common parasomnia reported in these children and the impact of restless sleep on the other parameters is indicated in Table 3.4.

	Restless sleepers (n=71) % (n)	*Non-restless sleepers (n=59) % (n)*	*P value*
Age years mean (SD)	5.42 (3.7)	5.58 (3.1)	0.7975
Gender F/M	37/34	32/27	0.8609
Age of onset, months (median – range)	4.5 (0-120)	6 (0-96)	0.1900
Sleeps too little	25.7/74.3 (18/52)	32.2/67.8 (19/40)	0.4405
Falls asleep within 20 mins	66.2/33.8 (47/24)	79.7/20.3 (47/12)	0.1154
Wakes >1 per night	41.4/58.6 (29/41)	40.7/59.3 (24/35)	1.000
Moves to other's bed in night	33.8/66.2 (24/47)	13.6/86.4 (8/51)	0.0083
Afraid of sleeping in the dark	45.7/54.3 (32/38)	27.1/72.9 (16/43)	0.0438
Needs parent in room to sleep	56.3/43.7 (40/31)	47.5/62.5 (28/31)	0.3786
Afraid of sleeping alone	52.2/47.8 (36/33)	47.5/52.5 (28/31)	0.7230
Trouble sleeping away from home	34.3/65.7 (24/46)	35.6/64.4 (21/38)	1.000
Daytime sleepiness			
b. Wakes up in negative mood	64.8/35.2 (49/22)	61.0/39.0 (36/23)	0.3603
c. Has a hard time getting out of bed	56.3/43.7 (40/31)	50.8/49.2 (30/29)	0.5974
d. Takes long time to become alert after waking	47.9/52.1 (34/37)	44.0/56.0 (26/33)	0.7252
e. Appears tired during the day	50.7/49.3 (36/35)	55.9/44.1 (33/26)	0.5989
f. Falls asleep while watching TV	76.1/23.9 (54/17)	66.1/33.9 (39/20)	0.2441
g. Falls asleep while riding in car	80.3/19.7 (57/14)	59.3/40.7 (38/21)	0.0489
Overall sleep disturbance mean (SD)	64.4 (8.4)	57.6 (6.9)	<0.0001

Table 3.4 – The effect of restless sleep on other sleep variables
All comparisons done using a Fischer's Exact test except for comparisons of age and overall sleep disturbance where an unpaired t-test was used.

Restless sleeping was not related to age, gender or age of onset of the AD nor was it associated with sleep duration, sleep anxiety or waking up more than once during the night, however it was significantly associated with moving to another's bed.

Restless sleeping was positively associated with being afraid of sleeping in the dark. There was no association between restless sleep and the various daytime sleepiness parameters except for falling sleep in the car.

Overall sleep disturbance was significantly higher in the restless sleepers (parasomnias) versus the non-restless sleepers.

3.6 The Impact of Snoring on Sleep Parameters

It was noted that about 1/3 of children have symptoms of sleep disordered breathing as evidenced by snoring loudly and the impact of snoring on the other parameters is indicated in Table 3.5.

Variable	*Snorers (n=66) % (n)*	*Non-Snorers (n=64) % (n)*	*P value*
Age mean (SD)	5.66 (3.4)	5.33 (3.4)	0.5820
Gender F/M	33/33	36/28	0.4881
Age of onset, months (median – range)	6 (0-96)	5 (0-120)	0.8578
Smokers	39.4/60.6 (26/40)	28.1/71.9 (18/46)	0.1977
Sleeps the right amount	90.9/9.1 (60/6)	95.3/4.7 (61/3)	0.4925
Parasomnias			
b. Talks during sleep	66.2/33.8 (43/22)	42.2/57.8 (27/37)	0.0081
c. Restless and moves a lot	83.3/16.7 (55/11)	68.8/31.2 (44/20)	0.0645
e. grinds teeth during sleep	33.3/66.7 (22/44)	17.2/82.8 (11/53)	0.0440
f. Awakens screaming sweating	53.0/47.0 (35/31)	29.7/70.3 (19/45)	0.0080
g. Alarmed by scary dream	47.0/53.0 (31/35)	35.9/64.1 (23/41)	0.2176
Daytime sleepiness			
b. Wakes up in negative mood	72.7/27.3 (48/18)	57.8/42.2 (37/27)	0.0971
c. Has a hard time getting out of bed	62.1/37.9 (41/25)	45.3/54.7 (29/35)	0.0781
d. Takes long time to become alert after waking	53.0/47.0 (35/31)	39.0/61.0 (25/39)	0.1177
e. Appears tired during the day	65.2/34.8 (43/23)	40.6/59.4 (26/38)	0.008
f. Falls asleep while watching TV	72.7/27.3 (48/18)	70.3/29.7 (45/19)	0.8466
g. Falls asleep while riding in car	72.7/27.3 (48/18)	73.4/26.6 (47/17)	1.000
Overall sleep disturbance mean (SD)	64.8 (8.5)	57.7 (6.8)	<0.0001

Table 3.5 – The effect of snoring on other sleep parameters
All comparisons done using a Fischer's Exact test except for comparisons of age and overall sleep disturbance where an unpaired t-test was used.

1. There were no age or gender differences in the snorers versus non-snorers.
2. Smoking at home did not affect the prevalence of snoring.
3. Snoring was not significantly associated with sleep duration. However, snoring was significantly associated with talking during sleep, with grinding teeth during sleep and with reported waking up screaming and sweating.
4. Snoring was significantly associated with daytime sleepiness – reported being tired during the day but not with falling asleep in front of the TV or while in the car.

Overall the total sleep disturbance rate with snorers was significantly higher than for non-snorers.

3.7 The Impact of Rhinitis on Sleep Parameters

It was noted that half the children in our AD population reported allergic rhinitis and the impact of rhinitis on the other parameters is indicated in Table 3.6.

