PREVALENCE OF ANAEMIA, IRON DEFICIENCY, IRON DEFICIENCY ANAEMIA AND RISK FACTORS FOR IRON DEFICIENCY IN KELANTANESE CHILDREN

By

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**Dissertation Submitted In
Partial Fulfilment Of The
Requirements For The Degree Of
Master Of Medicine
(Paediatrics)**

UNIVERSITI SAINS MALAYSIA
2001

ACKNOWLEDGEMENTS

First and foremost, I am greatly indebted to Associate Professor Dr. Quah Ban Seng and Dr. Wan Maziah Wan Mohamad for their guidance and assistance in every aspect of this dissertation and for making this dissertation possible.

I am profoundly grateful to Professor Hamish Simpson, Dr. Narazah, Dr. Sharifah Ainon Ismail Mokhtar and Dr. Bina Menon for their assistance, advices and encouragement in the preparation of this dissertation.

My warmest appreciation to Kementerian Kesihatan and Pejabat Kesihatan Kota Bharu for allowing me to conduct my study in their health clinics.

To my dearest husband, Dr. Nazri Mohd. Yusof and to my beloved parents I am very grateful for their unconditional love, support and prayers which have made my life possible throughout the preparation of this dissertation and the whole post-graduate programme.

I would like to express my sincere gratitude to all the nurses and doctors at the health clinics and staff of Haematology laboratory HUSM for their kind cooperation during the data collection and analysis of the blood samples.

Last but not least, my special thanks to the parents and children who participated in this study in which without them this project would have never been possible.

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ABBREVIATIONS

dL	Decilitre
FEP	Free erythrocyte protoporphyrin
g	Gram
Hb	Haemoglobin
Hct	Haematocrit
HUSM	Hospital University Sains Malaysia
ID	Iron deficiency
IDA	Iron deficiency anaemia
IS	Iron sufficient
kg	Kilogram
MCHC	Mean corpuscular haemoglobin concentration
MCV	Mean corpuscular volume
OD	Odds ratio
PPV	Positive predictive value
RBC	Red blood cell
RDW	Red cell distribution width
RM	Ringgit Malaysia
SF	Serum ferritin
SPSS	Statistical Package for the Social Sciences
TS	Transferrin saturation
US	United States
WHO	World Health Organisation

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ABSTRAK

Pengenalan

Kekurangan zat besi merupakan masalah yang sering ditemui di kalangan kanak-kanak. Kekurangan zat besi pada kanak-kanak 2 tahun ke bawah boleh mengganggu kesihatan mental, melembabkan perkembangan psikomotor serta membantutkan tumbesaran. Penentuan kadar prevalens kekurangan zat besi di kalangan kanak-kanak di Kelantan diharapkan dapat memberi gambaran kasar masalah ini di Malaysia, manakala pengenalpastian faktor-faktor risiko kekurangan zat besi dapat membantu strategi pencegahan.

Objektif

Menentukan kadar prevalens anemia, kekurangan zat besi dan anemia yang disebabkan kekurangan zat besi di kalangan kanak-kanak berumur 8 hingga 26 bulan di Kelantan serta mengenalpasti faktor-faktor risiko berkaitan dengan masalah tersebut. Kesahihan konjunktiva yang pucat sebagai tanda anemia turut dikaji.

Metodologi

Kajian hirisan lintang berdasarkan komuniti telah dijalankan dari bulan September 1999 sehingga November 1999 di lapan buah klinik kesihatan di daerah Kota Bharu. Kanak-kanak berusia 8 hingga 26 bulan yang hadir di klinik-klinik kesihatan tersebut dijemput mengambil bahagian dalam kajian ini. Kanak-kanak yang mengalami penyakit akut pada waktu temu-ramah atau yang berpenyakit kronik dikecualikan dari kajian. Ibu-bapa ditemuramah menggunakan pro forma piawai dan darah kanak-kanak diambil setelah mendapat persetujuan lisan. Soalan-soalan yang dikemukakan meliputi data demografi, faktor pemakanan, maklumat sosial dan faktor tumbesaran kanak-kanak.

