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Pediatric Education and Research
Volume 1 Number 2, April - June 2013

On the Way to Eradicate AIDS in 21st Century: Challenges and Emerging Issues

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India has the second highest burden in the world after South Africa and Nigeria so for as the HIV/AIDS cases are concerned.[1] India has an estimated 2.5 to 3.1 million people living with HIV/AIDS (PLWH) including children under 15 years and those aged 50 and beyond as per the National AIDS Control Organization (NACO) and UNAIDS.[2] India is a country with 35 states and out of that figure, six states have been documented to have HIV antenatal prevalence greater than 1%, viz, Andhra Pradesh, Tamil Nadu, Maharashtra, Karnataka, Manipur, and Nagaland. The adult HIV prevalence is 0.36% and the majority of HIV infections are in men aged 15 to 44 years. Nearly 40% of PLWH in India are women.[3] In case we analyse the molecular epidemiology of pediatric HIV, it is very less, but what we do know is it is primarily HIV-1 and that subtype C accounts for the majority of infections. Subtype A and B are reported but the numbers are quite small. Although HIV-2 has been reported, the numbers are also unknown. In Africa it's subtype A and C that predominate. They have slightly higher prevalence of HIV-2. Most of transmission among children with HIV in India is primarily mother to child, or vertical transmission which accounts for approximately 82% of all children in India infected with HIV. It is estimated that some 70,000 children below the age of 15 are infected with HIV and 21,000 children are infected every year through mother-to-child transmission (NACO estimates 2007).

The universal access to comprehensive health services is focused to address six needs: voluntary counseling and testing, prevention of HIV transmission, prophylaxis against opportunistic infections (OI), diagnosis and treatment for OIs and neoplasm's, anti retroviral therapy (ART), palliative care and health care infrastructure and capacity to provide quality care.[4] We have noticed that encouraging progress has been seen in scaling up services of the India's National AIDS Control Programme for Prevention, Treatment, Care and Support over the last decade, but gains are fragile and will be short-lived if not sustained, so the imperative remains to achieve better combined prevention approaches and to reach out to people most affected by the virus for whom services are often out of reach and for whom stigma and discrimination are daily companions. The marginalized populations face much more stigma and access to the services is giant challenge. The AIDS exceptionalism led to unwarranted support for fighting the war. But the thirty years down the lane, with a global recession leading to drying of funds for AIDS and dependency crisis unfolding-millions especially in Africa are without access to essential life saving medicines.

It has been observed that openness to learnings from field rather than central consultations of elite, who rarely are in touch with ground situation. Having a realistic plan driven by the PLHA community, with ownership and community based monitoring is need of the hour for effective programme implementation. Who will bell the cat? Community care centres were closed but the ground reality is that hospital staff attitudes leave a lot wanting; devoid of human touches and people need short stay home facility when the PLHA tread from remote area in hill terrain to ART centre and have to wait for up-to three days for their tests and results, with accessibility

getting difficult.[5] Bureaucracy is still boggled with its templates and sheets. Who will create the enabling space for the affected communities to step in and take charge?

Certainly, the country has an increasing population of children living with HIV/AIDS (PLWH) and those who have lost either one or both parents to an AIDS related illness. However, there are no official estimates available on children affected and orphaned by HIV and AIDS in India and that too in Africa. There is a lot unabridged gap between children orphaned and their back up services. Hence, there is a need to strengthen the support systems for PLWH and children affected by AIDS. Despite advantages and disadvantages of community foster care in India, still it is one of the options open for orphaned children who are vulnerable to sexual abuse and exploitation.[6] Also, to control this, minimum standards of care and protection need to be established for Institutional and community-based foster care systems. Despite the hype around the issue, it is still a taboo issue. Too many people still feel embarrassed to talk condom, get condom and negotiate safer behaviors. Youth are still into risk taking attitude and fall prey to drugs and risks. How can we engage youth if we focus only on the negative possible consequences of sexual behaviors and spend no time talking about the positives? Engaging and tapping the powerful energy of the over 35% adolescents and youth, the demographic dividends of the great Indian population constructively is an enormous challenge.

We have "n" number of challenges and emerging issues now in 21st century; right from epidemiology of disease to treatment to social rehabilitation of the victims. Despite all advances in anti retroviral therapy (ART), quality of life for PLHA is an unquestionably **grey area.** There is loss down the cascade from detection, to treatment, to effective viral suppression. We are unable to address psychosocial issues, depression and mental health comorbidities of PLHA. This leads to people missing out meds and dangerous drug resistance emergence. Instead of numbers of individuals on treatment, we should begin to evaluate treatment centers by the numbers of individuals who have been retained in care, consistently take their medications and achieve successful, long-term control of their HIV infections. Comorbidities like Hepatitis-C are still unaddressed. Staff has been seen to be demoralized with lack of salary hikes and attrition of trained good manpower is bound to occur. Improving the quality of counseling and care is a tremendous challenge. We can cure physical diseases with medicine, but the only cure for loneliness, despair, and hopelessness is LOVE and empathetic human touches. The fear and misconceptions can only be addressed by open talk. Let's demystify HIV/AIDS so that people feel comfortable talking about as to how to protect themselves. How to talk, age appropriate AEP modules development and its positive implementation is also one of the tremendous challenges. Last but not the least, we need to work with renewed zeal towards "beginning of the end of AIDS"- point at which the number of people newly added to treatment and retained in effective care outpaces the number of people newly infected with HIV in a given year. For this domestic spending on HIV needs a boost. Social rehabilitation will also find a forceful way out.

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Original Article

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Does Increase in Feed Volume from 150 Ml/Kg/Day to 200 Ml/Kg/Day Accelerate Growth in VlBW Babies without Significant Added Risk

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Abstract

Extra-uterine malnutrition is common in preterm very low birth weight (VLBW) newborns in spite of fortification with available human milk fortifiers. Hypothesizing that increasing the volume of feed would be safe and will lead to better postnatal weight gain we randomized 96 babies with birth weight less than 1500 gm after reaching the full feeds (i.e.150 ml/kg/day), to continue feeds at 150 ml/kg/day (standard volume) or to increase to 200 ml/kg/day (high volume) of expressed breast milk or preterm formula feed. Expressed breast milk was fortified with available fortifier. There was significantly higher daily weight gain in high volume group as compared to standard volume group. Appropriate for gestational age (AGA) babies showed significantly higher weight gain as compared to small for gestational age (SGA) babies, both in high and standard volume group. Incidence of feed intolerance did not differ significantly between two feeding groups. High volume feeds at 200 ml/kg/day was safe and resulted in better daily weight gain than standard volume feeds i.e.150 ml/kg/day in preterm very low birth weight babies.

Key words: Very low birth weight; Nutrition; Growth; Feeding volume.

Introduction

Optimizing the growth of very low birth weight babies is extremely important. Poor postnatal growth has been associated with increased risk of poor neuro-developmental out come at 18 months of age.[1] Current practice includes restriction of feed volume to 150 ml/kg/day in VLBW babies. Extra uterine malnutrition is common problem in VLBW babies on feeding volume of 150 ml/kg/day suggesting that it may be insufficient for adequate catch up growth. Fortification of milk is one of the available options to increase the nutritional value of feed. But proper fortification is not always possible in view of unavailability of good quality human milk fortifier. Fortification with routinely available human milk fortifier (Lactodex HMF) alone is insufficient to meet nutritional demands and to avoid extra uterine malnutrition in VLBW babies. High volume feeds have been shown to be safe in volumes up to 250 to 300ml/kg/day in some studies.[2,3,4] Increasing the enteral feeding volume from 150 to 200 ml/kg/day in addition to fortification with available fortifier (Lactodex HMF) would increase the caloric intake from 122 to 164 kcal/kg/day. We hypothesized that increase in milk volume along with routine fortification would be safe and will lead to better postnatal growth.

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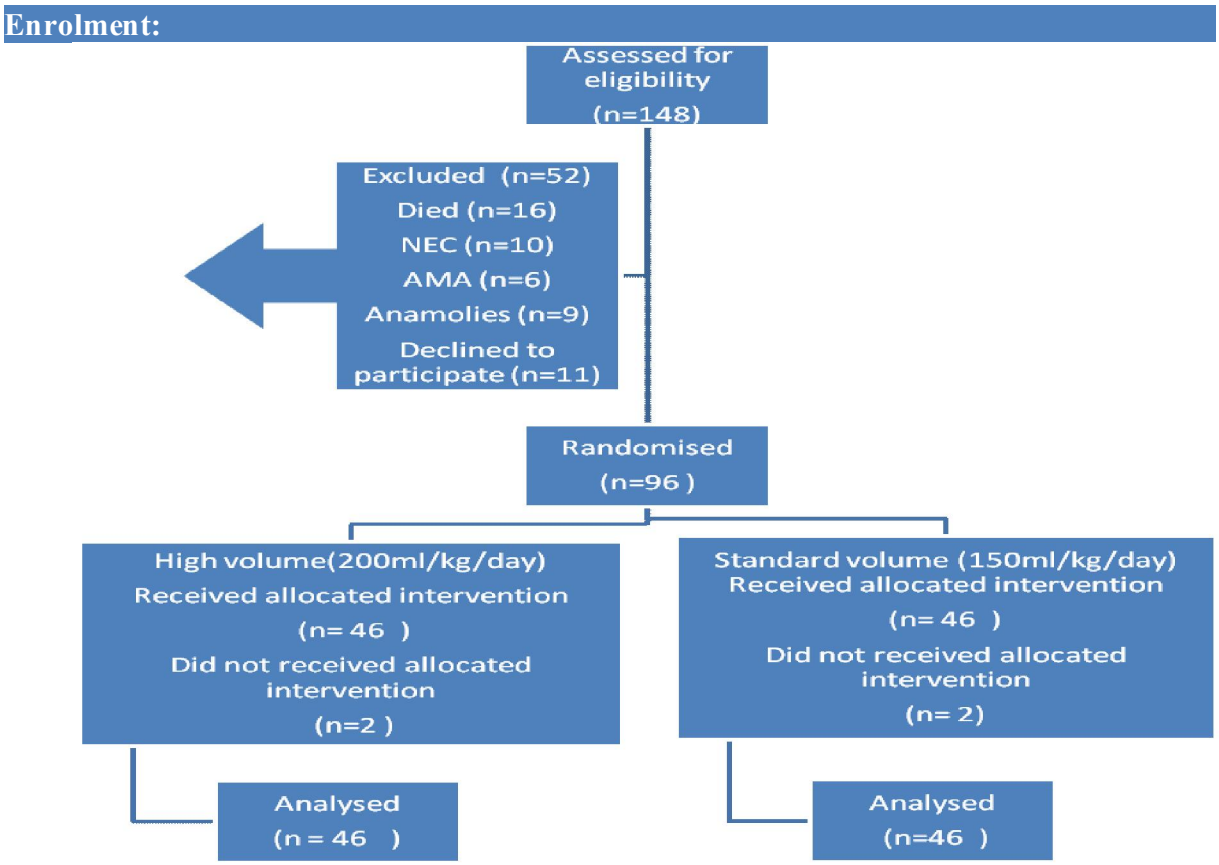


