CLINICAL STUDY IN PERIPHERAL ADENOPATHIES IN CHILDREN

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Abstract

Adenopathy, a common problem during childhood, may be the only clinical sign of disease, but it may as well represent one of the multiple typical signs of other illnesses. Sometimes, randomly finding an adenopathy might lead us to a severe disease. In the study we performed during the 11 years period, we noticed that infectious adenopathy is the most frequent since it was found in 694 cases (62,4%), followed by malignancy in 86 cases (7,7%) and collagen disease in 39 cases (3,5%). We also analized the onset and the course of the adenopathy, the frequency depending on the child′s age and the localization of the adenopathy.

Key words: peripheral adenopathy, etiology, clinical features, child.

Introduction

In children, the lymphatic ganglions are normally touchable, save for when they are newly born children, when the ganglions are hard to notice. Following exposure to various antigen factors of the environment, a reaction of the lymphoid tissue emerges resulting in the gradual increase of the lymphatic ganglions. The fact that adenopathies appear more commonly in children may be explained by the special reaction way of the system which is immune to infections and by the persistence of the pathogenic agents in the lymphatic ganglions even after their disappearance from the initial centre.

It is often difficult to establish whether the adenopathy is a normal response to the inter-current infections that are frequent in a certain age category, or it is serious enough to suggest the existence of a more severe disease. So, the real incidence of adenopathy in children is hard to determine. This is why it was our aim to study the main diseases that develop with peripheral adenopathy in children and the differential diagnosis problems it raises. Taking into account the high number of diseases that can trigger adenomegalic syndrome in children, this diagnostic must be rapidly replaced by the diagnostic of the causal disease in order to allow for a specific treatment to be established.

Patients and Methods

This study was conducted on children with various diseases that presented significant peripheral adenopathy, between 0 and 16 years of age, hospitalized in the Clinical Emergency Hospital and the Infectious Diseases Hospital of Craiova, for 11 years (01.01.1994 – 31.12.2004).

In all the cases, the common anamnesis, clinical and paraclinical exams were performed in order to establish the etiologic diagnosis. Generally, ganglions with the diameter of ≥ 1 cm were considered pathologic. However, in some cases, ganglions with the diameter of less than 1 cm were also considered pathologic in case they presented certain characteristics (hard texture, conglomerated, adherent, round-shaped, over-clavicle location).

The following parameters were examined in the studied group:

- the frequency of the main causes of peripheral adenopathy that required hospitalization;
- the development type of the adenopathy: acute or chronic;
- anamnestic peculiarities in connection with the age, gender;
- distribution of the cases depending on the extension of the adenopathy (localized or generalized).

Outcome and discussion

Our study was conducted only on children with significant peripheral adenopathy that required hospitalization for diagnosis and treatment.

The study on the span of 11 years revealed that the adenopathy of infectious etiology rank as first, with 694 cases (62.4%), followed by malignant diseases with 86 cases (7.7%) and auto-immune diseases with 39 cases (3.5%).

Among the serious diseases that manifest themselves by adenopathy, the most worrying both for the patients and the doctor is the possibility of a malignity. However, the presence of malignancy in patients with adenopathy is low.

Two studies conducted in the US by *Allhiser* (1981) and *Williamson* (1999) analyzing the risk of malignancy in patients with adenopathy, 3 children were found out of 238, and no case was found for the 80 children with adenopathy of undetermined adenopathy.

In the reference centers, the prevalence of malignancy in the biopsies performed on lymphatic ganglions was 40 – 60% (Lee, 1998). But these statements overestimate the probability of the existence of malignancy

in patients with adenopathy, as they exclude the high percentage of cases (aprox. 97%) with adenopathy where no biopsy is conducted.

In primary medicine, a study conducted by *Fitjen* and fellows (1988) shows that patients over 40, having adenopathy of an undetermined cause, run a risk of malignancy of 4%, while for patients under 40 the malignancy risk is 0.4%.