	Rhinitis (n=65) % (n)	*No rhinitis (n=65) % (n)*	*P value*
Age years mean (SD)	5.9 (3.4)	5.0 (3.4)	0.1084
Gender F/M	33/32	36/28	0.5978
Age of onset, months (median – range)	6 (0-120)	4.5 (0-96)	0.6748
Smokers in the house	33.9/66.1 (22/43)	33.9/66.1 (22/43)	1.000
Sleeps the right amount	90.8/9.2 (59/6)	95.3/4.7 (62/3)	0.4920
Sleeps too little	23.1/76.9 (15/50)	34.4/65.6 (22/42)	0.1767
Takes more than 20 mins	75.4/24.6 (49/16)	69.2/30.8 (45/20)	0.5569
Awakes more than once	40.0/60.0 (26/39)	42.2/57.8 (27/37)	0.8588
Struggles at bedtime	61.5/38.5 (40/25)	44.6/55.4 (29/36)	0.0784
Needs parent in room to sleep	59.4/40.6 (38/26)	46.2/53.8 (30/35)	0.1595
Any parasomnia	89.2/10.8 (58/7)	75.4/24.6 (49/16)	0.0644
Snoring	66.2/33.8 (43/22)	35.4/64.6 (23/42)	0.0008
Apnea and snorting	41.5/58.5 (27/38)	21.5/78.5 (14/51)	0.0229
Daytime sleepiness			
b. Wakes up in negative mood	67.7/32.3 (44/21)	63.1/36.9 (41/24)	0.7126
c. Has a hard time getting out of bed	55.4/44.6 (36/29)	52.3/47.7 (34/31)	0.8604
d. Takes long time to become alert after waking	55.4/44.6 (36/29)	36.9/63.1 (24/41)	0.0525
e. Appears tired during the day	56.9/43.1 (37/28)	49.2/50.8 (32/33)	0.4822
f. Falls asleep while watching TV	75.4/24.6 (49/16)	67.7/32.3 (44/21)	0.4371
g. Falls asleep while riding in car	76.9/23.1 (50/15)	69.2/30.8 (45/20)	0.4293
Overall sleep disturbance mean (SD)	64.1 (8.8)	58.6 (7.2)	0.0001

Table 3.6 – The effect of rhinitis on other sleep parameters
All comparisons done using a Fischer's Exact test except for comparisons of age and overall sleep disturbance where an unpaired t-test was used.

There were no significant statistical differences noted regarding reported rhinitis and demographics or a history of smoking at home, sleep duration, sleep onset delay, night waking, parasomnias, sleep anxiety, bedtime resistance or daytime sleepiness. However statistically significant difference was noted in the reported sleep disturbed breathing for snoring, apnoea and snorting in the rhinitis group compared to the group of children without rhinitis.

The overall sleep disturbance rate was significantly higher in the rhinitis group compared to non-rhinitis group.

3.8 The Impact of Family History of Allergies on Sleep Parameters

Family history of allergies did not contribute significantly to the overall sleep disturbance, the impact of family history of allergies on the other parameters is indicated in Table 3.7.

	Family history of allergies (n=98)	*No history (n=32)*	*P value*
	3=yes	1+2 = no	
Age years mean(SD)	5.4 (3.5)	5.8 (3.2)	0.5879
Gender F/M	56/42 (57.1/42.9)	13/19 (40.6/59.4)	0.1527
Age of onset months (median -range))	4 (0-120)	8 (0-96)	0.2765
Sleep the right amount	77/21 (78.6/21.4)	5/27 (15.6/84.4)	<0.0001
Sleeps too little	8/89 (8.2/91.8)	4/28 (12.5/87.5)	0.4906
Takes more than 20 minutes	50/48 (51.0/49.0)	17/15 (53.1/46.9)	1.000
Struggles at bedtime	34/64 (34.7/65.3)	6/26 (18.8/81.2)	0.1224
Needs parent in room to sleep	39/59 (39.8/70.2)	8/24 (25/75)	0.1443
Moves out of bed	15/83 (15.3/84.7)	5/27 (15.6/84.4)	1.000
Any parasomnia	85/13 (86.7/13.3)	22/10 (68.8/31.2)	0.0314
Snoring	53/45 (54.1/45.9)	13/19 (40.6/59.4)	0.2239
Daytime sleepiness			
b. Wakes up in negative mood	42/56 (42.9/57.1)	11/21 (34.4/65.6)	0.4171
c. Has a hard time getting out of bed	28/70 (28.6/71.4)	10/22 (31.2/68.8)	0.3810
d. Takes long time to become alert after waking	24/74 (24.5/75.5)	12/20 (37.5/62.5)	0.3520
e. Appears tired during the day	21/77 (21.4/78.6)	5/27 (15.6/84.4)	0.6136
f. Falls asleep while watching TV	40/58 (40.8/59.2)	14/18 (43.8/56.2)	0.8374
g. Falls asleep while riding in car	50/48 (51.0/49.0)	13/19 (40.6/59.4)	0.3183
Overall sleep disturbance mean (SD)	61.9 (8.4)	59.3 (8.6)	0.1282

Table 3.7 – The effect of family history of allergies on other sleep parameters
All comparisons done using a Fischer's Exact test except for comparisons of age and overall sleep disturbance where an unpaired t-test was used.

Children with a positive family history of allergies were found to be significantly more likely to sleep the right amount compared to children without a family history of allergies. The presence of a a positive family history of allergies was also found to be significantly

associated with the presence of parasomnias. It is well known that a positive maternal history of AD is a significant environmental influence on AD. Family history of allergies did not significantly contribute to other sleep parameters including sleep disordered breathing, daytime sleepiness and overall sleep disturbance.

CHAPTER 4

DISCUSSION

4.1 Discussion and Findings

All subjects studied had atopic dermatitis, 9.2% had asthma, 50% AR (allergic rhinitis), 58% AC (allergic conjunctivitis) 33% had a positive family history of eczema, 26% asthma, 54% AR, 40% AC (i.e., high rate of personal and family atopy in keeping with literature reports of the Atopic March).[11,12,37,38]

Our findings in this study of an overall sleep disturbance prevalence of 61.3% (SD=8.5) confirm the fact that children with AD are particularly at risk of being prone to various sleep disturbances and our results are consistent with overseas sleep patterns observed in children with AD (60%-83%).[3,4,5,63] Regarding various aspects of sleep considered in the validated questionnaire we used, the Children's Sleep Habits Questionnaire (CSHQ), our results of 61.3% (SD=8.5) (discussed fully below) fit in with those of Dahl et al[48] and Bartlet et al[63] of the Department of Paediatrics, John Hopkins University, USA, and the Department of Paediatrics, General Hospital, South Hampton, UK, respectively. The data in this study appears to be consistent with the clinical impression and the proposed hypothesis that AD children with itching and scratching may have higher rates of sleep disturbances versus normal children (10%-29%).[54,63]

4.1.1 Bedtime Resistance

Settling problems have been reported in the normal population in 10-22% of children.[51,63] However, in our study bedtime resistance and settling problems were much higher with a prevalence of 34.5% in our AD children.[63] Our prevalence rate was similar to the 32% rate quoted in a UK study[63] and 27% in a study in New York[53] on AD and sleep problems. The pre-bedtime routine for the management of AD of bathing, towelling dry, applying various emollients and therapeutic creams may be stressful and turbulent in terms of a child's settling down and may explain the higher bedtime resistance rates found versus normal children.