Materials and Methods

This prospective randomized control trial was carried out in the neonatal unit of KEM hospital, Pune. Newborn infants weighing d"1500 gm at birth were eligible for enrolment once they achieve full feeds (150 ml/kg/day). Babies with major congenital anomalies and gastrointestinal malformations, on ventilator support, necrotizing enterocolitis (NEC) stage II and III and symptomatic patent ductus arteriosus (PDA) were excluded. Parent's consent was obtained and babies were randomized into two groups using simple randomization. In the high-volume group, feeds were increased by 20 ml/kg/day till 200 ml/kg/day and in the other (control) group, feeds were continued at 150 ml/kg/day. All the babies were fed with expressed breast milk+ formula feed through the nasogastric tube, fortification were done in all babies after reaching feeds of 100 ml/kg/day (HMF /Simyl MCT) and other interventions in both groups were as per the unit's protocol. Weight were checked twice weekly by an electronic weighing machine. The primary outcome studied was weight gain in g/kg/day from enrolment till discharge. The secondary outcomes were complications like feed intolerance [defined as _2 episodes of vomiting/ increased aspirates (>50% of previous feed volume)], tachypnea (respiratory rate >60/min), NEC (Stage 2a or more). Babies were monitored daily for possible complications. All data were recorded in standard forms. Babies were analyzed at the time of discharge irrespective of what treatment they received. Appropriate for gestational age (AGA) and small for gestational age was categorized based on Fenton fetal infant growth chart for preterm infants.[5]

Sample size calculated was 48 (in each group) babies giving 80% power ,5% type one error probability and group one to two ratio being 1:1. We used software called PS: power

Table 1: The comparison of birth parameters between two feeding groups

Parameters	Standard vol. group 150ml/kg/day (n=46)	High vol. group 200ml/kg/day (n=46)	P-value
Sex			
Male	23 (50.0)	25 (54.3)	0.676
Female	23 (50.0)	21 (45.7)	
SGA / AGA Status			
SGA	25 (54.3)	27 (58.7)	0.674
AGA	21 (45.7)	19 (41.3)	
Birth weight (g)	1162.8 ± 234.8	1232.3 ± 181.6	0.116
Gestational age (wks)	30.9 ± 2.6	31.6 ± 2.2	0.199

Figure 1a: The distribution of sex between two feeding groups

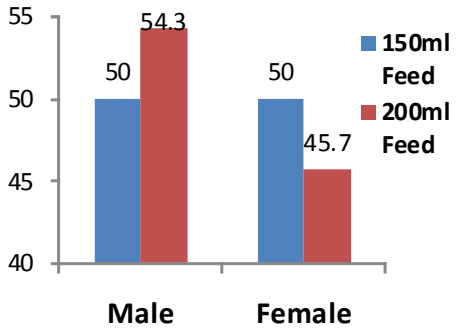


Figure 1b: The distribution of SGA/AGA status between two feeding groups

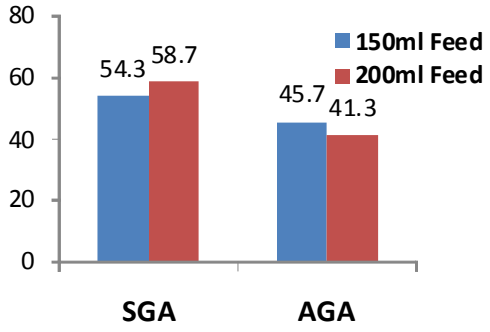


Figure 1c: The distribution of birth weight between two feeding groups

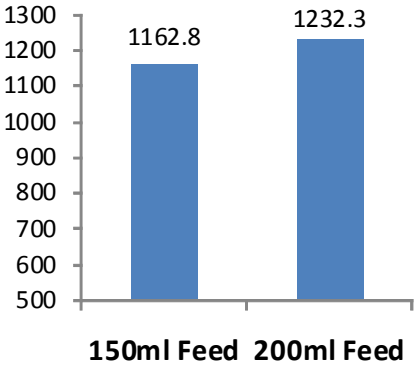
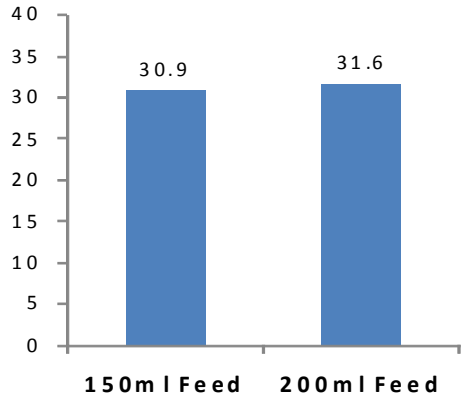


Figure 1d: The distribution of gestational age between two feeding groups



sample size calculation software to detect sample size.

Data analysis was by intention to treat. Of the 48 babies who were randomized to high volume feeds 4 did not achieve the targeted feed volume of 200 ml/kg/day.

Results

I) The comparison of birth parameters between two feeding groups

Values on Sex and SGA/AGA Status are n (%) whose p-values are obtained using Chi-Square test. Values on birth weight and gestational age are mean ± standard deviation whose p-values are obtained using independent sample 't' test.P-value<0.05 is considered to be statistically significant.

Comments

1) The sex distribution did not differ significantly between two feeding

Table 2: The comparison of weight gain between two feeding groups

	Standard vol. group 150ml/kg/day (n=46)	High vol. group 200ml/kg/day (n=46)	P-value
Weight gain (g/kg/day)	13.9 ± 1.2	18.0 ± 3.6	0.001

Figure 2: The distribution of weight gain between two feeding groups

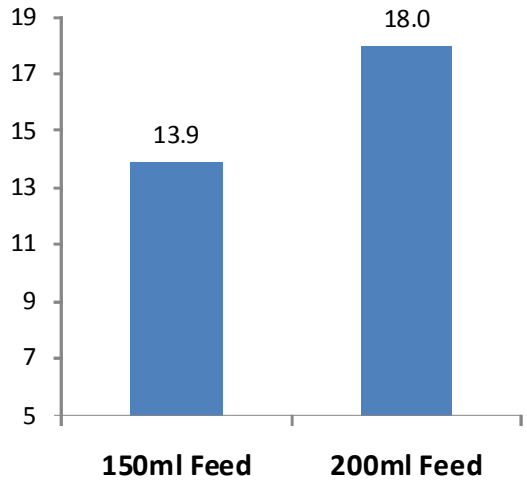
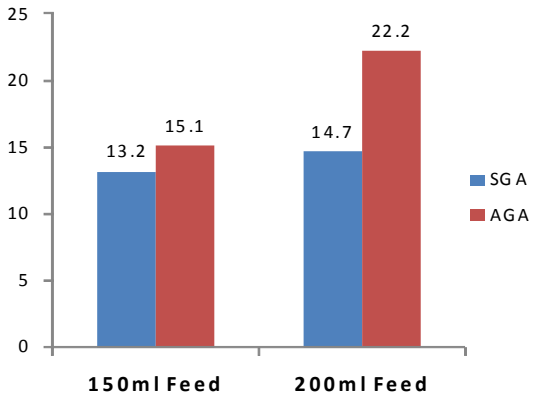


Figure 3: The comparison of weight gain according to SGA/AGA status in each feeding group



groups.

2) The SGA/AGA distribution did not differ significantly between two feeding groups.

3) The average birth weight did not differ significantly between two feeding groups.

4) The average gestational age did not differ significantly between two feeding groups.

II) The comparison of weight gain between two feeding groups

Values are mean ± standard deviation whose p-values are obtained using independent sample't' test. P-value <0.05 is considered to be statistically significant.

Comments

1) The average weight gain differs significantly between two feeding groups.

2) The high volume feeding group showed significantly higher weight gain compared to low volume feeding group.

III) The comparison of weight gain according to SGA/AGA status in each feeding group

Values are mean ± standard deviation whose p-values are obtained using independent sample't' test. P-value <0.05 is considered to be statistically significant.

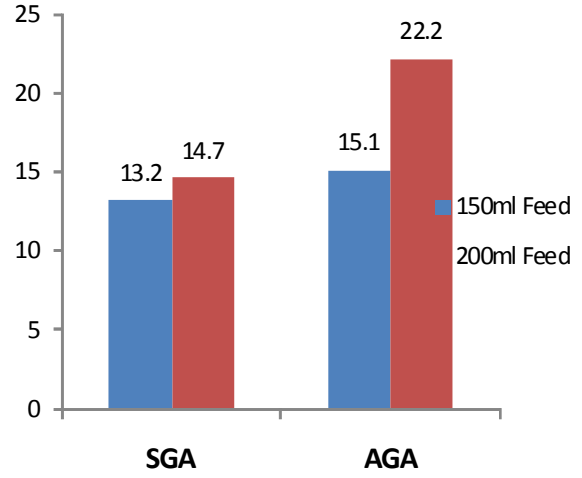
Table 3: The comparison of weight gain according to SGA/AGA status in each feeding group

	Standard vol. group 150ml/kg/day (n=46)			High vol. group 200ml/kg/day (n=46)		
	SGA (n=25)	AGA (n=21)	P-value	SGA (n=27)	AGA (n=19)	P-value
Weight gain (g/kg/day)	13.2 ± 0.9	14.7 ± 0.9	0.001	15.1 ± 1.0	22.2 ± 0.8	0.001

Table 4: The subgroup comparison of weight gain between two feeding groups in each group of weight for gestational age

	SGA (n=52)			AGA (40)		
	Standard vol. group 150ml/kg/day (n=25)	High vol. group 200ml/kg/day (n=27)	P-value	Standard vol. group 150ml/kg/day (n=21)	High vol. group 200ml/kg/day (n=19)	P-value
Weight gain (g/kg/day)	13.2 ± 0.9	15.1 ± 1.0	0.001	14.7 ± 0.9	22.2 ± 0.8	0.001

Figure 4: The subgroup comparison of weight gain between two feeding groups in each group of weight for gestational age

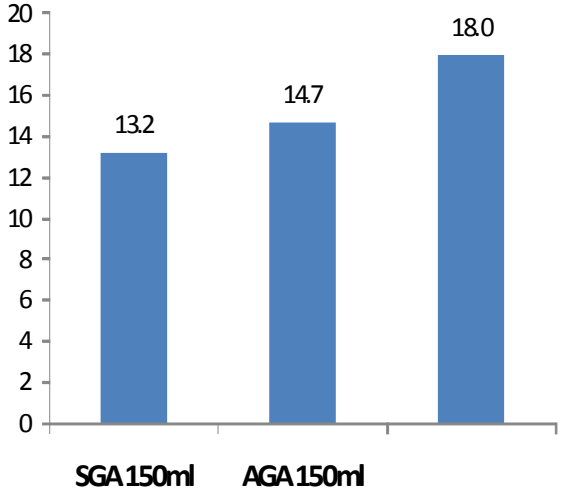


Comments

1) In low volume feeding group, the average weight gain is significantly higher among AGA cases compared to SGA cases.
2) In high volume feeding group, the average weight gain is significantly higher among AGA cases compared to SGA cases.