Table no.1 – The frequency of the main causes of peripheral adenopathy (N = 1112)

Causes of adenopathy			**No.**	**%**
Infectious N = 694 (62,4%)	Bacterian N = 324 (29,1%)	Pyogenic adenitis	313	28,1
		Cat scratch disease	11	0,9
	Viral N = 255 (22,9%)	HIV infection	184	16,5
		Infectious mononucleosis	36	3,2
		Rubella	28	2,5
		Measles	4	0,3
		CMV infection	3	0,2
	Mycobacteria N = 99 (8,9%)	A. tuberculosis	87	7,8
		A. with non-typical mycobacteria	12	1,07
	Parasitary N = 16 (1,4%)	Toxoplasmosis	16	1,4
	Fungi N=0		0	0
Malignant diseases N = 86 (7,7%)	Leukemias		61	5,4
	Lymphomas		21	1,8
	Metastases		4	0,3
Self-immune diseases N = 39 (3,5%)	ACJ		35	3,1
	LES		4	0,3
	The serum disease		0	0
Hystiocytosis N = 6 (0,5%)	Hystiocytosis with Langerhans cells celule		3	0,2
	Hemophagocytic syndrome		0	0
	Malignant hystiocytosis		0	0
	Sinusal Hystiocytosis with massive adenopathy		3	0,2
Treasury diseases N = 0	The Gaucher disease		0	0
	The Niemann-Pick disease		0	0
Drugs N = 1 (0.08%)	Fenitoin		1	0,08
Vaccines N = 1 (0,17%)	BCG, anti-measles		2	0,1
Immunodeficiency syndromes i N = 0	Chronic granulomatous disease		0	0
	Deficit of leucocyte adhesion		0	0
Various diseases N = 5 (0,4%)	*The Castleman disease*		3	0,2
	The Kikuchi disease		1	0,08
	Dermatopathic lymphadenitis		1	0,08
	The Kawasaki disease		0	0
	Sarcoidosis		0	0
Adenopathy of unknown cause, with spontaneous recovery N = 279 (25%)			279	25

Peters and *Eduards* (2002) prove that the most common cause of cervical adenopathy in children is reactive hyperplasia secondary to a viral infectious process located in the higher respiratory system. The anaerobe bacteria that trigger cervical adenopathy are usually associated with dental diseases.

Leung and fellows (1991) found that acquired toxoplasmosis, as the only symptom of the disease in 50%, was the cause of posterior chronic cervical adenopathy. The same authors found that malignancies located at the head, neck or cervical region are 25% of the total number of malignancies. In the first 6 years of life, cervical adenopathy was more frequently associated with leukemia, non-Hodgkin lymphomas and neuroblastoma, while after 6 years of age was more associated with the Hodgkin lymphoma, followed by non-Hodgkin lymphoma and rhabdomyosarcoma.

A study reported by *Dutch* on 2,556 patients (quoted by *Ferrer*, 2003) reveals an annual incidence of 0.6% of the adenopathy of still undetermined etiology in the practice of family medicine. 10% (256 cases) of them were sent to specialists in order to complete the investigations, 3.2% (82 cases) needed biopsy, and for 1.1% (29 cases) malignancy was diagnosed.

By analyzing the **way in which it appeared and duration of the adenopathy**, the adenopathies were classified in two main categories: acute adenopathies or adenitis and subacute adenopathies or chronic adenopathies.

Table no. 2 – The type of the debut of the adenopathy

Type of debut	Disease	No.	%
Acute N=662 (62,6%)	Pyogenic adenitis	313	47,2
	Infectious mononucleosis	36	5,4
	Rubella	28	4,2
	Measles	4	0,6
	Post-vaccine adenitis	2	0,3
	Adenopathies of unknown cause	279	42,1
Subacute/Chronic N=396 (37,4%)	Tuberculosis adenitis	87	21,9
	Adenitis with non-typical mycobacteria	12	3,03
	Cat scratch disease	11	2,7
	Toxoplasmosis	16	4,04
	Infection with cytomegallic virus	3	0,7
	HIV infection	160	40
	Leukemias	49	12,3
	Lymphomas	17	4,2
	Hystiocytosis	6	1,5
	Metastases	4	1,01
	ACJ	21	5,3
	LES	4	1,01
	Various diseases	5	1,2
	Drugs (Fenitoin)	1	0,2
TOTAL		1058	100

