Original Articles

Unusual Clustering of Diseases and Manifestations in Pediatric Admissions of a Tertiary Care Center

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Background: *Cluster investigations has been an important tool in investigations of diseases. While clustering of diseases or a manifestation in community can cause great public alarm, similar unexplained clustering in hospital admissions has baffled clinicians.* ***Objectives:*** *(a) To determine whether perceived unexplained clustering of diseases and manifestations among hospital admissions is real or significant. (b) To look for possible explanations of such clustering.* ***Design:*** *One-year prospective observational and two-year retrospective study.* ***Material and methods:*** *Cases admitted under pediatric and neonatal services (excluding rooming in babies) from September 2002 to August 2003 formed material for prospective and cases admitted for 2 years prior for retrospective study. Whenever an unexplained cluster of disease/manifestation was perceived, case definition was finalized and cases recorded. Retrospective cluster analysis was done for some significant unexplained clusters detected prospectively. These clusters case rate were analyzed in relation to age, sex, climatic conditions, etiology of case, etc. to detect any correlation. Pearson correlation coefficient, chi-square test, centroid method and Z test of proportion were used for statistical significance.* ***Results:*** *Eight unexplained clusters were perceived in prospective study. 3 (hyperbilirubinemia in exchange range hypocalcemic seizures and vesicoureteric reflux) proved statistically not significant. 3 were small clusters of uncommon diseases / manifestations (biliary atresia, cardiomyopathy, and acral gangrene). Two large significant clusters, major non-traumatic bleeding manifestations (MNTBM) and acute renal failure (ARF) occurred to which retrospective study was extended.* T_{max} *and* T_{min} *(average maximum and minimum daily temperature) had statistically significant positive correlation with ARF (*γ *= + 0.83, P <0.001 for* T_{max} *and* γ *=+ 0.56, P = 0.002 for* T_{min}*) and negative correlation with MNTBM (*γ *= – 0.34, P = 0.040 for* T_{max} *and* γ *= – 0.59, P <0.001 for* T_{min}*). Barometric pressure has significant negative and positive correlation with MNTBM and ARF respectively (*γ *=+ 0.57, P <0.001 for MNTBM and* γ *= –0.45,P = 0.006 for ARF). The clusters also had significant positive correlations with female sex and age under 1 year (Z = 2.48, P <0.001,* χ^2*=13.83, P<0.001 for sex and age of MNTBM and Z =3.11, P <0.001,* χ^2*=10.85, P <0.001 for age and sex of ARF cases respectively). Three small clusters and a small subgroup of MNTBM (subcutaneous nodules as manifestations of bleeding disorders) occurred predominantly under one year and different sexes were involved.* ***Conclusions:*** *Several significant unexplained clustering were noted among hospital admissions. There was significant correlation with climatic conditions, age and sex. Larger, longer and multicentric studies in different geographical areas are required to investigate more plausible but complex biological phenomenon and associations related to diseases or manifestations. Cluster awareness has diagnostic and management implications for clinician as it also helps in early recognition of disease outbreak and dissemination of information and hospital staff to be prepared to handle increased number of cases and its treatment.*

Key words: *Children, Clustering, Disease, Hospital.*

CLUSTERING of diseases is known to occur since ages(1). Unexplained and unusual clustering of cases occasionally comes to notice of clinicians. Various theories have been proposed with regards to its etiology. Of many studies investigating close case aggregations of any type, a few have come with creditable explanation. The examples include the links found between angiosarcoma of liver and vinyl chloride monomer exposure(2) and mercury poisoning in Minamata, Japan(3).

Climatic or meteorological factors have been implicated in triggering the pathogenic mechanism. It has been suggested that a meticulous study of "combination of changing factors" may help find the underlying pathophysiology of the "puzzling clusters". In the present study we investigated some unexplained perceived clusterings, among hospital admissions.