Bedtime resistance was reported as a significant finding in Dahl et al,[48] being three times more prevalent in AD children (18.6%) versus normal children (5.1%), and was corroborated in Bartlet et al,[63] where settling problems occurred in 32% of AD children (much higher than 10% in normal population).

Half of the children in the present study were reported to fall asleep in another person's bed (bedtime resistance). Part of bedtime resistance was the question regarding being afraid of sleeping alone (co-sleeping) with 28.4% being afraid of sleeping alone and 13.4% moving to another's bed during the night in our study. This correlates with other studies reporting a 30% prevalence for AD children in the parental bed.[63,68] Cultural practices of co-sleeping may have also played a part in our black population.[68]

Overall our results are in keeping with clinical impressions held that children suffering with AD were reported to have specific sleep disturbances namely difficulty in settling (bedtime resistance); waking up at night (night waking); snoring and sleep disordered breathing at night; daytime sleepiness and difficulty waking up in the morning for school;

and being frequently tired with reports of falling asleep while watching TV or riding in a car.

4.1.2 Sleep Onset Delay

The prevalence of sleep onset delay in our study identified as not falling asleep within 20 minutes was 27.8%. This closely correlates with the reported prevalence rate of 32%[63] and is much higher than the reported prevalence in normal children of 11.3%.[53] Sleep onset problems in the literature were correlated with nightwaking (not consistent with our study); more fears and sleep anxiety; more medical and psychiatric conditions;[53] and a history of other sleep problems needing more caregiver proximity and reassurance. Dahl et al reported double the prevalence rate of sleep onset delay in AD versus normal children, which was statistically significant, while our rates showed 2.5 times prevalence rates of sleep onset delay (27.8% vs. 11.3%). These higher reported rates in our study may be related to the child's sleep not being managed appropriately by parents or to the pruritic condition itself.[49,50,68] According to Blader,[53] sleep onset delay is a significant predictor of medical illness and this may have been the reason for our high prevalence rates. Another reason may have been the physical sleep arrangements with possible noise or light interference as a causal factor due to lower socio-economic group and possibly smaller homes leading to shared spaces and TV and music interference.

4.1.3 Sleep Duration

In this study, the majority of children were perceived to have the correct amount of sleep. A significant difference in reported adequate sleep duration has been noted between normal (69%) and AD children (44%).[48] This is in contrast to our study, where it was unexpected that the majority of parents thought that their children with AD had the right amount of sleep, while half the parents reported that their children slept the same amount each day. It would be more accurate to record more detailed questions regarding sleep duration, e.g., the number of hours slept and its relation to various severities of AD, in future studies. It is possible that where an adequate amount of sleep was reported by the parents, many of these patients did not suffer from severe AD or that parents had various definitions of the right amount of sleep.

4.1.4 Sleep Anxiety

About 1/3 of the children in this study had sleep anxiety. Sleep anxiety was reflected by the high percentage found in needing a parent in the room to sleep. Regarding being afraid of sleeping in the dark, there was consistency with the study by Dahl et al who also found high rates of 27.1% in AD for sleep anxiety versus the normal population of 11.6% prevalence using the Child Sleep Behaviour Scale.[48]

Being afraid of sleeping in the dark did not appear to be related to age in this study but rather to the AD.

4.1.5 Night Wakings

It was noted that very few children woke every night.

Our findings resemble those in other studies where certain aspects of sleep and associated bedtime behaviour were examined using a questionnaire quantitative method. 30% of normal infants were reported to awaken at least once every night in an Oxford study, and 29% in a New York longitudinal study.[54] In our South African study 41.1% woke more than once during the night.

Night wakings are reported at 6.5% prevalence in normal paediatric populations,[53] 15% in a Finnish population and up to 22%[63] in others. It is reported that 16.5% of patients who awake more than twice weekly returned to sleep in less than half an hour.[53] However, it is stated that once awake, up to 50.5% required more than 30 to 60 minutes to get back to sleep, 27.5% required 1 to 2 hours, and 3.7% spent 3 hours awake.[53] This data emphasises the seriousness and important consequences of night wakings. In our study, night waking was as high as 67.7% waking up “sometimes” and 41.1% waking up “often”. Our rate of 67.7% fits in with the 73% rate in AD reported by Bartlet (night waking defined as waking ≥ 3 nights per week).[63] These significantly high rates of night wakings in in our AD population could have serious implications. Night waking has shown a positive correlation with daytime sleepiness in the afternoon as well as with major discipline problems and thus has far reaching consequences.[48] Sleep disturbances have been associated with changes in daytime behaviour, mood problems and an increased ADHD risk in children with AD.[4,5,23,31,42,43]

Our study rate of 41.1% is lower than the one cited by Dahl et al’s study of 50.8% of night wakings in 6-12 year old AD children and much higher than the 11% in the general

population.[48] On the whole night wakings were significantly associated in this study with younger age, also were significantly negatively associated with the right amount of sleep, and significantly positively associated with too little sleep, bedtime resistance and daytime sleepiness as evidenced by falling asleep at the TV and falling sleep in the car.

In another study conducted in Manchester,[46] Department of Child Psychiatry, it was found that there was a 63% prevalence in sleep difficulty and sleep anxiety in a preschool cohort of AD patients versus those without AD. Sleep problems, defined in this cited study as waking at night ≥ 3 times per week, were found to be two times more common in the eczema group. This is interestingly higher than our findings where 41.1% woke once during the night. Their higher prevalence rate may be due to the varying definition of night waking and the fact that the Manchester study demographics and comorbidities results showed an excess (statistically significant) of child behavioural problems, of family disruption and of stressful parenting of children with AD that resulted in regular clinical attendance.[46] About 1/3 of the AD children studied had 'above morbidity' behavioural screening scores on the questionnaires and these were statistically significantly higher (23%) than in the general population samples (5%).[46] These behavioural disturbances in AD preschool groups were comparable to those in other severe chronic problems of childhood.[46] It was postulated, thus, that AD may be a risk factor in the development of childhood behavioural problems,[45,46] especially dependency, wakefulness and fearfulness, and concurs with previous study findings in this same area cited by Daud[46] and may explain the reason for the sleep anxiety prevalence in our study.