IV) The subgroup comparison of weight gain between two feeding groups in each group of weight for gestational age

Figure 5: The comparison of weight gain SGA and AGA of low volume group with whole high volume group



Values are mean ± standard deviation whose p-values are obtained using independent sample 't' test. P-value<0.05 is considered to be statistically significant.

Comments

1) High volume feeding SGA cases had significantly higher weight gain compared to the low volume feeding SGA cases.

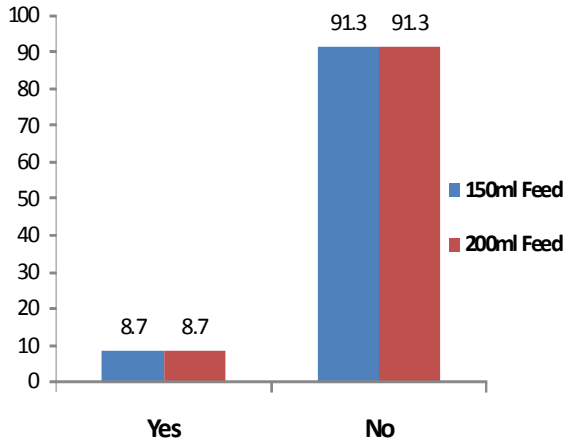
Table 5: The comparison of weight gain SGA and AGA of low volume group with whole high volume group

	SGA of Standard vol. group 150ml/kg/day (n=25)	AGA of Standard vol. group 150ml/kg/day (n=21)	High vol. group 200 ml/kg/day (n=46)	P-value	
				SGA 150ml/kg/day v/s Whole 200ml/kg/day	AGA 150ml/kg/day v/s Whole 200ml/kg/day
Weight gain (g/kg/day)	13.2 ± 0.9	14.7 ± 0.9	18.0 ± 3.6	0.001	0.001

Table 6: The comparison of incidence of feed intolerance between two feeding groups

	Standard vol. group 150ml/kg/day (n=46)	High vol. group 200ml/kg/day (n=46)	P-value
Feed Intolerance			
Yes	4 (8.7)	4 (8.7)	0.999
No	42 (91.3)	42 (91.3)	

Figure 6: The distribution of incidence of feed intolerance between two feeding groups



2) High volume feeding AGA cases had significantly higher weight gain compared to the low volume feeding AGA cases.

V) The comparison of weight gain SGA and AGA of low volume group with whole high volume group

Values are mean ± standard deviation whose p-values are obtained using one-way analysis of variance (AOVA) with Bonferroni's correction for multiple group comparisons. P-value<0.05 is considered to be statistically significant.

Comments

1) High volume feeding cases had significantly higher weight gain compared to the low volume feeding SGA cases.
2) High volume feeding cases had significantly higher weight gain compared to the low volume feeding AGA cases.

VI) The comparison of incidence of feed intolerance between two feeding groups.

Values are n (%) whose p-values are obtained using Chi-Square test. P-value<0.05 is considered to be statistically significant.

Comment

The distribution of incidence of feed intolerance did not differ significantly between two feeding groups.

Discussion

Growth velocity is much higher in preterm than in term babies but their nutrient stores are very little. Infants lose weight after birth and often regain birth weight in second week of life. Poor postnatal weight gain is common especially in SGA babies who form large portion of VLBW babies in countries like India. Maximizing postnatal weight gain is important in improving neuro-developmental outcome in VLBW babies. Fortification of feed is recommended to improve nutrition in preterm babies but often cannot be practiced in view of unavailability of good fortifier.

In our study sex distribution did not differ significantly in between two feeding groups. Similarly SGA and AGA distribution did not differ significantly between two feeding groups. Average birth weight and gestational age did not differ significantly between two feeding groups

We could find significant weight gain in VLBW babies (both groups SGA and AGA) secondary to use of high volume feeds (200 ml/kg/day) with fortification compared to standard volume feeding group (150 ml/kg/day) with fortification. Kuschel *et al* showed that infant fed with 200 ml/kg/day gained

weight better than those with 150ml/kg/day.[6] Mukhopadhyay *et al* comparing fortified and unfortified breast milk at 150 ml/kg/day demonstrated better weight gain in preterm babies fed fortified milk.[7] Similarly Lewis et al (250 ml/kg/day) showed that preterm infant gained weight at intrauterine rate without complications.[3]

In our study in subgroup analysis AGA babies showed significantly better weight gain in comparison to SGA babies in both groups. Niranjan Thomas *et al* showed that SGA babies with high volume feeds gained weight adequately but not as well as AGA babies.[2]

We also found that distribution of incidence of feed intolerance did not differ significantly in both groups. Similarly Niranjan Thomas *et al* did not find statistically significant difference in incidence of feed intolerance in both groups.[2] Lewis *et al* also mentioned that they could not find evidence of complication secondary to use of high volume feeds.[3] Valmen *et al* mentioned few complications using high volume feeds of 300ml/kg/day by continuous nasogastric drip. But all their patients thrived and SGA babies showed catch-up growth with high volume feeds.[4]

We demonstrated in this study that high volume feeds at 200 ml/kg/day with fortification were safe in preterm VLBW babies. Raising calorie and protein intake by giving high volume feeds led to better postnatal weight gain and can prevent extra uterine malnutrition. Long term nutritional and neuro developmental outcomes need to be studied.

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Review Article

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Coeliac Disease

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Abstract: Coeliac disease is an immune-mediated enteropathy caused by a permanent sensitivity to gluten in genetically susceptible individuals. It occurs in children and adolescents with gastrointestinal symptoms, dermatitis herpetiformis, dental enamel defects, osteoporosis, short stature, delayed puberty and persistent iron deficiency anaemia and in asymptomatic individuals with type 1 diabetes, Down syndrome, Turner syndrome, Williams syndrome, selective immunoglobulin (Ig)A deficiency and first degree relatives of individuals with coeliac disease. The Coeliac Disease Guideline Committee of the North American Society for Paediatric Gastroenterology, Hepatology and Nutrition has formulated a clinical practice guideline for the diagnosis and treatment of paediatric coeliac disease based on an integration of a systematic review of the medical literature combined with expert opinion.

The Committee examined the indications for testing, the value of serological tests, human leukocyte antigen (HLA) typing and histopathology and the treatment and monitoring of children with coeliac disease. It is recommended that children and adolescents with symptoms of coeliac disease or an increased risk for coeliac disease have a blood test for antibody to tissue transglutaminase (TTG), that those with an elevated TTG be referred to a paediatric gastroenterologist for an intestinal biopsy and that those with the characteristics of coeliac disease on intestinal histopathology be treated with a strict gluten-free diet (GFD).

Keywords: Coeliac disease (CD); Gluten free diet (GFD).

Introduction

Coeliac disease is an autoimmune disorder of the small intestine that occurs in genetically predisposed people of all ages from middle infancy onward. This condition has several other names, including coeliac sprue, non tropical sprue, endemic sprue, gluten enteropathy or gluten-sensitive enteropathy, and gluten intolerance. The term coeliac was derived from the Greek (koiliakos, "abdominal") and was introduced in the 19th century in a translation of what is generally regarded as an ancient Greek description of the disease by Aretaeus of Cappadocia.[1,2]

Symptoms include pain and discomfort in the digestive tract, chronic constipation and diarrhoea, failure to thrive (in children), and fatigue, but these may be absent, and symptoms in other organ systems have been described. Vitamin deficiencies are often noted in people with coeliac disease due to the reduced ability of the small intestine to properly absorb nutrients from food. Increasingly, diagnoses are being made in asymptomatic persons as a result of increased screening.[3]

The condition is thought to affect between 1 in 1,750 and 1 in 105 people in the United

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States.[4] Coeliac disease is caused by a reaction to gliadin, a prolamin (gluten protein) found in wheat, and similar proteins found in the crops of the tribe Triticeae (which includes other common grains such as barley and rye).[5] Upon exposure to gliadin, and specifically to three peptides found in prolamins, the enzyme tissue trans glutaminase modifies the protein, and the immune system cross-reacts with the small-bowel tissue, causing an inflammatory reaction. This leads to a truncating of the villi lining the small intestine (called villous atrophy). It interferes with the absor-ption of nutrients because the intestinal villi are responsible for absorption. The only known effective treatment is a lifelong gluten-free diet.[5] While the disease is caused by a reaction to wheat proteins, it is not the same as wheat allergy.

Pathogenesis

Susceptibility to CD, and its activation and perpetuation, involve a combination of environmental and genetic factors, and immunological mechanisms. A number of important factors and mechanisms underlying disease pathogenesis are well defined, whereas others are only now coming into focus.

A) The role of dietary proteins in disease pathogenesis

CD is activated by proteins in the dietary cereal grains wheat, rye, and barley. The disease-activating proteins in these grains are widely termed "gluten". Gluten includes 2 major protein types, the gliadins and glutenins, both of which contain disease-activating peptides.[6] The closely related proteins in barley and rye that activate CD are the hordeins and secalins, respectively.[7] Oats are thought to activate CD only rarely[8], and, consistent with this, oat avenins are more distantly related to the analogous proteins in wheat, rye, and barley and have a substantially lower proline content.[9] Gliadins, glutenins, hordeins, and secalins have a high proline and glutamine content. The high proline content renders these proteins resistant to complete proteolytic digestion by gastric, pancreatic, and brush border enzymes in the human intestine, since those enzymes are deficient in prolyl endopeptidase activity. This can result in the accumulation of relatively large peptide fragments (as many as 50 amino acids in length) with a high proline and glutamine content in the small intestine. Nonetheless, the relatively poor digestion of these proteins alone is not sufficient to cause CD. However, failure to digest these and other proteins might be exaggerated in the small intestine of individuals with active disease who manifest epithelial cell brush border injury and accompanying pancreatic dysfunction.[10]

B) Genetic factors

MHC class II HLA-DQ alleles. The pathogenesis of CD is firmly rooted in host genetic factors. It is known that CD is associated with specific MHC class II alleles that map to the HLA-DQ locus. The presence of speci-fic HLA-DQ alleles is necessary, although not sufficient, for the phenotypic expression of CD in virtually all affected individuals, irrespective of geographic location.[11] Indeed, almost all individuals with biopsy-confirmed CD express HLA-DQ alleles that encode specific HLA-DQ2 heterodimers or specific HLA-DQ8 heterodimers, and the alleles that encode these heterodimers are relatively common in the white population.CD is substantially more prevalent in those in whom 100% or approximately 50% of the HLA-DQ heterodimers are HLA-DQ2 than in those in whom only approximately 25% of the HLA-DQ heterodimers are HLA-DQ2. In this regard, the approximately 2% of the population who are homozygous for the HLA-DQ2 heterodimer account for approximately 25% of all patients with CD. Notably, an increased abundance of HLA-DQ2 heterodimers on APCs has correlated with an increased magnitude of in vitro gluten-specific T cell responses, which, if paralleled in vivo, might contribute to the increased risk of developing clinically apparent CD in individuals homozygous for HLA-DQ2. Once