Subjects and Methods

The study was conducted among pediatric admissions in a tertiary care hospital of Central India, which has moderate climate. A one-year prospective study from 1st September 2002 to 31st August 2003 of all perceived clusters of disease or manifestations and 2 years retrospective analysis from September 2000 to August 2002 of significant clusters namely major nontraumatic bleeding manifestations and acute renal failure noted prospectively was done. Communicable disease clustering or clusterings where explanations were obvious or known has been excluded. Only admitted cases or patients in retention room for nonavailability of beds for more than one hour were studied. Patients who refused admission or shifted to other hospital were also excluded from study. Cases who were brought dead or in whom case definition criteria were not fulfilled were also excluded. Disease manifestations, day of onset, place of onset, detailed history, physical examination, investigations and treatment were recorded in all patients. The meteorological (climatic) database including daily (average of 4 values) and monthly average values of 4 parameters was obtained from the All India Institute of Meteorology, Pune (Maharashtra). The parameters recorded were maximum average temperature (T_{max}), minimum average temperature (T_{min}) in degree Celsius, average humidity (H), and average barometric pressure (BP).

The study was divided into 4 phases. In the first phase, all perceived unexplained clusters were recorded and studied. Because the total number of admissions will affect the number of cases, we worked with case rate, that is number of cases divided by total number of admissions. In second phase, falsely perceived clusters were excluded and true clusters were studied in detail. In the third phase, detailed retrospective analysis on some large significant prospective clusters was also performed. In the fourth phase, related literature was reviewed.

Relation of the clustering with factors like age, sex, climate, etiology, *etc*. was looked into using Chi-square test, Z test and Pearson's correlation coefficient with SPSS software. Statistical analysis by centroid method was done using Cluster software.

The definitions, inclusion criteria for 8 identified clusters were as follows:

1. *Major nontraumatic bleeding manifestations* (*MNTBM*)*:* Any form of external or internal bleeding non traumatic in origin in which blood loss or its control required blood component therapy.
2. *Acute renal failure* (*ARF*)*:* Acute onset (less than 7 days) with serum creatinine levels >2 mg/dL on two occasions and/or urine output less than 0.5 mL/kg/hr for >12 hrs. ARF in children with chronic renal

failure (known chronic renal failure with acute worsening of renal parameters with or without oliguria) were also included.

3. *Hyperbilirubinemia in exchange range* (*HBER*)*:* Newborn with serum bilirubin above 20 mg/dL or serum bilirubin levels indicating need for exchange transfusion for baby's weight, gestational age and postnatal age.

4. *Hypocalcemic seizures* (*HC*)*:* Corrected serum calcium levels <7 mg/dL with seizures and other causes of seizures ruled out by commonly available investigations. Neonatal hypocalcemic seizures have been excluded.

5. *Vesicoureteric reflux* (*VUR*)*:* Grade 3, 4 or 5 vesicoureteric reflux demonstrated on micturating cystouretrogram.

6. *Biliary atresia* (*BA*)*:* Clinical and laboratory findings including HIDA scan suggestive of biliary atresia were included in study. Confirmatory diagnosis by liver biopsy not essential.

7. *Cardiomyopathy of unknown origin* (*CM*)*:* Dilated and poorly contracting left ventricle with ejection fraction <50% and where no other cause of myocardial dysfunction was demonstrable by investigations commonly available.

8. *Acral gangrene* (*AG*)*:* Diffuse cutaneous and deeper gangrenous patches of any etiology.

MNTBM and ARF case groups formed large clusters and 2 year retrospective study was carried out. BA, CM and AG case groups formed small cluster group of uncommon diseases, manifestations and studied separately. HBER, HCS and VUR case groups were falsely perceived clusters and excluded in the second phase of study.

Results

The prospective study had 1744 total admissions with male:female (M:F) ratio 1:0.6. The cluster study group formed 11.98% of total admissions. The month wise distribution of cluster study cases in the prospective study is shown in *Fig.1*.It is seen thatMNTBMcases were clustered in October, November and December months, while ARF cases were clustered in March, April and May months.HBER, HS and VUR formed falsely per ceived clusters. BA, Ag and CM formed the rare clusters seen in October and November months. Relation of climatic factors with clustering of MNTBM and ARF over 3 years is shown in *Fig.2*. The case rate of MNTBM decreases with rising temperatures and vice versa whereas the case rate of ARF increases with rising temperature and vice versa which is seen consistently over three year period.

MNTBM and ARF cases

In two-years retrospective and one-year prospective study of 5038 total admissions, MNTBM was noted in 288 cases (5.71% of total admissions) and ARF in 162 cases (3.22% of total admissions). Clustering of MNTBM was seen in months of October, November, December, and of ARF in months of March, April and May. These were statistically highly significant (χ^2 = 15.52, P <0.005 and χ^2 = 13.84, P <0.005 for MNTBM and ARF respectively) consistently over a 3-year period. Analysis by centroid cluster method revealed similar results.