There was a significant difference in the overall sleep disturbance rate in those with reported night waking versus those without. The above findings are noteworthy and point to what parents use to gauge that their children have had too little sleep.

4.1.6 Parasomnias

The most common parasomnia reported in this study was restless sleep with a prevalence of 54.6%. The overall prevalence of bedwetters in this study was 10%. These numbers are normal for younger children and not unexpected as enuresis is reported in 8.21% of boys and 2.62% of girls.[49,50,53]

Sleep walking had a reported prevalence of 7.7% and was not included in the comparisons due to this low percentage. Both bedwetting and sleep walking have previously been shown to not be statistically significantly different in AD and non-AD population.[48]

Up to 76.1% were reported as being restless and moving a lot, a much higher rate than in the AD group reported in the literature of 42.4% versus the normal population of 20.4%.[63] The significant association with restless sleep, the most common parasomnia in this study, may have been related to inadequate treatment possibilities, to the activity of the skin lesions, itching or scratching, or possibly related to poor quality of sleep related to the physical sleeping arrangement.[48] Restless sleep, in the literature, was positively correlated with a positive family history of allergies, snoring, night waking more than once per night, and moving to other's bed.[48] However in our study, restless sleep was only positively correlated to family history of allergies and snoring, but not to night

waking and moving to other's bed. Further studies in this regard would shed more light on the reason for these discrepancies.

There were no differences in demographics pertaining to restless sleepers and no relation to the amount of sleep received or to sleep onset delay. However, restless sleepers were more likely to move bed (night waking) and to be afraid of the dark (sleep anxiety) versus non restless sleepers, and were also more likely to fall asleep in the car versus non restless sleepers; i.e., there was a positive correlation between restless sleep (a parasomnia) and daytime sleepiness, corroborating the findings by both Dahl and Bartlet.[48,63] Restless sleep was significantly associated with a positive family history of allergies in this study. Allergies may be associated with rhinitis, in which, in addition to rhinorrhoea and congestion, inflammatory mediators, e.g., cytokines (IL-1β, IL-4, IL-10) and cells (mast cells and basophils) may be involved in the associated problems with sleep.[62] These proallergic cytokines have been shown to be associated with decreased REM sleep duration and increased latency to REM sleep.[62] However, it was unexpected that in the multivariate analysis on rhinitis using the Fishers Exact Test, no significant relation was found between rhinitis and any parasomnia. Future studies would be more accurate if objective examination for rhinitis were involved and formal ENT consultations undertaken to accurately quantify the presence of allergic rhinitis which may have been underreported in this study.

4.1.7 Daytime Sleepiness

The following significant findings are noted from the present study.

- Only 11% of children were found to wake by themselves.
- 39% were usually needing to be woken up by others.
- 65.4% woke up in a negative mood on 2 or more occasions per week.
- 29.2% had a hard time getting out of bed in the morning.
- 27.7% took a long time to become alert after waking.
- 41.5% and 48.5% were reported as falling asleep while watching TV or while riding in a car respectively.

In the study by Dahl[48] the AD children were significantly more difficult to wake up in the morning, as only 23.7% of AD parents compared to 58.7% of normal population parents reported that it was easy to wake up their child in the morning. This is higher than the rate in our study where 53.8% reported their child had a hard time getting out of bed in the morning; this difference may have been related to sedating medication not specified or other comorbidities in Dahl's study. A significant minority of the children, in our study, were reported to fall asleep while watching TV or riding in a car, in keeping with Bartlet, highlighting the long known notion that chronically sleep deprived children often experience these daytime behavioural abnormalities and deficits, irritability, hyperactivity, poor concentration and poor school performance. It is noteworthy to state that these daytime functioning deficits may be improved by the correction of the night time disturbances.[63]

4.1.8 Sleep Disordered Breathing

There were no differences in demographics between snorers and non-snorers or in the amount of sleep. Bed-wetters and sleep walkers were not included in these comparisons due to the very small numbers.

There was a significantly higher rate of parasomnias in the snorers with AD, versus non-snorers with AD with regards to talking during sleep, grinding teeth and awakening screaming or sweating at night. This may have been related to shared comorbidity or medications not accounted for that may have caused the presence of snoring and other symptoms. As would be expected from the literature citing the association between snoring, rhinitis, obstructive sleep apnoea (OSA) and sleep problems,[62] there was a significant difference in daytime sleepiness in the snorers with AD versus the non-snorers with AD. The treatment of rhinitis in the literature, resulted in significant alleviation of sleep problems, daytime sleepiness, daytime fatigue and nasal congestion,[62] stressing the important role that snoring and rhinitis play in the above parameters and that needs to be addressed concomitantly in AD.[62]

4.1.9 Rhinitis

There were no differences in demographics or sleep duration between the rhinitis versus non-rhinitis AD patients.

There was a 33% positive family history of eczema with a notable family history prevalence of associated atopy, namely asthma (26%), allergic rhinitis (54%) and allergic conjunctivitis (40%), in keeping with cited literature discussing the positive atopic genetic

link to atopic dermatitis.[5,10,12,17] The comorbid reported prevalence of asthma in 9.2% of the children in this study is much lower than the expected rate of 35% in infancy rising up to 50% in adolescence and adulthood[5,10] and higher rates may have been reported if this study had included an older age group above 12 years. This is equally applicable to the allergic rhinitis rate of 50% reported in the participants in this study and allergic conjunctivitis rate of 58%. Up to 90% of AD patients may develop allergic rhinitis in later years and about 10%-50% in younger children below 10 years of age.[2,25]

Allergic rhinitis is one of the comorbidities associated with AD.[2,10] Rhinitis was found to be present in 50% of our study AD population and was associated with a 54% positive family history in the same group. Allergic rhinitis, classically characterised by pruritus, rhinorrhoea, sneezing and nasal congestion, may interfere with nocturnal sleep and is reported to result in daytime somnolence.[62]However, as may have been anticipated, sleep onset delay, night waking, bedtime resistance, sleep anxiety, parasomnias and daytime sleepiness were not found to be significantly related to allergic rhinitis in AD patients in this study. Furthermore, snoring and apnoea, and snorting and gasping were found to be significantly reported in the rhinitis patients. Rhinitis did not change the reported daytime function in this study as may have been expected. But nonetheless, there was a significant difference in the reported rhinitis versus non-rhinitis sufferers with regards to the overall sleep disturbance prevalence.