The *acute debute* a few days in advance suggests a local infectious cause, while the insidious onset, in which adenopathy persists for a few weeks or months, suggests a systemic infectious disease or a malignancy. On the other hand, a transitory viral infection can determine a ganglionic reactive hyperplasia that may persist for a few months, and an acute leukemia can cause a rapid and acute increase of the lymphatic ganglions. So, this difference is not always telling for a diagnostic.

Lymphadenitis in children can manifest itself through local, sometimes general sign. The ganglions in the cervical region are most frequently affected.

So, *acute adenitis having a bilateral cervical location* are determined most frequently by infections in the upper respiratory system with adenoviruses, rhinoviruses, virus influenzae. The affected ganglions usually have a bilateral cervical location, their size is small, they have low consistence, mobility, are sensitive when touched, without erythema or local warmth in superjacent teguments.

In our study, we found 279 cases (25%) of adenopathy with clinical manifestations that are typical to viral adenopathies, in which the etiology was impossible to determine. In all these cases the debute was acute and the development favourable.

Cervical-located adenopathy can also be present in other viral diseases that usually trigger generalized adenopathy, such as infection with Epstein-Barr virus that we found in 36 cases (3.2%), rubella that we found in 28 cases (2.5%), measles that we found in 4 cases.

Bilateral cervical acute adenitis can be found in 25 – 50% of the children with rubella, mumps, chickenpox (Maureen, 2001).

Unilateral cervical acute adenitis or pyogenic adenitis was found in 313 cases (29.1%). Kelly (1998) is of the opinion that the pyogenic adenitis in children in triggered by bacterian infections with *s. aureus* or *streptococus piogenes* group A, in 40 – 80% of the cases. *S. aureus* and *streptococus group B* is more frequently found in newly-born children. The infections with streptococcus and staphylococcus are more frequent in children aged 1 – 4 years, while the infections with streptococcus group A and anaerobes in bigger children and teenagers. The infections

with anaerobe germs usually trigger unilateral adenitis with acute debut, in case of dental diseases.

The Kawasaki disease is another cause of unilateral bacterial acute adenitis that appears more often in suckling and the smaller children. It is an acute fever disease of unknown cause that can start by fever and acute cervical adenitis with unilateral location (50 – 70% of cases). This disease is rarely found in our area; no case was found during our study.

Subacute or chronic adenopathies **have countless causes that can be grouped in infectious and non-infectious ones.**

The most common causes of infectious chronic adenopathy that we have noticed were the followings: HIV infection – 160 cases (16.5%); tuberculose adenitis – 87 cases (7.8%); toxoplasmosis – 16 cases; adenitis with non-typical mycobacteria – 12 cases; the cat scratch disease – 11 cases; cytomegalic virus infection – 3 cases.

Other more seldom causes of infectious chronic adenitis are the followings:

- fungi infections: *aspergillosis, histoplasmosis, blastomycosis, paracoccidiomycosis;*
- bacteria infections: *actinomycetes, anthrax, brucellosis, leptospirosis,* syphilis, tularemia, inguinal granuloma.

The non-infectious etiology of the chronic adenopathies consisted of:

- malignancies: leucemia (49 cases), lymphomas (17 cases), ganglionic metastases (4 cases);
- collagen diseases (ACJ - 21 cases, LES - 4 cases) ;
- hystiocytosis (6 cases);
- various diseases (5 cases).

The subacute or chronic adenopathies are more often than not caused by the infection with mycobacteria, the cat scratch disease and toxoplasmosis. More rare causes include infection with Epstein-Barr virus and cytomegalic virus (Margileth, 1995, Malley, 2000).

The frequency of peripheral adenopathy depending on age and gender

Adenopathy is frequently noticed in children due to the immune system that reacts to the regular infections in this period. Adenopathy is rare in newly-born children who are hardly exposed to infectious agents, whereas other diseases that are associated with the adenopathy are seldom at this age.