1. *Effect of age:* MNTBM case rate (Number of cases divided by total number of admissions) among age group of 5-14 years was significantly higher (9.78%) than other age group, but during the cluster month's cases in age group 0-1 year predominated (26.67% of total BM cases). This was statistically highly significant

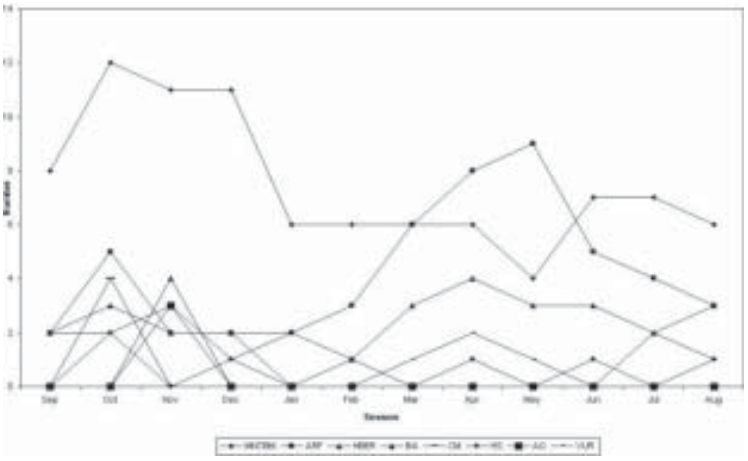

Fig. 1. Monthwise distribution of cluster study cases from September '02 to August '03

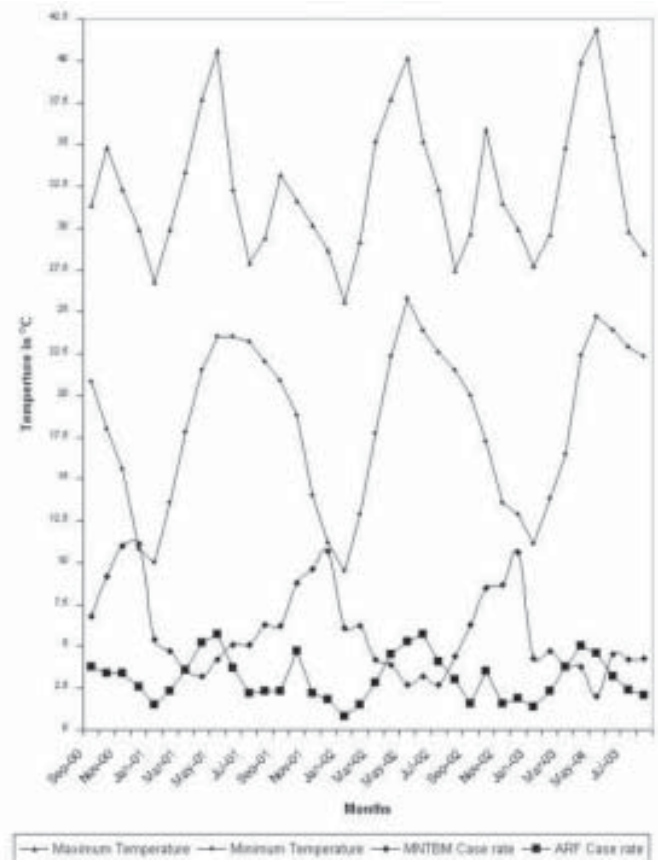

Fig. 2. Monthwise distribution of MNTBM and ARF case rates with temperature variation (*September '02 to August '03*).

(χ^2 = 9.26, P <0.005). ARF cases had predominantly cases between 0-1 year overall and in cluster group, both (χ^2= 8.96, P <0.005) (*Table I*).