Further comparative statistics revealed that snoring (also collaborated in the literature[62]) was associated with being tired during the day. Patients with allergic rhinitis have been reported to be significantly more likely to snore, have excessive daytime fatigue and

chronic nonrestorative sleep.[62] It is therefore proposed that by treating AR and relieving the nasal symptoms, we many enhance sleep quality.

4.2 Comparative Data

Table 3.8 gives a summary of the comparative data of the sleep patterns studied here and compares it to rates from the overseas literature, where available, followed by a summary of the results as they relate to the aims and objectives of this study, and how these were met.

	SLEEP PATTERN	**PREVALENCE RATES**		
		Prevalence in this study	Overseas studies on AD patients	Overseas studies on normal patients
	Overall sleep disturbance	61.3% SD 8.5%	60%-83%[3,4,5]	10%-40%[6,44,54,58]
1	Bedtime resistance	34.5%	18.6%-32%[48,63]	5.1%-22%[44,48,53,63]
2	Sleep onset delay	27.8%	32%[63]	11.3%[53]
3	Adequate sleep duration	80%	44%[48]	69%[48]
4	Sleep anxiety	36.2%	27.1%[48]	11.6%[48]
5	Night waking	67.7%	73%[63]	22%-33%[55,63]
6	Parasomnias (restlessness)	54.6%	42.4%[63]	20.4%[63]
7	Sleep disordered breathing Snoring Apnoea and snorting	- 50.7% 3.1%	- - -	3.7%[58] 7.5%[62] -
8	Daytime sleepiness (ease of waking up in the morning)	29.2%	23.7%	58.7%

Table 4.1 – Summary of the Comparative Data of Sleep Patterns

4.3 AD, sleep loss and implications

Sleep deprivation may have detrimental behavioural and psychological effects according to the sleep medicine literature.[1] The overall sleep disturbance prevalence of 61.3% (SD 8.5%) associated with AD in this study, consistent with overseas rates of 60%-83%,[3,4,5] raises the important and pertinent question regarding the known association of AD and ADHD as observed in the German meta-analysis.[43,60] Thus the prevalence rates observed in our study of sleeping problems and AD may have far reaching implications into the future functioning of these paediatric patients studied. The pooled OR (with 95% CI) studying the association seen between AD and ADHD was 1.43 (CI 95%, 1.25-1.64). This means that according to the four new epidemiological studies published in 2015,[43,60] there is consistent indication of a positive association existing between the presence of AD and ADHD. It is reported that children with AD (previous or prevalent) have almost a 43% increase in the risk for the diagnosis of ADHD or for displaying the clinical symptoms of ADHD.[43,60] This is highly significant and it is suggested that any future studies in the dermatological field regarding AD observations, consider ADHD as an important co-morbidity of note and that the biological mechanisms regarding this observed dual comorbidity be further investigated in depth, so that targeted therapeutic strategies as well as preventative regimens may be adopted and that further education regarding this significant comorbidity be largely publicised.

Research into the multi-dimensional impact of the link between sleep, stress / depression and immune function under the umbrella of psychoneuroimmunology is still required to establish the exact nature of the sleep disturbance associated with both AD and ADHD.[4,5,31,42,43] Sleep impairment was found to be highly prevalent in both AD and

ADHD[42,43] and sleep problems aggravated both AD and ADHD symptoms. Although the present study did not directly look into this association, because it has previously been considered that sleep problems may cause both AD and ADHD and because of the high prevalence rate of sleep disturbance (61.3% SD 8.5%) in our study, it is important to address this aspect of the association here. It is interesting to note that daytime sleepiness in restless sleepers, one of the important consequences of sleep disturbance associated with ADHD, was found to be significantly higher in our study in snorers vs non snorers as evidenced by falling asleep in a car; and in those that woke up more than once per night vs those that did not wake up as evidenced by falling asleep at the TV; and that snorers were generally more tired during the day versus non-snorers. In the study by Romanos,[42] on a large population based German sample it was found that there was a 14.7% lifetime prevalence of AD and a 4.9% lifetime prevalence of ADHD but that there was a definite association between AD and ADHD which was related to sleeping problems, in that AD and ADHD were strongly associated in children with sleeping problems versus those without sleep problems.[42]

Although our study did not directly address the ICD-10 criteria for the diagnosis of ADHD, that corresponded with the DSM-IV-R ADHD definition, it does raise the question of the possibility of exploring the ADHD association of AD and sleep problems mentioned in the literature regarding paediatric populations with AD.[42] This is particularly pertinent in light of the high prevalence rates of sleep problems found in our South African study that reflect similar high rates of sleep problems in the overseas studies in the AD population, and it is suggested that further research be conducted in our South African Dermatology Paediatric OPD regarding the presence and prevalence of ADHD in patients with AD and sleep problems.[43]

The better control of AD in paediatric patients with ADHD and AD may by assumption improve the sleep disturbances associated with both these conditions,[4,42] and again stresses the importance of a multidisciplinary approach between paediatrics, dermatology and psychiatry in these populations.

This is further corroborated by Schmidt et al[43,60] in, a meta-analysis of epidemiological data, looking at the fact that AD and ADHD are frequent paediatric disorders that have very important medical relevance. In this meta-analysis investigating the relationship between AD and ADHD investigators in the two cross-sectional studies as well as the two cohort studies, lifestyle factors as well as environmental factors and atopic comorbidities such as AD, asthma and allergic rhinitis were considered and the data were summarised as a meta-analysis. The data were adjusted for various demographic data namely, age, sex and atopy. It was interestingly noted in this meta-analysis of 4 studies that AD and ADHD were consistently associated independent of any environmental exposures or other morbidities.[43] It was found in particular that infant AD was associated with the later development of ADHD symptoms. This may be of relevance in our study population where the median age of onset of the AD was in infancy at 5 months.