Kepucatan pada konjunktiva dikenalpasti. Darah dianalisakan untuk pemeriksaan gambaran darah dan penentuan kadar feritin. Faktor-faktor risiko diantara kumpulan kanak-kanak yang kurang zat besi dengan kumpulan zat besi mencukupi telah dibandingkan.

Keputusan

Hampir dua pertiga (65.1%) (95% CI: 60.7-69.2%) daripada sejumlah 490 orang kanak-kanak mengalami masalah anemia (Hb<11.0g/dL). Kadar prevalens kekurangan zat besi (SF<12.0µg/L) ialah 38.9% (95% CI: 34.7-43.5%) manakala kadar prevalens anemia yang disebabkan kekurangan zat besi (Hb <11.0g/dL &

SF <12.0µg/L) ialah 31.6% (95% CI: 27.6-36.0%).

Faktor-faktor risiko independen bagi kekurangan zat besi adalah penyusuan susu badan yang berpanjangan (OR 2.5; 95%CI: 1.4-4.4%), kegagalan memberi susu formula (OR 1.7; 95% CI: 1.1-2.5%) dan kelewatan memberi makanan pejal (OR 0.37; 95% CI 0.15-0.90%). Faktor-faktor pemakanan lain, faktor perinatal, faktor-faktor sosial dan ekonomi keluarga serta faktor tumbesaran didapati tidak mencapai batas kemaknaan. Kepucatan konjunktiva mempunyai kesensitifan 70.5% dan kespesifikan 54.4% pada paras Hb <11.0g/dL.

Kesimpulan

Sebilangan besar kanak-kanak di Kelantan mengalami masalah anemia dan kekurangan zat besi. Kadar prevalens ini yang jauh lebih tinggi berbanding dengan perangkaan di negara-negara maju amat membimbangkan.

Kepucatan konjunktiva bukanlah tanda yang sesuai untuk meramalkan anemia.

Pengubahsuaian faktor-faktor pemakanan berkaitan dengan masalah ini (penyusuan susu badan berpanjangan dan kegagalan memberikan susu formula) diharapkan dapat mengurangkan kadar insidens anemia serta masalah kekurangan zat besi di negara ini.

ABSTRACT

Introduction:

Iron deficiency (ID) is the most common nutritional deficiency in childhood (Dallman et al, 1980). Iron deficiency anaemia (IDA) in children less than 2 years causes behavioural abnormalities and developmental delay (Lozoff et al, 1991). Prevalence figures are therefore needed to estimate the scope of the problem and identification of potential risk factors associated with ID and IDA will help to formulate preventive strategies.

Objectives:

Primary objective: To determine the prevalence of anaemia, ID and IDA in Kelantanese children aged 8 to 26 months.

Secondary objective: To identify risk factors that best predict the presence of ID and to determine the validity of pallor in assessment of anaemia.

Methodology:

A cross-sectional study was conducted from September 1999 to November 1999 in eight primary health clinics in the district of Kota Bharu. Children aged 8 to 26 months who attended these clinics were invited to participate in the study by convenience sampling.

Children with chronic diseases, thalassaemia or an acute infection at the time of visit were excluded. Parents were interviewed using a standard pro forma containing questions on demographic data, dietary history and socio-economic influences. Pallor of conjunctiva was noted. Blood samples which were taken after obtaining a verbal consent were analysed for full blood count and ferritin level. The possible risk factors for ID were compared between the iron deficient (SF<12µg/L) and iron sufficient (SF>12µg/L) groups using bivariate analysis and multiple logistic regression.

Results

Among 490 children studied, 65.1% (95% CI: 60.7-69.2%) were anaemic (Hb <11.0g/dL). The prevalence of ID (SF<12.0µg/L) was 38.9% (95% CI: 34.7-43.5%) and prevalence of IDA (Hb<11.0g/dL & SF <12.0µg/L) was 31.6% (95% CI: 27.6-36.0%). Independent risk factors for ID were prolonged breast feeding, (OR 2.5; 95% CI: 1.4-4.4%), failure to give formula milk (OR 1.7; 95% CI: 1.1-2.5%) and delayed weaning (OR 0.37; 95% CI: 0.15-0.90%).