Age is an important factor in assessing patients with adenopathy, as the frequency of the adenopathy increases with age and certain diseases appear more often in certain categories of age (Moore, 2001).

We noticed in the studied group that infectious adenopathies were more frequent in the small children, while the malignant ones and the collagen diseases were more frequent in bigger children.

Table no. 3 – The distribution of the main categories of adenopathy on etiology, age and gender.

Types of adenopathy	Age groups										Gender
	0-1 years N=60		1-3 years N=173		3-6 years N=163		6-10 years N=159		10-16 years N=207		M/F No. of cases
	Nr.	%	Nr.	%	Nr.	%	Nr.	%	Nr.	%	
▪ Infectious adenopathies	56	93,3	156	90,1	144	88,3	137	86,1	166	80,1	484/275
▪ Malignant diseases	4	6,6	15	8,6	14	8,0	15	9,4	18	8,6	38/28
▪ Self-immune diseases	0	0	1	0,5	1	0,6	6	3,7	17	8,2	14/11
▪ Post-vaccine	0	0	1	0,5	0	0	1	0,6	0	0	2/0
▪ Hystiocytosis	0	0	0	0	3	1,8	0	0	3	1,4	4/2
▪ Post-drug adenopathies	0	0	0	0	1	0,6	0	0	0	0	1/0
▪ Various diseases	0	0	0	0	0	0	0	0	5	2,4	4/1

In the 0 – 1 year of age group, infectious adenopathies prevailed (93.3%), particularly the pyogenic adenitis (85%); the malignant ones were noticed in 6.6% cases of acute leukemia.

In the 1 – 3 years of age group, infectious adenopathies also prevail (90.1%), out of which 67% pyogenic adenitis, 8% tuberculosis adenitis and 6.9% HIV adenopathy. We hardly noticed cases of infections with non-typical mycobacteria (2.3%) and infectious mononucleosis (1.1%). Malignant diseases were present in 8.6% cases.

In the 3 – 6 years of age group, there were 88.3% cases of infectious adenopathies, 8.1% of malignant adenopathies, and 1.8% of hystiocytosis.

In the 6 – 10 years of age group, there were 86.1% infectious adenopathies. We noticed an increase in the frequency of the cases with tuberculosis adenitis (13.8%).

Malignant diseases were present in 9.4% cases, while self-immune diseases in 3.7% cases.

In the 10 – 16 years of age group, there were 80.1% of infectious adenopathies. It was noticed an increase in the frequency of the cases of tuberculosis adenitis (16.4%), HIV infection (32.8%), infectious mononucleosis (10.6%), and toxoplasmosis (3.8%). There were 8.6% malignant cases, and 8.2% of self-immune diseases. In bigger children we also noticed rare diseases of unknown etiology: the Castleman disease (3 cases), the Kukuchi disease (1 case).

The distribution of adenopathy cases in children, based on its location

After their extension, the adenopathies were classified as: localized adenopathies and generalized adenopathies.

Table no. 4 – The connection between etiology and the location of adenopathy.

Etiology of the adenopathy	Localized Adenopathy N = 474 (60,2%)												Generalized adenopathy N = 313 (39,7%)	
	Cervical N=278 (58,6%)		Submento-nier; N=85 (17,9%)		Preauricullar; N=34 (7,1%)		Supraclavicular; N=6 (1,2%)		Axillar N=41 (8,6%)		Inguinal N=30 (6,3%)			
	No	%	No	%	No	%	No	%	No	%	No	%	No	%
▪ Infectious	262	94,2	85	100	34	100	2	33,3	37	90,2	30	100	226	72,2
▪ *Malignant diseases*	*12*	*4,3*	-	-	-	-	*4*	*66,6*	*3*	*7,3*	-	-	*51*	*16,2*
▪ *Immunologic diseases*	-	-	-	-	-	-	-	-	-	-	-	-	*26*	*8,3*
▪ *Post-drugs*	-	-	-	-	-	-	-	-	-	-	-	-	1	0,3
▪ *Post-vaccine*	1	0,3	-	-	-	-	-	-	1	2,4	-	-	-	-
▪ *Hystiocytosis*	-	-	-	-	-	-	-	-	-	-	-	-	6	1,9
▪ *Various diseases*	3	1,01	-	-	-		-	-	-	-	-	-	2	0,6

Localized or regional adenopathy was noticed in 60.2% cases, and generalized adenopathy was noticed in 39.8% cases.