2. *Effect of sex:* Sex distribution (M:F) in MNTBM cases was 1:0.9. However, during cluster months reversal of this ratio (1:2.1) was seen which was statistically significant (Z = 3.11; P <0.001). Sex distribution (M:F) in ARF was 1:0.9. Here, too we had reversal of ratio (1:1.6) during cluster months which was significant (Z = 2.48, P <0.001) (*Table II*). This phenomenon was also seen in retrospective period.
3. *Effect of T_{max} and T_{min}:* Negative correlation using Pearson correlation coefficient was seen between T_{max} and T_{min} with the clustering of BM cases ($\gamma = -0.34$, P <0.04 for T_{max} and $\gamma = -0.59$, P <0.001 for T_{min}). Positive correlation was seen between T_{max} and T_{min} with the clustering of ARF cases ($\gamma = +0.83$, P <0.001) for T_{max} and $\gamma = +0.55$, P = 0.002 for T_{min}) (*Fig. 2*).
4. *Effect of barometric pressure:* Positive and negative correlation was seen between barometric pressure with the clustering of BM and ARF cases respectively ($\gamma = +0.57$, P <0.001 for BM and $\gamma = -0.45$, P = 0.006 for ARF).
5. *Humidity:* Poor correlation was seen between humidity and clustering of BM and ARF ($\gamma = -0.11$, P = 0.54 for BM and $\gamma = -0.21$, P = 0.217 for ARF).

Biliary atresia, acral gangrene and CM: Four cases of biliary atresia and 3 cases of acral gangrene were seen in month of November. 4 cases of CM were seen in months of October. All of them were male between 0-1 year age group. Being small clusters, no statistical tests could be applied.

Discussion

In our study we had 8 perceived cluster study cases. Of these 5 were significant clusters namely major non-traumatic bleeding manifestations (MNTBM), acute renal failure (ARF), biliary atresia (BA), acral gangrene (AG) and cardiomyopathy of unknown origin (CM). MNTBM and ARF formed the major cluster cases, for which 2 years retrospective study was extended and BA, AG, CM formed minor cluster cases.

Three clusters namely vesicoureteric reflux (VUR), post-neonatal hypocalcemic

TABLE I–*Sex wise Distribution of True Cluster Cases in Prospective Study (September 2002 to August 2003)*

Name of the cluster	Male	Female	M : F
Major non-traumatic bleeding manifestations (MNTBM) - Total cases	47	43	1 : 0.9
MNTBM during non-cluster months	36	20	1 : 0.6
MNTBM during cluster months	11	23	1 : 2.1
Acute renal failure (ARF) - Total cases	27	24	1 : 0.9
ARF during non-cluster months	18	10	1 : 0.6
ARF during cluster months	9	14	1 : 1.6
Biliary atresia	4	0	–
Cardiomyopathy of unknown origin (CM)	4	0	–
Acral gangrene	2	1	1 : 0.5

TABLE II–*Agewise Distribution of True Cluster Cases in Prospective Study (September 2002 to August 2003)*

Name of the cluster	Age group (0 - 1 year)	Age group (> 1 - 14 years)	<1 : >1 (Year)
Major non-traumatic bleeding manifestations (MNTBM) - Total cases	45	45	1: 1
MNTBM during non-cluster months	21	35	1 : 1.7
MNTBM during cluster months	24	10	1 : 0.4
Acute renal failure (ARF) - Total cases	29	22	1 : 0.8
ARF during non-cluster months	13	15	1 : 1.2
ARF during cluster months	16	7	1: 0.4
Biliary atresia	4	0	–
Cardiomyopathy of unknown origin (CM)	4	0	–
Acral gangrene	3	0	–

seizures (HS) and hyperbilirubinemia in exchange range (HBER) were falsely perceived clusters as no statistical significance was noted on analysis and were, therefore, excluded from further investigations.

MNTBM, HBER, AG were manifestation clusters and rest disease clusters.

We had time clustering of MNTBM and ARF consistent over 3 years period during months of October, November and December (post-rainy season) and April, May, June (summer months) respectively. Small clusters of CM, BA and AG occurred in months of October and November.

The effect of climatic factors (meteorological factors) on MNTBM and ARF clusters has been investigated separately for prospective period and over entire 3 years period. Meteorological parameters vary each year; hence a prolonged study over several years is necessary.

Relationship between climatic (meteorological factors) and certain diseases like rheumatoid arthritis, acute gouty arthritis, SLE and Bechet's disease is well documented. This is besides the infectious diseases which have a typical seasonal relationship.

Detailed search did not reveal any similar studies, but a few studies showed significant effect of climatic factors on incidence of intracranial bleeding during cold season.