Regarding the management of sleep problems in AD, sleep has been noted to improve with effective AD anti-inflammatory treatment and wet wrap therapy used at bedtime may help in alleviating the intractable pruritus as well as to serve as a physical barrier to scratching.[2,23] As described in table 1.12 previously, sleep hygiene is a very important strategy in optimizing sleep, i.e., maintaining a consistent sleep bedtime and waking schedule and a relaxing routine at bedtime. A psychologist or sleep specialist consultation is further advised should sleep problems continue after the AD is under good

control, to explore behavioural treatment modalities for bedtime and night waking problems. Data is limited regarding the effectiveness or safety of the pharmacologic treatment used in sleep problems in AD patients and children in particular.[2,10,50] In some patients, sedating antihistamines at bedtime may be advantageous and may be of use on a short term basis especially if in conjunction with sleep hygiene, patient behavioural treatment and parent guidance.[23] It is paramount to break the scratch-itch cycle in these AD patients with sleep disturbances.[23] As previously mentioned, stress is a trigger of AD and thus the use of various psychological interventions, e.g., relaxation therapy, cognitive behaviour therapy, behaviour displacement and stress management may help in alleviating itch and the associated scratching behaviour in AD.[23]

Patients with AD may be at higher risk not only for sleep disturbances as found in this study, but also for depression and anxiety, and ADHD,[43,60] and these need to be taken into account over and above the sleep disturbance and the two way interaction with the latter addressed.

4.4 Limitations

The limitations of this South African study need to be considered regarding the suitability of the CSHQ used as the questionnaire. As with any parent report questionnaire measured, there may be some degree of parental / caregiver bias in the completion of this questionnaire. Although it appears from the literature review that parental report may be reasonably accurate in unravelling many sleep disturbances,[6,7] compared to sleep Actigraphy testing which is a more objective method of obtaining sleep data, parents of the older children may not always know or be aware of sleep initiation / maintenance

problems.[57] Objective sleep measurements (polysomnography and actigraphy) may thus have disclosed different findings had they been used in this study.

The survey used did not explore the differences in sleep wake cycles relating to school vs non-school night bedtimes, or school vs school holiday bedtimes and other sleep parameters.

Considering the importance and the relevance of the role that developmental factors play in sleep disturbances, our results may not be representative of older children outside the age range studied in this sample, nor is it necessarily applicable to any other demographic population or economic group.

The fact that 100% of study population were of the black race and interviewed at a South African government hospital servicing mostly lower socio-economic groups may have some bearing on the results discussed, including various cultural issues such as co-sleeping habits and the influence of the physical sleeping arrangements.

The age range in this study tried to limit possible hormonal pubertal effects on sleep patterns (associated with ≥12 year olds) and future studies in this field may be warranted. This study also lacked control subjects. It would be worthwhile to be able to compare the AD sleep data with a normative data sample from the same government hospital / similar community sample with similar demographics.

Distribution of AD varies in infantile versus childhood versus adolescent / adult AD. There may be periods of quiescence between stages. Since this data represents a cross sectional analysis of sleep patterns with AD, it may not have taken the various AD distribution groups into account. Sleep disturbances may develop early on in AD and

become chronic and this study did not look at the early versus later age sleep disturbances associated with AD.

Sleep problems appear to be frequent in AD and may affect the course of AD and its diagnosis. The small population size in this study may limit the generalisation of the reachable conclusions and additional larger studies in future with more participants are suggested.

4.5 Strengths of this study

One major strength of this study is that for the first time, local South African statistics are obtained regarding sleep disturbances in AD, a condition that is representative of a chronic inflammatory skin condition with a high prevalence worldwide. Our statistics can be compared with overseas data and appear to be very comparable despite a different economic and racial setting.

As the paediatric dermatology outpatient department at Chris Hani Baragwanath Academic Hospital has a large number of patients, data was collected over a short period of time (less than two months) and thus possible seasonal variations on rhinitis and AD would have played a lesser part in this study.

A further strength was the novel use of the CSHQ in our South African population with AD which provided further evidence regarding the utility of the CSHQ in a variety of settings as suggested by Owens.[6,7] It is recommended that the CSHQ be routinely used as a crucial sleep screening instrument in our paediatric clinics in order to identify co-morbid sleep

disturbances in not only AD but as complicating factors in the presentation of various paediatric medical and dermatological conditions that are chronic.

CHAPTER 5

CONCLUSIONS

It is well documented that AD has a significant impact on sleep and quality of life with itching and scratching reported by both AD children and parents, and the associated sleep patterns and disturbances being documented as very problematic aspects of AD.[21,23,58,69]

This is the first time that local sleep data were researched in a chronic skin condition in South Africa in a government hospital setting.

This was a prospective descriptive study of paediatric AD patients based on parent reported questionnaires, conducted at the Chris Hani Baragwanath Academic Hospital in Johannesburg, South Africa. It is quite evident from this local study that sleep problems in AD children are varied and have a prevalence that is consistent with the high reported rates from overseas studies.[3-5]

Sleep disturbances resulting from pruritus and scratching commonly seen in children with AD, include a variety of sleep patterns considered in this study, namely difficulty falling asleep (sleep onset delay), frequent awakenings (night waking), sleep anxiety, overall reduced sleep efficiency (sleep duration, parasomnias etc.) and daytime sleepiness and tiredness.[4,23,48] As previously described sleep disturbances may be associated with daytime behaviour changes and an increased ADHD risk and mood problems in children with AD.[4,5,33,23,42,43]

It is hoped from the observations in this study, that sleep disturbances in AD paediatric patients are considered in the management of AD patients, whether seen at dermatology, paediatric, psychology / psychiatry or various other clinics. Frequent follow-ups and ongoing programmes of education will aid both the patient and the family to better manage sleep disturbances associated with AD and noted in this study. This management, education and support is suggested to aid and hopefully cause a tremendous difference both in the quality of life, sleep quality and associated comorbidities in AD patients.

Thus, it is reiterated that management of this complicated condition requires a multipronged approach, that takes the molecular milieu as well as the multifaceted psycho-social aspects and environmental background into consideration, that the prevention of AD could possibly alter the actual course taken by the Atopic March[2,19] and the development of certain early biomarkers (such as specific IgE to allergens), which if detected before the actual development of clinical AD, may play a very critical role in the identification of participants for prevention / intervention studies.[19,23]

Therefore, future therapies in AD will hopefully target the various molecular pathways previously elucidated and also address the multifactorial aetiopathogenesis of AD and comorbidities, combining medical, practical, psycho-social and biologic interventions.

It is also hoped that this study on sleep patterns in paediatric patients with atopic dermatitis at Chris Hani Baragwanath Academic Hospital, Johannesburg, South Africa, will prove instrumental in highlighting the crucial sleep-atopy relationship.