CD develops, the clinical course seems generally similar whether or not 100%, 50%, or 25% of the HLA-DQ molecules form the HLA-DQ2 heterodimer. Most recently with the use of genome-wide screening approaches Candidate genetic regions that possibly increase CD susceptibility have been noted in some populations on chromosomes 2, 3, 4, 5, 6 (telomeric of the HLA locus), 9, 11, 18, and 19.[12]

HLA-DQ2 and HLA-DQ8 heterodimers on APCs can bind and subsequently present "gluten" peptides to populations of CD_4^+ T cells in the lamina propria of the small intestine. Tissue TGase, which is released in the intestinal mucosa during tissue injury, has a role in tissue repair and cross-links proteins by forming isopeptide bonds between glutamine and lysine residues. However, tissue TGase also has a high avidity for "gluten" peptides and, under certain conditions (for example, low p^H) and in the absence of lysine residues, can deamidate glutamine, which converts neutral glutamine to negatively charged glutamic acid. Some, but not all, of the deamidated "gluten" peptides, by virtue of having negatively charged glutamic acid residues, manifest an increased binding affinity for the disease-relevant HLA-DQ2 or HLA-DQ8 molecules. Once bound to HLA-DQ2 and HLA-DQ8, the "gluten"-peptide–HLA-DQ complexes can activate T cells in the mucosa of the small intestine that recognize these complexes. Glutamine deamidation is not an absolute requirement for T cell activation early in the course of disease in children. It is now known that T cells in adults with CD also are reactive to multiple peptides from α- and γ-gliadins.[13]

'The production of IFN-γ is a signature of "gluten" peptide–specific HLA-DQ2– and HLA-DQ8–restricted T cells and it is considered to have a key role in the downstream initiation of mucosal damage. Neutralization of IFN-γ has been shown to prevent "gluten"-induced mucosal damage, at least in biopsies of CD mucosa maintained in organ culture. Recent studies suggest that activation of the innate immune system is important in the pathogenesis of CD and in some of the complications of this disease, namely in refractory CD (that is, severe villous atrophy and malabsorption that either does not respond or no longer responds to a GFD). In particular, an increase in the number of IELs in the mucosa of the small intestine is a characteristic feature of CD, and those cells are likely to be important for the ongoing pathogenesis of CD. Following activation, IELs from patients with CD change from being typical antigen-specific T cells to being NK-like cells able to mediate epithelial cell damage through the recognition of stress-induced molecules on intestinal epithelial cells. The cytokine IL-15 takes center stage in this process. Up regulation of IL-15 expression by epithelial cells in CD seems to contribute to altered signalling properties of the CD_8^+ IEL population.[14]

Clinical features

The clinical manifestations of CD vary markedly with the age of the patient, the duration and extent of disease, and the presence of extra intestinal pathology. Depending on the features at the time of presentation, together with the histologic and immunologic abnormalities at the time of diagnosis, CD can be subdivided into the following clinical forms.

a) Classical (typical) form

The onset of symptoms in the classical form generally occurs between 6 and 18 months of age. This form is typically characterized by chronic diarrhea, failure to thrive, anorexia, abdominal distention, and muscle wasting. Growth is usually normal during the first months of life. Symptoms begin within weeks to a few months after the introduction of weaning foods containing prolamines, and soon there is a progressive decrease in weight gain with a decline in the child's percentile for weight and weight for height. On examination, the children are often pale and noticeably thin with a protuberant abdomen, decreased subcutaneous fat, and reduction in

muscle mass. The stools are characteristically pale, loose, bulky, and highly offensive because of fat malabsorption. A small number of these infants also have severe hypoproteinemia and edema and may present in a shock like state that has been termed "coeliac crisis".[15]

b) Atypical forms

In recent years there has been a noticeable change in the age of onset of symptoms and the clinical presentation of CD. Ma¨ki *et al*[16] first reported an up-shift of age at diagnosis in Finland to 5–6 years, with fewer than 50% of new cases presenting with typical gastrointestinal symptoms. Reports from Scotland, England, Canada, and the United States have also shown that almost 50% of patients with newly diagnosed CD do not present with gastrointestinal symptoms.

c) Dermatitis herpetiformis

Dermatitis herpetiformis is currently regarded as a variant of CD ("skin CD"). It is a blistering skin disease characterized by pathognomonic granular immunoglobulin (Ig) A deposits in uninvolved skin. The most typical sites of the rash are the elbows, knees, and buttocks. Intestinal symptoms are not common, but a varying degree of enteropathy, ranging from the infiltrative-type lesion to flat mucosa, can be found on small intestinal biopsy in almost 100% of cases. Both the enteropathy and the rash slowly clear with a gluten-free diet (GFD) and relapse when patients return to a regular diet.[17]

d) Iron-deficiency anaemia

Iron deficiency with or without anaemia, typically refractory to oral iron supplementation, can be the only presenting sign of CD.[18]

e) Short stature

Short stature is well described as the only symptom of CD in some older children and adolescents, and it is believed that as many as 9%–10% of those with "idiopathic" short stature have CD. In these patients, both the bone age and growth velocity are significantly impaired. Some patients have also demonstrated impaired growth hormone production after provocative stimulation testing. This value returns to normal after introduction of a GFD.[19]

f) Dental enamel Hypoplasia

It has been found in up to 30% of untreated patients with CD.[20]

g) Arthritis and Arthralgia

CD has been described in 1.5%–7.5% of patients with rheumatoid arthritis. These symptoms were reported by Ma¨ki *et al* as the only presentation of CD in 7 adolescent patients. In each case, the symptoms resolved on introduction of a GFD and all other anti-inflammatory medications could be discontinued.[21]

h) Chronic hepatitis and Hypertransaminasemia

Idiopathic chronic hepatitis as the initial presentation of CD has been reported occasionally.[22] Vajro *et al* described 3 children with cryptogenetic chronic hepatitis secondary to CD. In all cases, GFD induced complete remission with normalization of the biochemical and histologic changes of hepatitis. Resolution of the biochemical abnormalities associated with hepatic damage has been reported in a high percentage of paediatric patients with CD who adhered to a strict GFD.[23]

i) Osteoporosis

Patients with CD are at high risk for developing low bone mineral density and bone turnover impairment. Persistent villous atrophy is associated with low bone mineral density. In adult patients responsive to diet, the bone density seems comparable to that of healthy individuals. Children who followed a

GFD for at least 5 years had normal bone mineralization and bone turnover.[24]

j) Neurologic problems

Gluten sensitivity is common in patients with neurological diseases of unknown cause and may have etiologic significance.

k) Other extra-gastrointestinal symptoms

A delay in onset of puberty secondary to CD has been described in a number of adolescent patients. Recurrent abortions and reduced fertility caused by CD have also been reported in this age group.[25,26]

l) Asymptomatic (silent) form

This form is characterized by the presence of histologic changes, probably limited to the proximal intestine, that occur in individuals who are apparently asymptomatic. Most cases in this category have been identified through screening programs involving apparently healthy subjects. However, a more careful clinical anamnesis typically reveals that many of these "silent" cases are indeed affected by low-intensity illness often associated with decreased psychophysical well-being. Common problems behavioral disturbances, such as tendency to depression, irritability, or impaired school performance in children; impaired physical fitness, feeling always tired, and easy fatigue during exercise. Current evidence suggests that subjects with "silent" CD are at risk to develop the same long-term complications experienced by individuals with typical symptoms.[27,28]

Associated conditions

Conditions associated with coeliac disease are IDDM, autoimmune hepatitis, autoimmune thyroiditis, Sjogren syndrome, Addison disease, autoimmune atrophic gastritis. Gluten independent conditions are Down syndrome, Turner syndrome, Williams syndrome, congenital heart disease, IgA deficiency.

Complications Associated With Unrecognized CD

1) Malignancies

The persistence of mucosal injury with or without typical symptoms can lead to serious complications, and gastrointestinal malignancies (particularly lymphoma) have been reported in 10%–15% of adult patients with known CD who do not strictly comply with a GFD. It has been reported that the mortality rate in CD patients is almost double (1.93) the rate calculated for the general population, mainly because of the occurrence of neoplasms.[29]

2) Autoimmune diseases

CD seems to meet the criteria of a true autoimmune disease for which the genetic predisposition (HLA), exogenous trigger (gluten), and auto antigen (tTG) are known. It seems that tTG is only one of the auto antigens involved in gluten dependent autoimmune reactions. Other auto antigens that are normally "cryptic" can be unmasked and cause a self-aggressive immunologic response following the gliadin-initiated inflammatory process. Recent data suggest that the prevalence of autoimmune diseases among patients with CD is proportional to the time of exposure to gluten.[30]

Diagnosis

Testing for CD should be offered to the following groups:

Group 1: Children and adolescents with the otherwise unexplained symptoms and signs of chronic or intermittent diarrhoea, failure to thrive, weight loss, stunted growth, delayed puberty, amenorrhoea, iron-deficiency anaemia, nausea or vomiting, chronic abdominal pain, cramping or distension, chronic constipation, chronic fatigue, recurrent aphthous stomatitis (mouth ulcers), dermatitis herpetiformis–like rash, fracture with inadequate traumas/osteopenia/osteoporosis, and abnormal liver biochemistry.

Group 2: Asymptomatic children and adolescents with an increased risk for CD such as type 1 diabetes mellitus (T1DM), Down syndrome, autoimmune thyroid disease, Turner syndrome, Williams syndrome, selective immunoglobulin A (IgA) deficiency, autoimmune liver disease, and first-degree relatives with CD.

Diagnostic tools

CD-specific antibody tests

CD-specific antibody tests measure anti-Tissue transglutaminase2 or endomyecial antibody in blood.

It is not sufficient to state only positivity or negativity. Reports on EMA results should contain the specification of the investigated immunoglobulin class, cut-off dilution, interpretation (positive or negative), highest dilution still positive, and specification of the substrate tissue. For the interpretation of antibody results, total IgA levels in serum, age of the patient, pattern of gluten consumption, and intake of immunosuppressive drugs should be taken into account. If gluten exposure was short or gluten had been withdrawn for a longer period of time (several weeks to years) the negative result is not reliable. For IgA-competent subjects, the conclusions should be drawn primarily from the results of IgA class antibody tests. For subjects with low serum IgA levels (total serum IgA < 0.2 g/L), the conclusions should be drawn from the results of the IgG class CD-specific antibody tests.

HLA testing for HLA-DQ2 and HLA-DQ8

Typing for HLA-DQ2 and HLA-DQ8 is a useful tool to exclude CD or to make the diagnosis unlikely in the case of a negative test result for both markers. HLA testing should be performed in patients with an uncertain diagnosis of CD, for example, in patients with negative CD-specific antibodies and mild infiltrative changes in proximal small intestinal biopsy specimens. If CD is considered in children in whom there is a strong clinical suspicion of CD, high specific CD antibodies are present, and small-bowel biopsies are not going to be performed, then the working group recommends performing HLA-DQ2 and HLA-DQ8 typing to add strength to the diagnosis.