In localized or regional adenopathies, each ganglionic group drains the lympha in a certain region of the body. So, the ganglions are grouped in the cervical, axillary, inguinal, mediastinal, and abdominal areas.

This study does not focus on deep mediastinal or abdominal adenopathies.

The anatomical location of the adenopathy guides us to locating the primary lesions that trigger the increase in the lymphatic ganglions.

Localized adenopathy was most of the time noticed in the cervical region (58.5%), followed by submandibulary and submentonier region (17.9%).

Cervical adenopathies were primarily benign (94.2%), caused by pyogenic adenitis (63.6%), tuberculosis adenitis (15.4%), infectious mononucleosis (10.7%).

Malignant etiology was present in 4.3% cases, being triggered by the Hodgkin disease, non-Hodgkin lymphoma and ganglionic metastases.

The adenopathy located exclusively submentoneric, pre-auricular or inguinal had benign, infectious etiology.

The super-clavicle adenopathy was rarely found (6 cases): 2 cases of tuberculosis adenitis, 3 cases with non-Hodgkin lymphomas and one case of ganglionic metastasis.

Axillary adenopathy had an infectious etiology in 37 cases (90.3%), malignant in 3 cases (7.3%), and postvaccinal in 1 case (2.4%).

Benign generalized adenopathy (72.2%) was found in viral infections (HIV infection, infectious mononucleosis, rubella, smallpox, cytomegallic virus infection),

tuberculosis, toxoplasmosis and immunologic diseases. Herpetic virus, chickenpox-zoosterian virus and adenoviruses can also determine generalized adenopathy.

Generalized malignant adenopathy (16.2%) was found in acute leukemia and the Hodgkin disease.

Making the difference between localized and generalized adenopathy is important in setting the differential diagnosis and guides us in conducting the next investigations.

According to the studies performed by Allhiser (1981), ¾ of the studies cases presented localized adenopathy, with the rest of them having generalized adenopathy.

Herzog (1983) underlines that retro-auricular and occipital adenopathy are mostly present in sucklings and small children, while the cervical and submandibular ones are frequently present in bigger children. Cervical adenopathy, mostly noticed in children aged 2 – 12, is a response to various antigenic stimulations.

Conclusions

1. Judging by the distribution of cases with peripheral adenopathy based on etiology, we noticed that infectious diseases rank first (62.4%), followed by malignant diseases (7.7%) and self-immune diseases (3.5%). Reactive adenopathy with favourable development, with unknown etiology, was found in 25% cases.

2. The acute debute was noticed in 62.6% cases in the following diseases: pyogenic adenitis, infectious mononucleosis, rubella, smallpox, post-vaccine adenitis and acute adenopathies of unknown cause. The subacute or chronic debut was present in 37.4% cases in: tuberculosis adenitis with non-typical mycobateria, the cat scratch disease, toxoplasmosis, infection with cytomegallic virus, leukemias, lymphomas, hystiocytosis, metastases, immunologic diseases and various diseases.

3. Judging by the frequency of the peripheral adenopathies depending on age, we have noticed that infectious adenopathies were more frequent at the 0 – 1 years of age group (93.3%), malignant adenopathies at the 6 – 10 years of age group (9.4%), and adenopathy in self-immune diseases at the 10 – 16 years of age group (8.2%).

4. The distribution of the cases with peripheral adenopathy depending on location highlights the presence of localized adenopathy in 60.2% cases, and generalized adenopathy in 39.8% cases. As for the localized adenopathies, the most frequently found were peripheral adenopathies with a cervical location (58.6%), followed by submandibular location (17.9%).

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