5.1 Assessment of AIMS and OBJECTIVES:

1. **To describe the various sleep disturbances associated with AD in children up to and including 12 years of age in a government hospital dermatology clinic in Johannesburg, South Africa.**
2. **To compare the characteristics of children with sleep problems to those without sleep problems in AD**.

   Children waking often during the night (night waking as a sleep problem) were significantly younger, did not get the same amount of sleep and were reported to have too little sleep. They were also significantly more likely to struggle at bedtime (bedtime resistance), and to fall asleep at the TV or in the car (increased daytime sleepiness). These children also had a significantly higher overall sleep disturbance prevalence than those who did not wake frequently.

   Parasomnias (restless sleepers) were significantly associated with night waking more than once and moving to other's bed in the night, as well as with daytime sleepiness (falling asleep in the car). Overall sleep disturbance in restless sleepers was significantly higher than in non-restless sleepers.

   Sleep disordered breathing : snorers were found to have significantly higher parasomnia rates as evidenced by talking during sleep and waking up screaming and sweating, as well as a positive association with daytime sleepiness. Overall sleep disturbance was also significantly affected by snoring in the analysis versus non-snoring.
3. **To compare sleep symptoms between males and females**

   There was no significant difference in sleep disturbances noted between males and females.

4. **To determine a possible association between smoking in the household and symptoms of sleep disordered breathing.**

   There was no significant difference found or association noted with regards to this objective.

5. **To determine a possible association between rhinitis and sleep disordered breathing**

   Snoring as well as apnoea and snorting were significantly different in the rhinitis versus non-rhinitis group. The overall sleep disturbance rate was significantly different in those with rhinitis versus those without.

6. **To explore the association between a family history of allergies and sleep disturbances**

   A positive family history of allergies was found to be significantly related to sleep duration and to parasomnias. Family history of allergies did not relate to any other sleep disturbance including snoring. The overall sleep disturbance rate was not affected by a family history of allergies.

5.2 Suggestions for Further Research

Further studies looking at a demographically similar non-AD cohort regarding the parameters studied would be suggested as this is the first study in AD on a South African population at a government hospital regarding sleep issues.

Our study which is in keeping with previous overseas studies on the subject of AD and associated sleep problems emphasizes the fact that AD children may have a wide range of

sleep disturbances, and suffer with disrupted sleep as well as daytime sleepiness issues as a result of insufficient sleep. Further prospective studies into the efficient impact of improved sleep, as a crucial treatment focus in the clinical management of children with AD is suggested and will have implications for clinical practice as well as public health services.

Since AD children experience significant sleep disruption as seen in our study, and since the disease is clinically known to worsen following a circadian manner at night, the more severe the eczema the more significant the sleep disruption associated.[70] There are many negative and significant consequences of AD viz. impaired linear growth, which may be uniquely related to impaired sleep.[70] As a result of this very important association, current clinical guidelines recommend that the assessment of sleep in AD patients be a crucial parameter reflecting disease control with treatment instituted.[23,58] Future directions for research should importantly include interventional studies addressing sleep disturbances as well as dermatological treatment modalities, specifically aimed at nocturnal itch and the circadian rhythms.

Further studies are recommended on the quality of sleep, various sleep disorders and the effect of intervention viz. effective sleep therapies on the course of AD and other chronic dermatological conditions.

An important first step forward toward early identification in sleep abnormalities may be the use of simple self-rating questionnaires for older patients or parent administered questionnaires for the paediatric population, scored by the practice or hospital nursing staff while the patient is waiting to be seen by the dermatologist / paediatrician.

It is suggested that following the findings from this study of substantial sleep abnormalities, that large South African based studies be undertaken in various academic centres with control groups in order to confirm the high frequency rates of sleep problems observed in patients with AD in our study.

Furthermore having undertaken this study, the following areas of interest have arisen:

1. Are sleep problems related to mood problems in AD or related directly to AD.
2. Is it proven that sleep problems may trigger future mood problems in AD patients?
3. Is there possibly a common causal agent e.g., abnormal neuropeptide viz substance P levels, that would explain the skin, mood and sleep problems, knowing that substance P is a widely distributed neuropeptide in both peripheral as well as central nervous system. It is also noteworthy that substance P is involved in reducing sleep efficiency and increasing sleep latency as well as the number of awakenings.[44] It has also been shown to affect both sleep and mood as well as increased skin inflammation.[44]

In closing it is crucial to note the importance of the global assessment of patients with AD spanning various disciplines (dermatology, paediatrics, ENT, sleep medicine, psychiatry) as evidenced by the interconnectedness of atopic dermatitis and sleep problems and the consequent ramifications. It is timeous at this juncture to stress that at the recent 4th international HOME initiative consensus meeting held in Sweden in 2015,[71] sleep loss was stressed as 'integral' for the patient reported symptoms in the assessment of atopic dermatitis and was regarded as an 'essential' aspect of AD symptoms.[71]

Thus as very aptly written by Dr. Karen Spruyt of the University of Chicago Children's hospital "questions about sleep must and should always be included in assessing a paediatric patient with AD!"[7]

CHAPTER 6

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APPENDICES

APPENDIX A

Sleep Patterns in Paediatric Patients with Atopic Dermatitis at Chris Hani Baragwanath Hospital, Johannesburg, South Africa

Parent - Report Questionnaire

Age of child:

Age of onset of skin condition:

Gender: Male Female

Ethnicity: Black White Coloured Asian Indian

Source of Heat/cooking at home : Electricity Gas Paraffin Coal

Does anyone smoke in the house: Yes No

Any Allergies:

What medication is the child currently on:

History of having	Child	Family
Eczema	Y N	Y N
Asthma	Y N	Y N
Allergic Rhinitis	Y N	Y N
Allergic Conjunctivitis	Y N	Y N