Histological analysis of duodenal biopsies

The histological features of the small intestinal enteropathy in CD have a variable severity, may be patchy, and in a small proportion of patients with CD appear only in the duodenal bulb. The alterations are not specific for CD and may be found in enteropathies other than CD. Biopsies should be taken preferably during upper endoscopy from the bulb (at least 1 biopsy) and from the second or third portion of duodenum (at least 4 biopsies). The pathology report should include a description of the orientation, the presence or not of normal villi or degree of atrophy and crypt elongation, the villus-crypt ratio, the number of intraepithelial lymphocytes (IELs), and grading according to the Marsh-Oberhuber classification.[31,32]

Diagnostic approach for a child or adolescent with symptoms or signs suggestive of CD

A test for CD-specific antibodies is the first tool that is used to identify individuals for further investigation to diagnose or to rule out CD. Patients who are consuming a gluten-containing diet should be tested for CD-specific antibodies. It is recommended that the initial test be IgA class anti-TG2 from a blood sample. Tests measuring antibodies against DGP may be used as additional tests in patients who are negative for other CD-specific antibodies but in whom clinical symptoms raise a strong suspicion of CD, especially if they are younger than 2 years.

Tests for the detection of IgG or IgA antibodies against native gliadin peptides (conventional gliadin antibody test) should not be used for CD diagnosis. Tests for the detection of antibodies of any type (IgG, IgA, secretory IgA) in faecal samples should not be used.

If IgA class CD antibodies are negative in an IgA-competent symptomatic patient, then it is unlikely that CD is causing the symptom at the given time point. Further testing for CD is not recommended unless special medical circumstances (e.g., younger than 2 years, restricted gluten consumption, severe symptoms, family predisposition or other predis-posing disease, immunosuppressive medication) are present.

In seronegative cases for anti-TG2, EMA, and anti-DGP but with severe symptoms and a strong clinical suspicion of CD, small intestinal biopsies and HLA-DQ testing are recommended. If histology shows lesions are compatible with CD but HLA-DQ2/HLA-DQ8 heterodimers are negative, then CD is not likely and an enteropathy caused by a diagnosis other than CD should be considered. In these patients, the diagnosis of CD can be made only after a positive challenge procedure with repeated biopsies.

When duodenal biopsies, taken during routine diagnostic workup for gastrointestinal symptoms, disclose a histological pattern indicative of CD (Marsh 1–3 lesions), antibody determinations (anti-TG2 and, in children younger than 2 years, anti-DGP) and HLA typing should be performed. In the absence of CD-specific antibodies and/or HLA-DQ2 or HLA-DQ8 heterodimers, other causes of enteropathy (e.g., food allergy, autoimmune enteropathy) should be considered.

In children and adolescents with signs or symptoms suggestive of CD and high anti-TG2 titers with levels >10 times ULN, the likelihood for villous atrophy (Marsh 3) is high. In this situation, the paediatric gastroenterologist may discuss with the parents and patient (as appropriate for age) the option of performing further laboratory testing (EMA, HLA) to make the diagnosis of CD without biopsies. Antibody positivity should be verified by EMA from a blood sample drawn at an occasion separate from the initial If EMA testing confirms specific CD antibody positivity in this second blood sample, then the diagnosis of CD can be made and the child can be started on a GFD. It is advisable to check for HLA types in patients who are diagnosed without having a small intestinal biopsy to reinforce the diagnosis of CD.

Diagnostic approach for an asymptomatic child or adolescent with CD-associated conditions

If it is available, HLA testing should be offered as the first-line test. The absence of DQ2 and DQ8 render CD highly unlikely and no further follow-up with serological tests is needed. If the patient is DQ8 and/or DQ2 positive or HLA testing is not done, then an anti-TG2 IgA test and total IgA determination should be performed, but preferably not before the child is 2 years old. If antibodies are negative, then repeated testing for CD-specific antibodies is recommended.

Individuals with an increased genetic risk for CD may have fluctuating (or transient) positive serum levels of CD-specific antibodies, particularly anti-TG2 and anti-DGP. Therefore, in this group of individuals (group 2) without clinical signs and symptoms, duodenal biopsies with the demonstration of an enteropathy should always be part of the CD diagnosis

To avoid unnecessary biopsies in individuals

Table 1: Sensitivity, Specificity, and Positive and Negative Predictive Values of Serologic Screening Tests Reported in the Literature for the Diagnosis of CD[33]

Test	Sensitivity	Specificity	PPV	NPD
AGA IgG	57–100	42–98	20–95	41–88
AGA IgA	53–100	65–100	28–100	65–100
AEA IgAa	75–98	96–100	98–100	80–95
Guinea pig tTGb	90.2	95		
Human tTGb	98.5	98		

PPV, positive predictive value; NPD, negative predictive value

with low CD-specific antibody levels (i.e., <3 times ULN), it is recommended that the more specific test for EMA be performed. If the EMA test is positive, then the child should be referred for duodenal biopsies. If the EMA test is negative, then repeated serological testing on a normal gluten-containing diet in 3 to 6 monthly intervals is recommended.

Treatment

The only treatment available for CD is gluten free diet(GFD) for life. It is recommended that treatment for CD be started only after the diagnosis has been confirmed by intestinal biopsy. Wheat, rye and barley are the predominant grains containing the peptides known to cause CD. Triticale (a combination of wheat and rye), kamut and spelt (sometimes called farro) are also known to be harmful. Other forms of wheat are semolina (durum wheat), farina, einkorn, bulgur and couscous. The harmful potential of rendered gluten-reduced wheat starch is controversial. Many coeliac societies in southern Europe exclude wheat starch; however, there is some evidence that it does not cause villous damage.[34] Malt is also harmful because it is a partial hydrolysate of barley prolamins. It may contain 100-200 mg of barley prolamins per 100 g of malt.[35] In general, any ingredient with malt in its name (barley malt, malt syrup, malt extract, malt flavorings) is made from barley.

Previously, oats were implicated in the development of the villous damage in CD. More recently this has been questioned as both in vivo and in vitro immunologic studies suggest oats are safe.[36] Despite the accumulating evidence that oats are safe for individuals with CD, there remains some concern about recommending consumption of this grain to CD patients. Contamination of oats with gluten during the harvesting and milling process is known to occur, so unless the purity of the oats can be guaranteed, their safety remains questionable.

There is evidence to demonstrate that even small amounts of gluten ingested on a regular basis can lead to mucosal changes on intestinal biopsy. However, the strict definition of a GFD remains contentious. Products containing less than 200 ppm (<200 mg/kg) were previously regarded as effectively gluten free. Currently, <20 ppm (<20 mg/kg) is being considered in the proposed Codex Alimentarius Guidelines to define "gluten free." The National Food Authority has recently redefined their term for "gluten free." By their definition "gluten free" now refers to no gluten, and <200 ppm is regarded as low gluten.

The American Dietetic Association (ADA) recently published guidelines for the dietary treatment of CD.[37] However, given the dynamics of this field, the diet requires ongoing collaboration between patients, health care professionals and dieticians, and the recommendations require periodic review and modification in the light of new scientific evidence. At this time, a GFD for life remains the only scientifically proven treatment available for symptomatic individuals with CD.

Most children with newly diagnosed CD will tolerate ingestion of lactose, particularly in moderate amounts; therefore dietary lactose restriction is not usually necessary. Young children with more severe disease may benefit from a lactose-free diet initially.[38]

How to monitor?

It is recommended that children with CD be monitored with periodic visits for assessment of symptoms, growth, physical examination and adherence to the GFD . The range of adherence to a strict GFD as reported by patients is 45% to 81%. These may be overestimates, as some patients reporting strict adherence have abnormal intestinal histopathology.[39] The range of reported complete lack of adherence is 6% to 37%. These may be underestimates, as patients are reluctant to admit they are not following physician advice. The rate of adherence in patients who were detected as part of a population screening may be comparable to that of patients who had symptoms that led

to detection of coeliac disease.[40]

There is little evidence on the most effective means of monitoring patients with CD. The Coeliac Disease Guideline Committee recommends measurement of TTG after 6 months of treatment with a GFD to demonstrate a decrease in antibody titer as an indirect indicator of dietary adherence and recovery. Measurement of TTG is also recommended in individuals with persistent or recurrent symptoms at any time after starting a GFD, as a rise in antibody levels suggests dietary non adherence. In the asymptomatic patient measurement of TTG at intervals of 1 year or longer may serve as a monitor of adherence to the GFD

Conclusion

Coeliac disease is a unique autoimmune disease in which some of the genes involved, the target auto antigen, and, most importantly, the environmental trigger, are all known. Therefore, coeliac disease represents a superb model to study the genetic, immunological, epidemiological, and clinical aspects of multifactorial diseases. Given the undisputable role of gluten in inducing the autoimmune intestinal insult typical of coeliac disease, the GFD is considered the only effective treatment for individuals with coeliac disease. However, the implementation of a GFD is challenging and most of the time suboptimal. A better understanding of the complexity of the genetic/environmental interaction responsible for coeliac disease development opens the way to explore alternative therapeutic strategies.

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Pediatric Journals' Contribution to Evidence-Based Pediatrics and Child Health: A Special Perspective

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Abstract

This article aimed to provide a special perspective on role of pediatric journals in evidence-based pediatrics and child health through a preliminary search of PubMed for articles that analyzed pediatric journals. There were studies on analyses of pediatric subspecialty-specific journals such as orthopedics, surgery, dentistry, dermatology, and nursing. The various pediatric journals analyzed for their contribution to evidence-based pediatrics and child health were Journal of Pediatric Orthopaedics-A (JPO-A), Journal of Pediatric Orthopaedics-B (JPO-B) and Journal of Children's Orthopaedics (JCO); Journal of Pediatric Surgery, Pediatric Surgery International and European Journal of Pediatric Surgery; six pediatric dentistry journals; four pediatric nursing journals; Journal of Pediatric Psychology, Journal of Clinical Child and Adolescent Psychology, Journal of Abnormal Child Psychology, and Child Development. The topics researched in analyses of pediatric journals were levels of evidence, citation analysis, traumatic dental injuries, instructions to authors and editorial policies, referencing accuracy, and reporting rates of demographic, methodological and ethical information, and methodological standards.

Keywords: Evidence-based pediatrics; Journal evidence; Publication analysis; Scientific trend.

Pediatric journals provide online access to table of contents, abstracts and full article text for free or for subscription. Most of the pediatric journals offer easy search and navigational options, but only a few allow electronic submission of manuscripts.[1] With an ensuing open-access paradigm shift in evidence-based medicine,[2] pediatric journals need to buck up their scientific process and publication policies to improve their role in evidence-based pediatrics.[3]

This article aimed to provide a special perspective on role of pediatric journals in evidence-based pediatrics and child health through a preliminary search of PubMed for articles that analyzed pediatric journals.

Cashin *et al*[4] identified 750 articles from Journal of Pediatric Orthopaedics-A (JPO-A), Journal of Pediatric Orthopaedics-B (JPO-B) and Journal of Children's Orthopaedics (JCO) and graded them according to levels of evidence. There were more prevalence of level-IV evidence articles (58%), followed by level-III (24.1%), level-II (5%) and level-I (3%). The JPO (B) published the greatest number of level-I studies at 4.3%, followed by JPO (A) at 2.6%, and JCO at 1.2%. The study or levels of evidence were not different between articles published before and after 2003 for all the three journals.