Other dietary factors were not significantly associated with ID. None of the perinatal factors, socio-economic factors or the growth parameters were independently associated with ID. The sensitivity and specificity of pallor for detecting a Hb < 11.0g/dL were 70.5% 54.4% respectively.

Conclusion

ID and IDA is a common problem among Kelantanese children. Prolonged breast feeding and failure to give formula milk were significantly associated with ID. Pallor of conjunctiva was not a sensitive or specific indicator for anaemia.

Improvements and appropriate interventions of these potentially modifiable risk factors may reduce the incidence of anaemia and ID in Kelantanese children.

1. INTRODUCTION

1.1 Background of the study

Anaemia is a common problem in childhood especially in children aged 6 to 24 months old. It was estimated that 12% of children aged 0-4 years in developed countries and 51% in developing countries were anaemic (DeMaeyer, 1985).

Iron deficiency anaemia (IDA) is the most commonly recognized form of nutritional deficiency in developing countries (Dallman, 1980) as well as in developed countries (Mills 1990). Worldwide, approximately 600 million individuals had IDA (DeMaeyer, 1985). The deficiency is in most cases of dietary origin and probably due to inadequate weaning (Mills, 1990). Other causes of anaemia include infection, inflammatory diseases, malignancies and hereditary disorders such as haemoglobinopathies.

IDA can no longer be considered a simple anaemia readily reversed by iron therapy (Dallman, 1982). It has been associated with lowered scores on tests of mental and motor development in infancy (Dallman, 1986), poorer psychomotor development and behavioural changes of young children (Walter, 1989).

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Iron deficiency (ID) has many other negative effects on health including changes in immune function, cognitive development, temperature regulation, energy metabolism and work performance (Lozoff et al., 1982). Iron is necessary for maintaining normal structure and function of virtually all mammalian cells. It is also involved in the immune and non-immune host defence. In vitro studies have shown that iron and iron-binding proteins are important for lymphocyte proliferation, for satisfactory functioning of natural killer cells, for B cells and antibody production and for the activity of phagocytic cells (Farthing, 1989).

Children who have IDA in infancy was found to be at risk for long lasting developmental disadvantages as compared with their peers with better iron status (Lozoff et al., 1986). Thus, it has been suggested that infants and toddlers should be screened for ID.

Screening for anaemia was mostly carried out in Western countries where it was found that children of Asian origin were at higher risk of being iron deficient (Ehrhardt 1986, Grindulis et al., 1986). Similar studies of screening for IDA is lacking in our population. The prevalence of ID and IDA in this country is expected to be higher as compared to the figures in the developed countries. However, to the best of our knowledge, only few studies had been carried out to determine the prevalence for ID and IDA in children less than 2 years old in this country.

This study was carried out to investigate the prevalence and the risk factors for ID and IDA among the Kelantanese children aged 8 to 26 months. From this study, we will be able to identify a group of children at risk of developing ID and IDA in this part of country and it is hoped that in the future, children with these particular risk factors will be looked into seriously to prevent iron deficency anaemia thus preventing them from developing the complications that might occur as a consequence of this disease.

2.   REVIEW OF LITERATURE

2.1 IRON REQUIREMENTS

At birth, most term infants have about 75 mg of elemental iron per kilogram of body weight, found primarily as haemoglobin (Hb) (75%) but also as storage (15%) and tissue protein (10%) (Oski, 1982). Infants of mothers with poorly controlled diabetes and small-for-gestational-age infants have approximately 10% and 40% of normal storage iron, respectively, meaning that they may have less of a buffer protection from postnatal ID (Petry et al.,1992, Georgieff et al., 1995).

During the first 4 postnatal months, excess fetal red cells break down and the infant retain the iron. This iron is used, along with dietary iron, to support the expansion of the red blood cell mass as the infant grows.