The Children's Sleep Habits Questionnaire				
		Occurrence times/week		
Category	Habits	Usually 5-7 times	Some 2-4 times	Rarely 0-1 times
1. Bedtime Resistance	a. Goes to bed at same time b. Falls asleep in own bed c. Falls asleep in other's bed d. Needs parent in room to sleep f. Struggles at bedtime g. Afraid of sleeping alone			
2. Sleep Onset Delay	a. Falls asleep within 20 minutes			
3. Sleep Duration	a. Sleeps too little b. Sleep the right amount c. Sleep same amount each day			
4. Sleep Anxiety	a. Needs parent in room to sleep b. Afraid of sleeping in the dark c. Afraid of sleeping alone d. Trouble sleeping away from home			
5. Night Wakings	a. Moves to other's bed in night b. Awakes once during night c. Awakes more than once			
6. Parasomnias	a. Wets the bed at night b. Talks during sleep c. Restless and moves a lot d. Sleepwalks			

	e. Grinds teeth during sleep f. Awakens screaming, sweating g. Alarmed by scary dream			
7. Sleep Disordered Breathing	a. Snores loudly b. Stops breathing c. Snorts and gasps			
8. Daytime Sleepiness	a. Wakes by himself b. Wakes up in negative mood c. Others wake child d. Hard time getting out of bed e. Takes long time to be alert f. Seems tired g. Watching tv h. Riding in car			

APPENDIX B

INFORMATION AND CONSENT LETTER

Study Title: Sleep Patterns in Paediatric patients with Atopic Dermatitis at Chris Hani Baragwanath hospital, Johannesburg, South Africa

Good Morning Dear Parent

My name is Dr. Mary Rouhani and I am studying to become a dermatologist at Wits Medical School. To complete my training I need to conduct research study as part of a master's degree. Research is the way to learn the answer to a question. In this study we want to answer the question regarding what sleep problems occur in children with eczema (skin rash and itching). Studies done overseas tell us that lots of children with eczema have sleep difficulties but we have no idea whether that is the same situation in South African children or not.

I would like to ask you, the parent/guardian of a child with atopic dermatitis, whether you would please consider taking part in this research.

We will be asking 100 parent from this dermatology OPD that you attend to take part in the study. If you agree to participate we would like you to please sign a consent form and then fill in a questionnaire which should not take more than 10 minutes. The questions you will be asked relate to your child's eczema, sleep patterns / problems and related information. You are welcome to look at the questionnaires before you agree to take part.

There are no risks or costs to you to participate and we will keep your information confidential. This means that no-one will be able to find out who your child is just by looking at the questionnaires. Therefore please do not write your name, hospital number or identity number anywhere except on the consent form. While there are no direct benefits to you, the result may help all children, and parents, with this condition in future because we may learn more about the problem.

Your participation is voluntary and therefore you can pull out of the study at any time. You may choose whether to participate or not without any consequences to the ongoing medical treatment of yourselves or members of your family. The study has been approved by the Human Research Ethics committee of the University of the

Witwatersrand. If you have any questions about your rights as a research participant please contact Prof Peter Cleaton-Jones on 011 717 2301.

Thank you for taking the time to read this letter. Your participation in this research study will be appreciated. I do hope you will agree to take part and if so please will you sign the consent form below. Then we can start with the questions.

Yours sincerely

Dr. Mary Rouhani

082 372 0256

APPENDIX C

Department of Internal Medicine

Faculty of Health Sciences, University of the Witwatersrand. Area 553, Blue Block, Charlotte Maxeke Johannesburg Academic Hospital. Tel 011 488 3621

INFORMED CONSENT

I hereby confirm that I have been informed by the study doctor about the nature, conduct, benefit and risk of this clinical study titled: **Sleep Patterns in Paediatric Patients with Atopic Dermatitis (AD) at Chris Hani Baragwanath Hospital, Johannesburg, South Africa**

I am aware that the results of the study, including the personal details regarding my sex, age, date of birth, and diagnosis will be anonymously processed into a study report.

I agree that the data collected during the study can be processed in a computerized system by the investigator or his sponsor.

I understand that I am allowed at any stage to withdraw my consent to participate in the study without any prejudice.

I have had adequate opportunity to ask questions about the study and declare myself prepared to participate in the study.

PARENT / LEGAL GUARDIAN

Name Signature/mark or thumb print Date and Time

I hereby confirm that the above participant has been fully informed about the nature, conduct and risk of the above study.

STUDY DOCTOR

Name Signature Date and Time

APPENDIX D

CHILDREN ASSENT DOCUMENT

UNIVERSITY OF THE WITWATERSRAND

Dear kids

My name is Dr Mary Rouhani and I am doing a study to look at the sleep problems in kids with eczema (skin rash and itching) like you have. This study will help us to understand how eczema and sleep affect each other.

I would really like it if you take part in my study.

All you have to do is answer some questions about your skin problem and your sleep. Your parent or legal guardian can answer most of them but some you can help with the answers. The answers to the questions are private and will not be given to anyone – we don't even take your name on the questionnaire so nobody can find out what you said.

If you are happy to answer some questions or let your parent or legal guardian answer some questions about your sleep please sign in the space below.

My name is (child's name & surname),_____ and I am happy to take part in this research project which has been explained to me by my parent / legal guardian and / or Dr Mary Rouhani.

I know that taking part in this project is voluntary and that I don't have to participate. I know that I take part in this project because I want to and that I can stop taking part anytime I want to without affecting my treatment.

_____ _____

Child signature Date

_____ _____

Investigator name and signature Date

APPENDIX E

R14/49 Dr M Rouhani Najafabadi

HUMAN RESEARCH ETHICS COMMITTEE (MEDICAL)

CLEARANCE CERTIFICATE NO. M140738

NAME: (Principal Investigator)	Dr M Rouhani Najafabadi
DEPARTMENT:	Dermatology Chris Hani Baragwanath Academic Hospital
PROJECT TITLE:	Sleep Patterns in Paediatric Patients with Atopic Dermatitis at Chris Hani Baragwanath Hospital, South Africa
DATE CONSIDERED:	25/07/2014
DECISION:	Approved unconditionally
CONDITIONS:	
SUPERVISOR:	Dr Alison Bentley
APPROVED BY:	Professor P Cleaton-Jones, Chairperson, HREC (Medical)
DATE OF APPROVAL:	01/10/2014

This clearance certificate is valid for 5 years from date of approval. Extension may be applied for.

DECLARATION OF INVESTIGATORS

To be completed in duplicate and **ONE COPY** returned to the Secretary in Room 10004, 10th floor, Senate House, University.
I/we fully understand the conditions under which I am/we are authorized to carry out the above-mentioned research and I/we undertake to ensure compliance with these conditions. Should any departure be contemplated, from the research protocol as approved, I/we undertake to resubmit the application to the Committee. **I agree to submit a yearly progress report**.

Principal Investigator Signature _____ Date _____

PLEASE QUOTE THE PROTOCOL NUMBER IN ALL ENQUIRIES