Celayir *et al*[5] performed a citation analysis of articles published in three pediatric surgical journals (Journal of Pediatric Surgery, Pediatric Surgery International and European Journal of Pediatric Surgery) and found 20,271 citations in 600 articles (200 for each journal).

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The overall mean number of citations per article was 33.78, and the articles originated from 39 countries and 256 institutions. United States, Germany and Japan were the commonest countries of origin, and the leading topics researched in the articles were gastro-intestinal, respiratory and urological systems. JPS predominated with the greatest number of cited articles.

Feldens *et al*[6] performed a bibliometric analysis of articles on traumatic dental injuries (TDI)published in six pediatric dental journals and found 119 out of total 3720 TDI articles (3.2%), which were mostly from India (19.3%), followed by the USA (15.1%), Brazil (13.4%), and Italy (11.8%). More than half of the articles were case reports and case series, and 63% of articles addressed treatment and 68% described permanent teeth injuries such as avulsion and crown fractures.

Hayden[7] reviewed 2,010 articles published in pediatric and dermatologic journals, and found that 4% of articles in pediatric journals had primary dermatologic focus and 6% had a secondary focus, and 65% of those articles were case reports, with lesser research reports and review articles. Whilst articles on cutaneous manifestations of systemic disease, hereditary skin disorders, and bacterial skin infections were more frequent, prospective studies on natural course of pediatric skin diseases or the effects of various therapies upon these diseases were scarce.

Meerpohl *et al*[8] investigated the extent of endorsement of Uniform Requirements for Manuscripts of the International Committee of Medical Journal Editors (ICMJE) by the 41 pediatric open-access journals by analyzing 'instructions to authors' and found that 27 mentioned the uniform requirements, 13 required trial registration, 25 stated conflicts of interest policies, 12 endorsed CONSORT, 8 endorsed MOOSE, PRISMA or STARD, and 3 journals endorsed STROBE. The study findings suggested a moderate level of endorsement by the journals, which indicate further improvement.

Meerpohl *et al*[9] identified 69 pediatric journals and studied their online author instructions for endorsement of Uniform Requirements for Manuscripts (URM) of the International Committee of Medical Journal Editors and of 5 major reporting guidelines, disclosure of conflicts of interest, and trial registration. Only 38 mentioned URM in author instructions, 14 endorsed CONSORT, 54 journals required explicit statement of conflicts of interest, and 16 recommended trial registration.

Oermann *et al*[10] examined 190 references and found 79 had errors at a rate of 41.6%, with major errors in 28.9% and minor errors in 13.7%. The common referencing errors occurred in four pediatric nursing journals were in the titles of articles, chapters, and books, followed by errors in author's name.

Sifers *et al*[11] examined the reporting of 18 important demographic, methodological, and ethical information variables, such as participants' gender, socioeconomic status, ethnicity, inclusion/exclusion criteria, and consent and assent procedures in four pediatric and child health journals. High rate of reporting was observed for participant's age, gender, and ethnicity, with lesser reporting of socioeconomic status. Inadequate reporting of study setting and location, the participation/ consent rates, or attrition rates, consent and assent procedures was found.

Raad *et al*[12] examined reporting rates of demographic, methodological, and ethical information in articles from four journals (Journal of Pediatric Psychology, Journal of Clinical Child and Adolescent Psychology, Journal of Abnormal Child Psychology, and Child Development) and compared them between the years 2005 and 1997. The authors found an increasing trend in reporting ethnicity, attrition, child assent procedures, socioeconomic status, reliability, and reward/ incentive offered to participants.

Thakur *et al*[13] analyzed 111 clinical studies out of total published 642 articles in Journal of Pediatric Surgery (JPS) and Pediatric Surgery International (PSI) in 1998 to evaluate the frequency of reporting of 11 basic elements of design and analysis was evaluated in randomized clinical trials (RCT),

nonrandomized clinical trials (NRCT), and retrospective cohorts (RC). 48 RC, 12 NRCT and 3 RCT were found among 63 comparative studies, and 431 articles were case reports or case series. JPS had a better quality of reporting with more than 66% of all RCT reporting on eligibility criteria, admission before allocation, random allocation, method of randomization, patient's blindness to treatment, treatment complications, statistical analyses, statistical methods, loss to follow-up and statistical methods, with poor reporting of blinded assessment of outcome and statistical power.

There were studies on analyses of pediatric subspecialty-specific journals such as orthopedics, surgery, dentistry, dermatology, and nursing. The various pediatric journals analyzed for their contribution to evidence-based pediatrics and child health were Journal of Pediatric Orthopaedics-A (JPO-A), Journal of Pediatric Orthopaedics-B (JPO-B) and Journal of Children's Orthopaedics (JCO); Journal of Pediatric Surgery, Pediatric Surgery International and European Journal of Pediatric Surgery; six pediatric dentistry journals; four pediatric nursing journals; Journal of Pediatric Psychology, Journal of Clinical Child and Adolescent Psychology, Journal of Abnormal Child Psychology, and Child Development. The topics researched in analyses of pediatric journals were levels of evidence, citation analysis, traumatic dental injuries, instructions to authors and editorial policies, referencing accuracy, and reporting rates of demographic, methodological and ethical information, and methodological standards.

Clinicians and researchers in the field of pediatrics and child health need to keep abreast with updated evidence in order to inform decisions for current practice, education, research and administration. With relatively lesser reporting of pediatric articles in other specialty journals,[14,15] there is demand on the pediatric journals to provide updated scientific information in evidence-based pediatrics and child health.

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Omental – Fibrous Myxoid Hamartoma a Rare Lesion Presenting as Malignancy in a 3 Yrs Old Male Child (a Case Report)

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Abstract

Background: The Omental fibrous hamartoma is a very rare lesion, mainly seen in children characterised by single/multiple, Omental/mesenteric large solid mass, which may be confused with malignant neoplasm. Microscopically these are composed of fibroblast in bundles separated by myxomatous stroma. Lesion has benign clinical course without recurrence.

Case Presentation: We present a 3 yrs old male child with history of complaints of abdominal lump since 2 yrs, which was increasing progressively in size over period of time. No history of nausea, vomiting, fever etc. Contrast enhanced computed tomography (CECT) revealed large well-demarcated heterogeneously hyperdense lesion in right hypochondriac, right lumbar and umbilical region displacing bowel loops on either side without penetration & showing minimal enhancement on contrast study. Histological examination of entire mass confirmed the diagnosis of OMENTAL FIBROUS MYXOID HAMARTOMA. No evidence of recurrence noted during follow up period of 2 yrs.

Conclusion: Fibrous hamartoma of omentum is a very rare lesion and its aggressive appearance needs to differentiate from malignancy. The clinical picture of our case also led to high suspicion of malignancy. However by consideration of histological findings we could achieve the correct diagnosis.

Keywords: Omental–Fibrous Myxoid Hamartoma; Omentum; Abdominal mass; Childhood.

Introduction

Omental-mesenteric myxoid hamartoma (OMMH) is the entity initially described by Gonzalez-Crussi *et al* in 1983. There work described three infants who presented with multiple nodular tumours of the omentum and mesentery characterized Histologically by plump mesenchymal cells in well vascularised Myxoid stroma. Electron microscopy of one tumor revealed reticulated inclusions in dilated cisterna of endoplasmic reticulum. All of these patients survived with no evidence of recurrence following excision.[1] OMMH shares the morphologic features with inflammatory myofibroblastic tumor (IMT) and, in other words it may represent a variant of IMT.[2] These lesions may show features of immaturity and high cellularity that can be confused with a true malignancy. If surgeons are more aware with this rare disease, the accurate diagnosis can be made earlier, thus avoiding some unnecessary postoperative options.

Case presentation

A 3 year old male child presented with lump in abdomen since 2 years with history of occasional post prandial discomfort, no history of nausea, vomiting, distension, constipation etc. Clinical examination revealed nontender,

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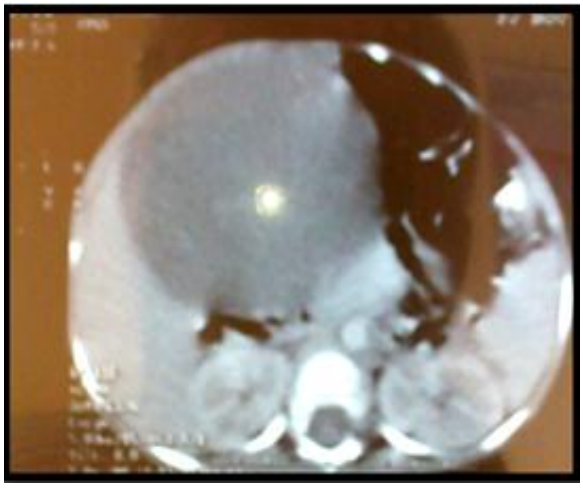
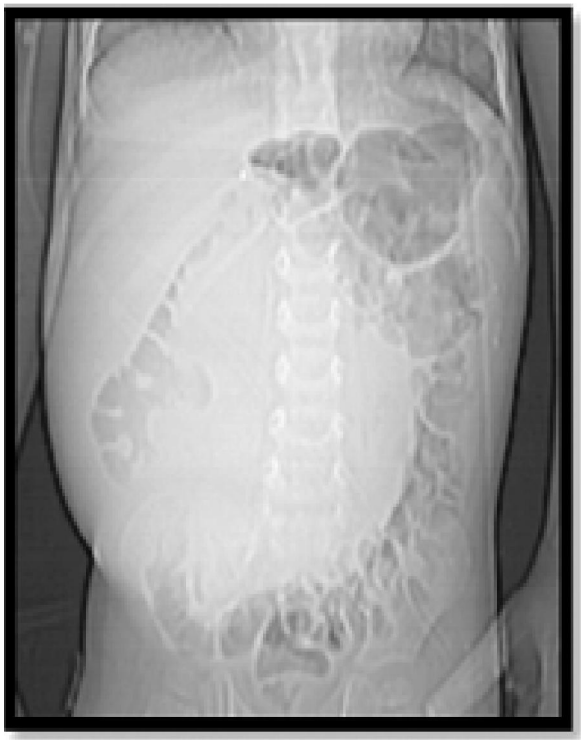
Fig 1: CECT of abdomen



firm mass in right Hypochondrium extending to umbilical and right lumbar region. Ultrasonography showed well defined heterogeneously hyperechoic lesion in right Hypochondrium and lumbar region extending up to umbilical area, displacing bowel loops on either side and measuring 11.5 cm x 11.8 cm.

Contrast enhanced computed tomography revealed a huge well demarcated hyperdense mass which displaced bowel loops without

Fig 2: Reconstructed coronal Section



obvious penetration to the Intestinal walls and normal intrabdominal organs. There was no paraaortic lymphadenopathy, no contrast enhancement (Fig 1 & 2). The laboratory studies were all within normal limits.