The Nutrition Committee of the American Academy of Pediatrics , recommended that term infants be given 1 mg iron per kg of elemental iron daily to a maximum of 15 mg, starting no later than 4 months of age and continuing until 3 years of age (American Academy of Pediatrics, 1976). Low birth weight infants however require a higher amount at 2mg/kg per day to a maximum of 15 mg daily starting no later than 2 months of age. Higher doses have been suggested for infants in the lowest birth-weight categories (Dallman 1990). Infants with birth weights of less than 1000 g should receive 4 mg/kg per day, and infants   with birth

weights between 1000 and 1500 g should receive 3 mg/kg per day.

For these infants, iron supplementation at the higher dose should continue throughout the first year life (Oski, 1993).

The above recommendation are nutritional guidelines advocated to prevent IDA. The final amount of iron being absorbed is dependent on the availability of iron stores in the body as well as on the type and composition of food in the child's diet.

2.2 IRON METABOLISM IN INFANCY

Iron deficiency is the most commonly recognized form of nutritional deficiencies in developing countries as well as in affluent societies (Dallman et al., 1980). It is particularly prevalent among infants and young children because their rapid growth imposes large iron needs but on the other hand most infant diets contain only a marginal supply of iron.

Iron containing compounds in the body may be divided into 2 categories:

I. Those that serve metabolic or enzymatic functions such as Hb. and cytochromes. These compounds account for 25 to 55mg/kg body weight, more than 80% of which is in Hb (Sjolin & Wranne 1968, Smith & Rios 1974).

II. Those that are associated with iron storage. These primarily consist of ferritin and haemosiderin and account for 5 to 25 mg/kg body weight. These compounds are involved in the maintenance of iron haemostasis (Dallman et al., 1980).

2.2.1 Iron Balance

The quantity of iron in the body is normally maintained within narrow limits at each stage of growth and development. It is regulated mainly by the intake and absorption of iron. Iron excretion occurs primarily through desquamation of cells in the intestinal mucosa (Green et al. 1968, Finch et al. 1977).

The amount of iron absorbed from the duodenum depends on the adequacy of iron stores, the form of iron in foods in the diet (Monsen et al.,1978). In adults, about 95% of the iron required for the production of red blood cells is recycled from the breakdown of senescent red cells and only 5% comes from dietary sources (Hillman et al., 1974). In contrast, the one year old infant, due to his rapid growth, is estimated to derive less than 70% of red cell iron from senescent red cells and requires about 30% from the diet (Fomon, 1974).

2.2.2 Food Iron

Iron deficiency is more common than iron excess because most of the iron in food and the environment is relatively insoluble and difficult to assimilate. As a result, the form of iron in the diet is more important than the amount (Dallman, 1986). In infants, milk is the main form of diet. Breast and cow's milk each contains less than 1.5mg of iron per 1000 calories (0.5 to 1.0 mg/L).

The bioavailability of iron is influenced by the type of foods in the diet. It is therefore important to know how much iron is absorbed from each food item. It has been found that a much higher percentage of iron was absorbed from breast milk (about 50%) than from cow's milk or formula prepared cow's milk (Saarinen et al. 1977, Oski et al. 1980).

The lower calcium and protein content of breast milk compared to cow's milk, and the presence of high concentration of the iron-binding protein and lactoferrin, have been postulated to play a role in the better iron absoption from breast milk as compared to cow's milk or infant formula (Saarinen et al., 1977). However, infants who were exclusively breast-fed for more than 6 months may eventually become iron deficient (Siimes et al., 1984). This is because the amount of iron in breast milk is limited even though the absorption of iron in breast milk is better than cow's or formula milk.

Estimates of iron absorbtion from infant formula range from less than 5% in term infants fed casein – predominant formula to to 40% in very low birth weight infants fed whey-predominat formula (Stekel 1986, Ehrenkranz 1992, Saarinen 1977). About 7% to 12% of iron being absorbed in infants being fed with cow milk formula. The percentage of iron absorbed from soy formula is lower than from cow milk formula and ranges from less than 1% to 7%. Nevertheless, infants fed soy formula containing 12mg/L of iron remain comparably iron

sufficient to infants fed iron-fortified cow milk formula (Hertrampf et al., 1986).