Viral hemorrhagic fevers are known to form clusters; however, etiology analysis of our cases did not prove it as the reason for clustering. Only 4 cases of dengue hemorrhage fever were seen in cluster study group. Some studies mention unusual temporal clustering of bleeding disorders, viral hemorrhagic fever and sudden increase in non-specific syndrome as red flags of bioterrorism. Chyalte, *et al.* and Feiginul, *et al.* observed temporal clustering of bleeding in form of subarachnoid hemorrhage or intracranial bleeding during winter season(4,5). By contrast other studies showed clustering of subarachnoid hemorrhage in spring season(6-8), and autumn(8,9). Strangely females were more commonly affected by MNTBM (M: F ratio 1:2.1) during cluster months in our study despite the fact that males predominated amongst admission (M: F ratio 1: 0.67), which

were consistent over 3 years. This higher susceptibility of females may have a genetic basis. Age group especially less than 1 year was significantly affected among cluster cases. ARF cases also clustered among females, children aged 0 - 1 years and during hot season which was consistent over 3 years. This suggests immature immune system and poor adaptive response to environmental changes or triggering cause clustering. Clustering of ARF during hot seasons suggest that dehydrating effect of the season especially on young has potentiated or enhanced expression of ARF.

Three rare clusters of BA, CM and AG occurred in months of Oct and Nov. The study group was not big enough to extract positive correlation. Such cases did not or only exceptionally occurred in rest of the months.

According to the latest literature BA can occur in some epidemics and clustering can be explained. Paula et al mentions it to be caused by environmental exposure(9,10). USA has also identified biliary atresia in seasonal clusters(11). Clustering of CM may be a result of cardiopathic viral infections during that season, however, we could not do viral studies to substantiate or mitigate the same. The clustering of AG remains unexplained.

We have taken manifestation clusters also and not disease clusters alone for investigating possible etiology or propounding factors. Manifestation analysis has been a primary tool of diagnosis and also of management for centuries in older medical systems like Ayurveda, Yunani, Chinese, Homeopathy, etc. The number of diseases defined only by manifestations are being identified more in modern medicine also e.g. fatigue syndrome, syndrome-X. Many patients with varied etiology presents with arthritis with seasonal variations(12-16). Manifestation analysis and management form a large part of clinicians practice and symptomatic and supportive therapy have great role to play. Under the circumstances, analysis of causative or potentiative factors of certain manifestations has its own importance.

The Center for Disease Control and prevention (CDC) USA has its own "Cluster Investigation Protocol". No such protocol is available in India and needs to be prepared. The cluster study also will increase the awareness amongst us in early identification of cases and treatment when clusters occur.

The study cases included disease and manifestation cases which were labeled as disease clusters and manifestation clusters respectively. Manifestation clusters mean aggregation of similar signs/symptoms *i.e.*, common features whatever may be the etiology or disease. In other words, various disease or etiology can present with similar manifestations. The analysis of unexplained clusters of disease/manifestations will help health professionals in hospital and community surveillance. This method is a new tool, which can unearth epidemiological, ecological and other identified and unidentified causes of diseases or manifestations. The hospital staff will also be prepared to handle increased number of cases and will also be prepared for its treatment. Our aim shall be to make a protocol to investigate a cluster disease and also have criteria to stop investigating a cluster. Secondly, it will give a common theme of transparency of action and candid approach for investigation and hypothesis to test. A negative finding will be possible outcome for allaying concerns. The unusual temporal clustering of illness or a sudden increase in nonspecific illness or manifestations should be given the heightened state of alert and an appropriate time to review red flags for bioterrorism. Our knowledge of medicine has

Key Messages

- Temporal unexplained clustering of diseases and manifestations occur.
- Age, sex, climate and other factors are important determinants of clustering.
- Cluster investigations are an important tool in study of various causative and propounding factors of diseases and manifestations.

classified disease into category. The pathophysiological mechanism was well understood, when causative agent to most cases were found. It is a known fact that this arbitrary classification of pathology into disease or syndrome group in any field of medicine is not perfect. Hence, to discover new etiology or disease, we have to look into signs and symptoms and other associations.

This study has some limitations. Although case rate was used to eliminate the bias due to changes in total admissions, a change in admissions of any type of disease or condition can bring a change in case rate of the types investigated. Cluster significance was based only on one statistical analysis. Reconfirmation of cluster significance using another statistical method based on Euclidean distances to confirm a cluster would be more appropriate.

We conclude that the seasonal or temporal unexplained clustering of not only the diseases, but also the manifestations occurred and meteorological factors had a role in the possible causation. More factors may be operative and await study. Further prospective multicentric studies over long periods should be done on clusters for investigating influence of environmental and other factors on disease and manifestations.

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