With suspicion of malignant neoplasm the patient underwent aspiration biopsy of the

Mass which was inconclusive. Thus a

Fig 3: Tumor on exploration

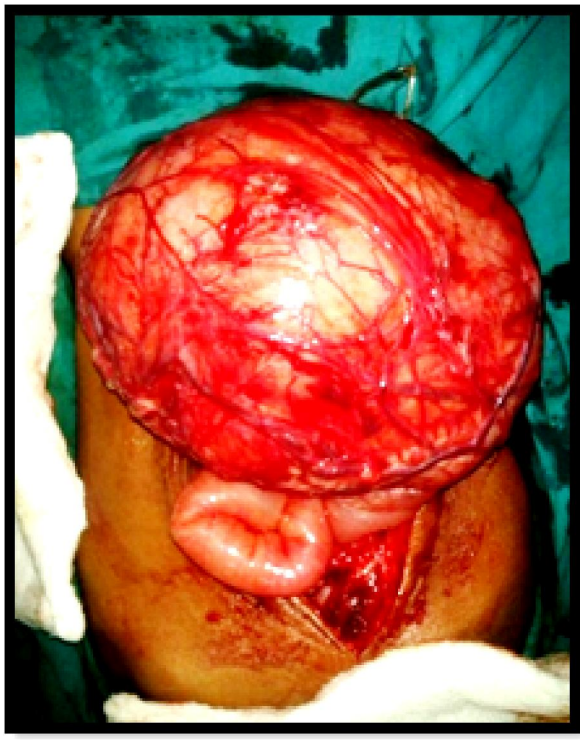


Fig 4: Tumor origin from Greater omentum

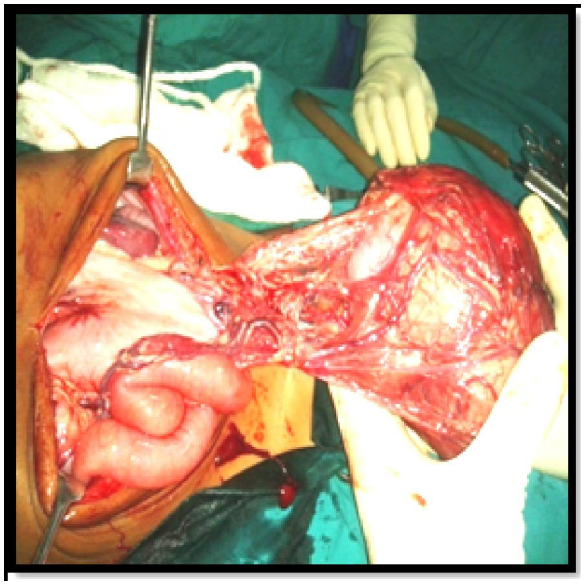
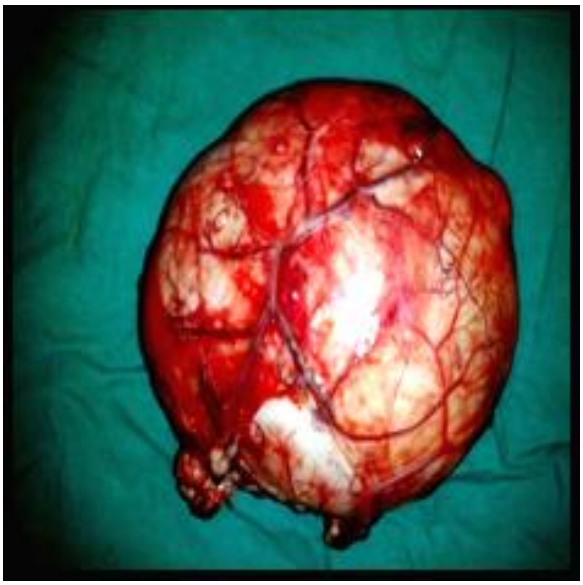


Fig 5: Well circumscribed Excised tumor mass.



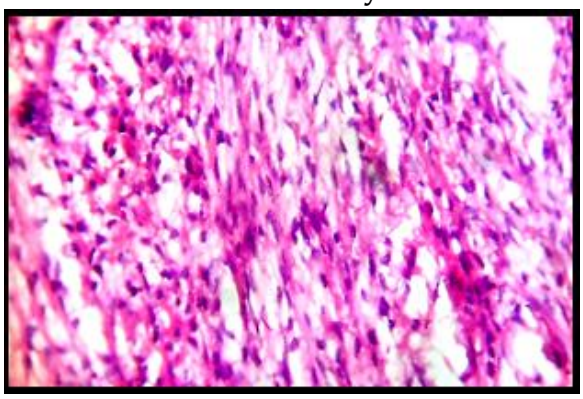
presumptive diagnosis of neuroblastoma was made.

The patient underwent laparotomy; a huge, smooth surfaced, well-circumscribed tumor was found within peritoneal cavity (Fig 3). Origin of tumor was from greater omentum without any attachment to internal organs (Fig 4). It was accompanied by mesenteric lymphadenopathy. Tumor mass was removed completely with mesenteric lymph node biopsy.

Gross examination revealed a huge (12x 14 cm), solid, smooth surfaced, well encapsulated mass weighed 1100 grams (Fig 5 & 6).

Fig 6: Cut surface of tumour showing Solid and Myxoid areas.

Fig 7: High magnification – fibroblasts in bundles separated by myxomatous stroma, spindle cells arranged in bundles, with a few inflammatory cells



Histologically tumor showed fibroblasts in bundles separated by myxomatous stroma, spindle cells arranged in bundles. Lipocytes admixed with spindle cells. Presence of few inflammatory cells but no evidence of neuroblastoma & malignant cells (Fig 7). There was no evidence of mitosis or necrosis.& secondaries in lymph nodes. Immunohisto-chemmically, tumor cells were strongly positive for vimentin and desmin. They were negative for EMA, NSE and MYO-D1.

All these findings confirmed the diagnosis of Omental- fibrous myxoid hamartoma. The patient had an uneventful postoperative course and was discharged from the hospital on the 10th post-operative day. No evidence of recurrence was noted during 2 years follow up.

Discussion

OMMH is a very rare lesion seen mainly during childhood [2]. As per previous available literature, only thirteen cases, including ours, have been reported. OMMH is considered as a variant of IMT, term used for nonspecific chronic inflammatory expansive lesions. Variants of IMT include : plasma cell granuloma or pseudotumor, inflammatory myofibrohistiocytic proliferation, myofi-broblastoma and OMMH[3].

Three basic tissue patterns are considered in IMT: a) myxoid/vascular pattern, b)

compact spindle cell pattern, and c) hypocellular fibrous pattern [4,5]. The clinical presentation seen is usually abdominal mass accompanied by variable symptoms of malaise, anorexia, vomiting, and abdominal distension, abdominal lump (the same as in our case).

The gross appearance of OMMH is a soft to firm, lobulated, smooth, pinkish white circumscribed mass with myxoid areas accompanied by numerous smaller myxoid masses in peritoneum.[4,6]

Microscopically, these lesions consist of a richly vascularised myxoid stroma with plump basophilic mesenchymal cells having vesicular nuclei and prominent nucleoli. Cellular foci alternate with areas of collagenisation. Occasionally, vacuolated and multinucleated cells are seen. Mesenchymal cells are immunoreactive for vimentin, smooth muscle actin and sometimes for desmin and S- 100 protein.[5]

Clinically OMMH is not a malignant neoplasm despite its cellularity, immature appearance, and resemblance to myxoid liposarcoma and other myxoid sarcomas. Lipoblasts are not a feature of Omental-mesenteric myxoid hamartoma and their absence differentiates it from lipoblastomatosis.[4] Other tumours which may be considered in the differential diagnosis of (OMMH) are atypical gastrointestinal stromal tumor, malignant fibrous histiocytoma, leiomyosarcoma, neuroblastoma and solitary fibrous tumor.[5]

However, the histological and immunohistochemical findings of our patient's tumor suggest the above-mentioned diagnosis.

Complete surgical resection is the treatment of choice for OMMH. In all previous reported cases of OMMH, no recurrence was noted with favourable prognosis.[5] Same was true for our case. All of the reported cases have survived with no evidence of recurrence following excision[5], OMMH is considered as a variant of IMT which can show unpredictable course with local recurrences, and hence long-term postoperative follow-up is recommended.[7]

Conclusion

Lesions of OMMH show features of aggressiveness along with immaturity and high cellularity that are more likely to be confused with a true malignancy. OMMH is a very rare lesion and because of its aggressive appearance, differential diagnosis with malignancy should be considered. The initial clinical picture of our case also led us to high suspicion of malignancy. However the histological and immunohistochemical findings helped us to achieve exact diagnosis and save the patient from unnecessary postoperative adjuvant treatments.

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Original Article

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Clinico: Epidemiological Study of Dengue Fever

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Abstract

Children with dengue fever presenting to the Basaveshwar Teaching And General Hospital and Sangmeshwar Teaching and General Hospital Attached to M.R. Medical College, Gulbarga, during the months of January 2011 to December 2012, were prospectively followed up for clinical profile and outcome.

Commonest clinical features were fever, vomiting, bleeding, body pain and Hepatomegaly. Elevated liver enzymes and low platelet counts were common laboratory findings in dengue. Hepatomegaly and thrombocytopenia were more common in DHF and DSS group. Retro-orbital pain was slightly more in DHF and DSS groups and there was a tendency for DSS to present at an earlier age.

Keywords: Dengue,Hepatomegaly,Thrombocytopenia.

Introduction

Dengue is the most important of the arboviral infections of humans.[1] Global incidence of Dengue fever (DF) and Dengue hemorrhagic fever (DHF) has increased dramatically in the recent decades.[1,2] In India, epidemics are becoming more frequent.[1,2] Involvement of younger age group and increase in the frequency of epidemics are indicators of higher incidence of infection.[1] If untreated, mortality from complications of DF is as high as 20%, whereas if recognized early and managed properly, mortality is less than 1%.[2] Early diagnosis is essential and clinical suspicion is based on the frequency of symptoms in the population. Additional data about the disease lead to implementation or alteration of public health programs. Thus there is a need to keep track of various manifestations and gather descriptive data of the disease in each epidemic.

Subjects and Methods

This prospective study was done on cases of DF/DHF reporting at Department of pediatrics, M.R. Medical College, Gulbarga between January 2011 and 31st December 2012 when dengue occurred in Gulbarga. A total of 146 children identified as probable cases by clinical suspicion (any acute febrile illness with one of the following: myalgia, headache, retro-orbital pain, bleeding, altered sensorium, shock or low platelet count) were registered in the study, informed consent was obtained and detailed clinical history was taken. For all cases, the rapid IgM-IgG capture ELISA test, which has become the standard for serological diagnosis of dengue fever[3], was done at our laboratory, Gulbarga. Children positive for NS1, IgM alone or both IgM and IgG were followed up for clinical profile. Cases of typhoid and leptospirosis were

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excluded by serological tests done at the appropriate time interval after the onset of fever. Cases where malarial parasite was seen in peripheral smear were also excluded. The number of cases included based on the above criteria was 146. Children who were dengue seropositive were classified on basis of WHO criteria[1] as follows: (*i*) dengue fever (DF): dengue seropositive satisfying WHO; (*ii*) dengue hemorrhagic fever (DHF); and (*iii*) dengue shock syndrome (DSS): evidence of peripheral circulatory failure.