Iron occurs in the food primarily as non-haem iron. A smaller amount is found in the haem proteins, haemoglobin and myoglobin, which are present in meat. Haem iron and non-haem iron differ markedly in their mechanism of absorption and bioavailability (Hallberg 1981, Charlton et al., 1983). The non-haem iron in food is primarily in the form of ferric complexes.

During digestion, this iron is reduced to the more readily absorbed ferrous form. This is facilitated in the stomach by the hydrochloric acid- containing gastric juice and continues in the small intestine. Achlorhydia will reduce the absorption of ferric iron administered with food by about 50% (Jacobs et al 1964). Assimilation of ionic iron is enhanced by the formation of readily absorbed complexes with other components of the diet, such as fructose, ascorbic acid, citrate and some amino acids.

On the other hand, absorption is decreased by the formation of insoluble compounds such as phosphates, tannates, polyphenols and oxalates. Bran in cereals, polyphenols in many vegetables and tannin in tea can all play a major role in inhibiting iron absorption (Charlton et al., 1983). Solid foods that are fed near the time of a breast feeding can substantially inhibit the absorption of the iron from that breast milk feeding (Oski et al., 1980, Saarinen et al., 1979).

Dietary iron in the form of haem protein is handled in a different manner. Haem is split from the globin portion of the molecule in the intestinal lumen. The haem is then assimilated intact, and a haem-splitting enzyme within the mucosal cell releases ionic iron. The absorption of haem iron is readily affected by other dietary constituent, and a larger percentage of the total tends to be assimilated, in comparison to non-haem iron (Bjom-Ramussen et al. 1974, Layrisse et al. 1974).

2.2.3 Mechanism of Intestinal Absorption

The major portion of iron is absorbed in the duodenum and diminishing amounts are absorbed as food advances toward the ileum. The mucosal cell of the duodenum and jejunum is believed to take up iron from the intestinal lumen and release it to the blood stream by a carrier system involving transferrin (Huebers et al., 1983). The mucosal cell, by virtue of its brief 2- to 3- day life span, constitues a temporary holding zone for the ferritin iron between the intestinal lumen and the blood. In the iron-loaded individual, much of the iron that is taken up by the mucosal cell is retained and later returned to the luminal contents by desquamation (Dallman et al., 1980). By contrast, in ID more iron crosses through the mucosa into the circulation, and very little is retained within the cell to be lost by desquamation.

Normally the diet contains 5 to 20 times the amount absorbed. Iron absorption increases during the period of development that are characterized by a rapid rate of growth (e.g. during infancy and adolescence) and consequently diminished iron stores. At all ages, the more iron that is ingested, the less is the percentage absorbed, but the greater is the absolute amount that is absorbed (Dallman et al., 1980).

2.2.4 Iron losses

Iron losses from the body are small and relatively fixed, in contrast to wide variations in iron intake and lesser fluctuations in absorption. In the normal infant, the loss of iron is at least 20μg per kg per day (Garby et al., 1964).

Cow milk feeding in early infancy is commonly associated with occult intestinal blood loss detectable by the guaiac test (Formon et al., 1981). Over a one month period of observation, about 40% of a group of 4 month old infants had at least one guaiac-positive stools collection in contrast to 10% among formula fed infants. At 6 months of age, there was no longer a significant difference between the two groups. Severe anaemia and more substantial blood loss is occasionally associated with ingestion of large volumes of fresh cow's milk (Woodruff et al. 1972, Wilson et al. 1974).

2.3   CAUSES OF IRON DEFICIENCY

The most common factors that contribute to the development of ID in children are rapid growth, blood loss and insufficient absorption of iron; many cases result from combination of three (Dallman, 1980).

2.3.1 Rapid growth

Rapid growth and lack of dietary iron are usually of primary importance. At two to three months of age the concentration of Hb decreases in response to its lowest point and there will be increase in the rate of erythropoeisis. Iron stores gradually decreases at 3 months of age and subsequently become depleted unless replenished by an adequate exogenous supply of iron. In adult men only about 5% of the iron required for Hb production is derived from the diet; the remaining 95% is recycled from the red blood cell (RBC) degradation. By contrast, in the infant because of the rapid expansion of blood volume during growth, 30% must come from the diet and only 70% is from recycled iron (Dallman, 1987).

2.3.2 Blood loss

Blood loss as the sole cause of ID in children is less frequent than in adults. It is a common primary cause of ID only when associated with ingestion of

unprocessed cow's milk in infancy (Formon et al., 1981) and in areas where hookworm infestation and other parasitic infections are prevalent. Hookworm infestation particularly Ancylostoma duodenale are likely to contribute to high prevalence of ID and anaemia particularly in children and women (Hopkins et al., 1997). Tasker (1958) found an inverse relationship of the Hb level with the proportion of patients who had hookworms infestation, the lower the Hb level, the higher the proportion of patients had hookworms. Using a radioactive tracer technique, he estimated that daily blood loss increases from about 2 ml. with a light infestation of about 20 hookworms to about 90 ml. in a heavy infestation of greater than 1,500 hookworms.

There is evidence that blood and serum protein losses represent an intestinal intolerance to large amounts of fresh cow's milk (Woodruff & Clark 1972, Wilson & Lahey 1974). It has been postulated that intestinal blood loss is to some extent secondary to the effects of ID on the mucosal lining (Kimber & Weintraub 1968), for example by a deficiency of iron containing enzymes in this tissue. What distinguish this type of bleeding from that associated with gross anatomic lesions is that it ceases shortly after initiation of treatment with iron (Woodruff & Clark 1972, Wilson & Lahey 1974).

Indeed, providing processed formula milk even in the absence of iron treatment has proved effective in stopping blood loss in some infants. In rare instances,

intestinal blood loss is associated with severe IDA and hypoproteinaemia

(Kimber & Weintraub, 1968). The abnormality appears to be reversed by iron treatment alone, without a change in diet.

A common but often neglected form of intestinal blood loss is associated with the use of medications that inhibit platelet aggregation and thereby prolong the bleeding time. The most important of these is aspirin which even in relatively small doses increases occult intestinal blood loss to 5 ml per day, greater than 5 times the normal value of less than 1 ml per day (Person et al., 1961).

In children, blood loss due to anatomic lesions is easy to overlook because it is rare. Occult intestinal blood loss should be suspected when there is no dietary basis for anaemia, when anaemia persists or recurs despite iron treatment or when severe anaemia is detected after infancy. Causes of bleeding in the perinatal period include foetal-maternal haemorrhage, placental injury about the time of delivery and twin-to-twin transfusion through placental communications. An exchange transfusion also involves blood loss because blood with a high haematocrit concentration is usually replaced by blood with a lower haematocrit level (Dallman, 1987).

Beyond infancy, recurrent ID particularly in the absence of parasitic infestation or symptomatology, should suggest a Meckel's diverticulum, often a cause of intermittent painless intestinal blood loss in children (Brayton 1964, Spencer 1964, Shandling 1965). Other congenital anomalies, such as intestinal duplications and intestinal haemorrhagic telangiectasia are less common but may also result in IDA.

As in adults, bleeding ulcers and hiatus hernia are usually symptomatic but these disorders are relatively rare in children. ID may also develop in patients with haemophilia and other bleeding disorders not only as a result of external blood loss but also because the iron lost through soft tissue bleeding may not be completely resorbed and reutilized.

2.3.3 Insufficient absorption of iron

A reduced absorption of iron into the body can occur as the result either of low levels of dietary iron or a poor biological availability of dietary iron or both. These are important causes of IDA in developing countries where the economy is restricted, so that the diets are commonly made up almost wholly of rice or maize and very little foods of animal origin. Dietary inadequacy amongst vegetarians would also be an important factor for ID.

Food iron exists primarily in the non-haem form of inorganic iron III (ferric) complexes which are broken down during digestion and the iron being reduced to the more readily absorbed iron II (ferrous) form (Dallman et al., 1980).