Laboratory investigations carried out in these patients included hemoglobin, total and differential leukocyte count, hematocrit, platelet count and Complete blood counts including hematocrit were repeated daily during the acute phase of the illness. Chest x-ray was taken to demonstrate pleural effusion in all cases. CSF analysis was done in patients with convulsions or meningeal signs.

The clinical manifestations and laboratory findings of each group of illness were taken for study. Cases were managed according to the WHO protocol[1] and outcome was analyzed.

Results

Hundred and forty six seropositive cases were reported in our hospital during the study period of which 12 were DSS, 10 were DHF, and 124 were DF. The age group of the affected children less then 1year was 29 cases, 1year to 5year was 45 cases and with a modal age group of 6years to 12 years was 42 cases and 13 years to 18 years were 16 cases. DSS occurred at a lower age group than other complications of dengue fever, but the difference was not statistically significant.

Most common presentations were fever (100%), vomiting, headache, pain abdomen and myalgia (*Table I).* Fever, vomiting and body pain. The mean duration of fever at the time

Table I: Symptoms and Signs of Dengue Cases

S.No.	*Feature*	*Dengue infection*	*DF*	*DHF*	*DSS*
1	*Number of cases*	*146*	*124 [84.9]*	*10 [6.8]*	*12 [8.2]*
2	*Male sex,no.(%)*	*80 [54.7]*	*69 [55.6]*	*6 [7.5]*	*5 [6.2]*
3	Fever, no. (%)	146[100]	126 [86.3]	8 [5.4]	12[8.2]
4	Mean duration of fever days: (s.d.)	5.3	6	4	6
5	Vomiting, no. (%)	56(38.3)	44 [78.5]	5 [8.9]	7 [12.5]
6	Bleeding, no. (%)	2 [1.3]	0	2 [100]	0
7	Body pain, no. (%)	24 [16.4]	12 [50]	0	12 [50]
8	Headache, no. (%)	22 [15.0]	21 [95.4]	0	1 [4.5]
9	Drowsiness, no. (%)	19 [13.0]	10 [52.6]	4 [21.0]	5 [26.3]
10	Abdominal pain, no. (%)	22 [15.0]	16 [72.7]	2 [9.09]	4 [18.1]
11	Bleeding from >1 site,no (%)	2 [1.3]	0	0	2 [100]
12	Retro-orbital pain, no. (%)	16 [10.9]	15 [93.7]	0	1 [6.3]
13	Cough	17 [11.6]	15 [88.2]	1 [5.8]	1 [5.8]
14	Convulsions	14 [9.58]	10 [71.4]	0	4 [28.5]
Signs					
15	Hepatomegaly, no. (%)	85 [58.2]	67 [78.8]	8 [9.4]	10 [11.7]
16	Tourniquet+ve, no. (%)	19 [13.01]	8 [42.1]	8 [42.1]	3 [15.7]
17	Shock, no. (%)	15 [10.27]	2 [13.3]	1 [6.6]	12 [80]
18	Conj. suffusion, no.(%)	38 [26.02]	26 [68.4]	6 [15.7]	6 [15.7]
19	3rd space fluid, no (%)	41 [28.08]	25 [60.9]	6 [14.6]	10 [24.3]
20	Lymphadenopathy, no. (%)	2 [1.36]	2 [100]	0	0
21	Pallor	67 [45.8]	55 [82.08]	6 [8.9]	6 [8.9]
22	Rashes, no. (%)	32 [21.9]	20 [62.5]	8 [25]	4 [12.5]

Table II: Investigations and Management of Dengue Seropositive Cases

S. No.	Investigation	Dengue Infection	DF	DHF	DSS
1	Mean Hemoglobin, g/dL	9.9	10.1	9.3	10.3
2.	Hematocrit, mean	30.4	32.3	27.7	31.3
3.	Platelet count cells/ cumm, mean	1,16,513	126 [1,10,540]	10 [1,37,000]	12 [1,01,999]
4	Platelet count >2, 00,000 cumm, no (%)	27 [4,31,500]	26 [2,83,000]	1 [5,80,00]	0
5.	Platelet count >1,00,000 to 2,00,000 cumm, no (%)	40 [1,44,000]	38 [1,48,000]	O	2 [1,40,000]
6.	Platelet count 50,001-100000/cumm, no (%)	38 [64,106]	31 [69,903]	4 [60,750]	3 [61,666]
7.	Platelet count <50,000 Cumm, no (%)	43 [23,855]	31 [25,900]	5 [23,500]	7 [22,166]
8.	Differential lymphocyte count no (%)	46.5	44.9	50.1	44.7
9.	AST > 50 IU/L, no (%)	23 (54.7)	14 (45.1)	5 (71.4)	2 (50)
10.	ALT > 50 IU/L, no. (%)	21 (50)	15 (48.3)	4 (57.1)	2 (50)
11.	S. Alkaline Phosphatase >200 IU/L, no (%)	18 (42.8)	14 (45.1)	2 (28.5)	2 (50)
12.	Urine albumin present	17 (40.4)	13 (41.9)	2 (28.5)	2 (50)
13	NS1 Ag positive	46	40	2	4
14	IgM positive	100	84	6	10

Table III:Out come of dengue infection

Outcome of dengue infection	Dengue fever	DHF	DSS
Improved discharged	124	10	10
Death	0	0	2

of admission to the hospital was 5.33 days. Common signs were, conjunctiva suffusion, pallor, third space fluid, and Hepatomegaly (58.2%) (Table I).

Tourniquet test was positive in 19 and bleeding tendency noted in 2 cases. Patients with DHF and DSS had a higher proportion of tourniquet test positivity. Frank bleeding was noted in 2 cases and hematemesis was the commonest bleeding tendency.

On clinical examination the most consistent finding was Hepatomegaly. DF cases had significantly Hepatomegaly. Other findings included epigastric tenderness in 13 and splenomegaly in 17 cases respectively, besides those shown in *Table I*. Meningeal signs were noted in 7 cases. Only 12 were classified as DSS because these cases showed evidence of plasma leakage.

Laboratory investigations (*Table II*) revealed a large proportion of mildly anemic patients among our cases. A hematocrit more than 40 was noted in only 16 children. A fall of hematocrit by more than 20% on treatment was noted in 14 cases. Platelet counts were also significantly lower in the DHF and DSS groups. There was no correlation between the platelet counts and bleeding in classical dengue fever.

Liver enzymes were markedly elevated in more than 60% of the children who were dengue seropositive. Aspartate aminotransferase (AST) was elevated in a larger proportion of the patients. There was no significant difference between the subgroups of dengue with respect to liver function tests. Albuminuria was seen in a one third of the patients.

Outcome of dengue infection, dengue fever 124 cases, dengue hemorrhagic fever 10 cases and dengue shock syndrome 10 cases were improved and discharged and 2 cases of

dengue shock syndrome were death. (Table III)

Discussion

The age group affected by dengue fever and its complications is lower in this study compared to previous Indian studies. This supports the view that endemicity of dengue fever is increasing in India. Among the subgroups of dengue there is a distinct tendency for DSS to occur at lower age, though the difference is not statistically significant. However, previous studies have not noted any difference in age between dengue with and without shock.[3-6]

Fever and vomiting were the most frequent symptoms and Hepatomegaly was the most frequent sign in these children, as observed in earlier studies.[4,6,7] Vomiting, body pain, drowsiness and bleeding are slightly more common in DSS and DHF group than the others, though the difference is not statistically significant. Hepatomegaly is a less frequent finding among adults as reported in Philippines and Delhi.[8,9] We found Hepatomegaly to be more in DHF and DSS groups than others, in contrast to previous studies.[6,10]

Hematemesis is the most common bleeding manifestation in our cases as reported in other studies on Indian children.[4,7,10] Studies in other countries especially South-East Asian countries, report tourniquet test positivity as the commonest bleeding manifestation.[3,8] Low proportion of positive tourniquet test in Indian studies [4,5,7,9, 10] may be due to the darker skin color or may be the result of different strain of the dengue virus affecting the Indian subcontinent. The proportion of patients having positive tourniquet test among those with frank bleeding is 42.8% which is not very different from the proportion among those without frank bleeding 20%. Thus tourniquest test does not correlate well with other bleeding manifestations in dengue fever, similar to the finding reported by Wali *et al.* [11] This may be because tourniquet test positivity and other bleeding manifestations have different pathogenesis. This has resulted in the modified 1997 WHO criteria for DHF[1], where tourniquet test is no longer essential for the diagnosis of DHF.

There are a low proportion of children with evidence for hemoconcentration in our study group. If this was not taken as an essential criteria for DHF as in Aggarwal *et al*[7], nine more cases could have been included in DHF group and three more in DSS group. The overall mean hematocrit value in the non DHF/DSS group was only 32.2%. Thus it is necessary to conduct studies towards defining the cutoff points for raised hematocrit to diagnose DHF in Gulbarga population as conducted by Gomber *et al*[5] in Delhi, which identified the cutoff value as 36.3%. In cases without evidence for hemoconcentration (DF or DFB), there was no correlation between platelet count and bleeding manifestation. This supports the finding by other studies of the important contribution of factors other than thrombocytopenia in bleeding in dengue fever cases[6,9] However studies which include only DHF cases show correlation between platelet count and bleeding manifestations.[11] This gives further evidence that bleeding manifestations due to classical dengue fever (DFB) are multifactorial.

The other important laboratory finding is the rise in serum levels of liver enzymes (LFTs) as reported in various studies.[3,10,12] However, our study failed to demonstrate a significant difference in the LFTs between the subgroups of Dengue, unlike other studies.[4,12] The high incidence of vomiting, Hepatomegaly and elevated liver enzymes can serve as markers for suspicion of dengue during an epidemic. Subclinical hepatitis may contribute to the abdominal pain and vomiting in these children.

The mortality in our series was comparable with other Indian studies.[4,7,9] Both the children who died had DSS and expired within 24 hrs of hospitalization. In these cases, the period of defervescence preceding shock was found to produce a sense of complacency in parents and contributed to the late

presentation at the hospital. Hence health education regarding manifestations of DSS is important during an epidemic. It needs to be emphasized that a child between 3 months -6 years becoming drowsy or cold after a period of fever lasting 3-4 days has to be immediately brought to the hospital.

Conclusion

To conclude, this study shows that DF is becoming more prevalent in India. In children, importance should be given to symptoms like fever, vomiting, bleeding and musculoskeletal pain. If these are associated with Hepatomegaly and elevated liver enzymes in context of a low platelet count, a strong possibility of DF or DHF is present, especially in an epidemic setting. There are few symptoms or signs which can reliably differentiate between DF, DHF and DSS. Retro-orbital pain, Hepatomegaly and positive tourniquet test are certain markers that predict DHF.

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