A lesser amount of food iron is present in the haem proteins, Hb and myoglobin, which are present in foods of animal origin. Haem iron in the diet is easily absorbed whereas non-haem iron is of a very much poorer bioavailability (Dallman et al. 1980, Cook et al. 1972).

Dietary iron content and the bioavailability of iron in the diet will determine the quantity of iron available to the intestine for absorption. The intestinal mucosa,

however does not necessarily take up all the available iron. Absorption will be determined by the iron status of the body. Absorption normally decreases as stores increase and increases as stores become depleted. (Heinrich 1970, Aisen 1982).

Mean iron absorption from foods of plants origin, vary from 1 % - 5% as compared to 3% - 22% of iron absorption from foods of animal origin (Layrisse, 1975). However, foods of animal origin are frequently not present in the diets of poorer communities so that only a small proportion of the iron in the diet is haem iron.

Mild ID tends to be self-correcting, since iron absorption from food is increased as iron stores in the body diminish. On the other hand, severely iron-deficient children, as well as chronically deficient animals, may lose the normal adaptation response of absorbing higher amounts of dietary iron. However, this abnormality is promptly corrected after treatment with iron.

2.4 CONSEQUENCES OF IRON DEFICIENCY

Iron deficiency, even in the absence of anaemia, results in biochemical alterations that impair behaviour in infants who are 9 to 12 months of age (Oski et al., 1983).

Children who had severe, chronic ID in infancy scored lower on measures of mental and motor functioning. After control for background factors, differences remained statistically significant in arithmetic achievement and written expression, motor functioning and some specific cognitive processes (spatial memory, selective recall and tachistocopic threshold) (Lozoff, 2000).

More of the formerly iron-deficient children had repeated a grade and /or been referred for special services or tutoring. Their parents and teachers rated their behaviour as more problematic in several areas, agreeing in increased concerns about anxiety or depression and attention problems (Lozoff, 2000). The administration of iron produced a significant increase in the mental developmental index scores in the infant with ID (Oski et al., 1983).

ID is significantly associated with retardation of physical and psychomotor parameters (Walter et al 1989, Lozoff et al 1991), while repletion of the body's iron stores rapidly reverses these developmental anomalies (Addy 1986, Aukett et al., 1986). Studies in animals have shown that irrespective of anaemia, ID produced metabolic and functional defects in muscle and impaired function of

white cells (Mackler et al., 1984). Functional abnormalities of both lymphocytes and neutrophils have been shown in anaemic children (Srikantia et al., 1976).

A study in California found ID to be more common in 1-year-old infants who had a history of recurrent mild infections (Reeves et al., 1984). Whether the infections preceded or followed the ID is not clear. Most importantly, there is now substantial evidence that ID has an adverse effect on brain function. In rats ID leads to disturbed enzyme function in the brain affecting cerebral serotonin metabolism (Mackler B et al., 1978) and learning ability (Massaro & Widmayer, 1981).

Pica in children is a symptom of ID and more than 50% of patients with ID have pica (Crosby, 1976). Pica is quickly cured by therapy with iron. After a week or two of therapy with iron, the pica invariably ceased, well before the anaemia had been corrected (Coltman, 1969).

Oski and Honig (1985) studied 24 iron deficient anaemic children aged 9 to 26 months. Twelve were given intramuscular iron and 12 placebos, and tests of mental development and of behaviour were administered before the injection and five to eight days later. Improvement was found at the second testing in those who had been given iron but not in the placebo group. In particular, the treated children tended to become more responsive to their environment.

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In similar study in Guatemala, Lozoff (1982) and her colleagues showed that children with IDA scored less well than other children in tests of mental development and that the iron-deficient children were more tense and fearful but otherwise less responsive. In their study no improvement in test scores was seen after one week of treatment with oral iron.

Oski et al (1983) showed an improvement in mental development test scores one week after intramuscular iron injection in babies aged 9 to 12 months who were iron-deficient but not anaemic. Walter et al (1983) in Chile obtained similar results in 15 months old children using treatment with oral iron and retesting after 11 days. The most noticeable behavioural characteristic of the anaemic Chilean babies was that they were more unhappy than non-anaemic babies. Studies in Java and Egypt have shown deficits in mental performance in schoolchildren with ID, which was reversible with treatment (Pollitt et al., 1985).

The other consequences of IDA include abnormalities of immune function. ID may at least contribute to impaired T lymphocyte function (defect in cell-mediated immunity and bacterial killing) and subsequently leads to an increased risk of infections (Dallman, 1987), poor growth (Chwan et al., 1988) delayed language and cognitive development (Walter, 1983), attention deficit disorder, impaired school performance, impaired exercise capacity (Booth et al., 1997) and clumsiness (Cantwell, 1974).

Neurological sequelae such as irritability, lethargy, headache, papilloedema and stroke have also been reported (Hartfield, 1997). Studies in young children and adults indicate that both cell-mediated immunity and bactericidal activity of neutrophils are impaired in patients with IDA (Chandra, 1973) although the phagocytic function of the neutrophil may be normal, bacterial killing is diminished. Neutrophils are defective in reducing the dye nitroblue tetrazolium, suggesting the possibility that an iron containing enzyme required for this reduction may be present in diminished amounts. After administration of parenteral iron, the bactericidal abnormalities and the nitroblue tetrazolium test were corrected within four to seven days, before the Hb concentration would have increased appreciably.

Early identification and treatment of ID and IDA is therefore one of the highest health care priorities. Treatment with iron has been shown to improve the behaviour, cognitive skills and general learning ability in children with ID (Oski, 1985). To avoid long term morbidity, ID can be prevented by dietary modification, iron fortification of nutritional products and iron supplementation (Hallberg, 1994). Children who received iron supplement had an increased rate of weight gain and achieved the expected rate of development (Aukett, 1986).

2.5   DIAGNOSIS OF IRON DEFICIENCY

Iron deficiency anaemia develops as the end result of a series of steps that begins with depletion of stored iron (Oski, 1993). First, iron disappears from the bone marrow and the red cell distribution width becomes abnormal. Next, there is a loss of transport iron, reflected by a reduce in serum iron level. Then erythropoeisis becomes iron-deficient, as indicated by a reduced men corpuscular volume and increased concentration of red-cell protoporphyrin. The end result is overt anaemia (Oski, 1993).

The staging of iron status by Oski et al (1983) is a useful concept and various measurements can be used to define the stages.

(A) Iron sufficiency:

    Iron stores and erythropoeisis normal

(B) Iron depleted:

    Erythropoeisis normal but iron stores reduced.

    In normal subjects, SF is directly proportional to body iron stores (Cook, 1982). During infancy and childhood, SF closely parallels the developmental changes in iron status. The advantage of SF is its relative stability with repeated measurements in the same subjects. SF value of < 12ug/L indicates reduction of iron in the bone marrow, liver and other parts of the reticuloendothelial system.

(C) Iron-deficient erythropoeisis.

When iron stores have been exhausted, the serum iron and transferrin saturation (TS) will decline (Cook, 1982).

   (a) *Abnormal RBC biochemistry:* Serum iron, total iron binding capacity & free erythrocyte protoporphyrin:

        i. decreased serum iron (<30µg/dL in children aged 1-2 years)

        ii. Increased total iron-binding capacity (>480µg/dL in children aged 1-3 years)

        iii. Elevated free erythrocyte protoporphyrin (FEP) level (≥90µmol/mol of haem in children aged 1-5 years)

   (b) *Abnormal RBC morphology:* Hypochromic microcytic red cells: MCV <70fl, MCH less than 23pg , MCHC less than 30% and anisocytosis: RDW >14.5% (Values vary with age)

   (c) *Reduced transport iron:* Transferrin saturation < 8% in children 1-2 years.

There is a pronounced diurnal variation in serum iron and TS which can result in a wide normal variation. Therefore, serum iron and TS are not recommended for the routine confirmation of diagnosis of ID in favour of FEP and SF (Cook, 1982).

(D) Iron deficiency anaemia: The above plus Hb < 11.0g/dL