

## THE ROLE OF PARACLINICAL INVESTIGATIONS IN DIAGNOSING ADENOPATHIES IN CHILDREN

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### Abstract

No laboratory investigations are necessary for most of the children with peripheral adenopathy, as the etiological diagnosis can be performed only based on the anamnesis and clinical examination. Paraclinical investigations and ganglionic biopsy may be necessary in order to make a diagnosis if there are signs of malignity or if the adenopathy persists even under proper antibiotics therapy. This study refers primarily to cases of adenopathy requiring ganglionic biopsy in order to identify the etiology.

**Key words:** adenopathy, biopsy, child.

### Introduction

In most cases, based on the anamnesis and the clinical exam, the cause of adenopathy can be diagnosed. However, a part of the patients still remain with an unknown etiology adenopathy. In these cases, if the adenopathy is localized, without other associated clinical signs, a period of monitoring is required for 3 to 4 weeks, before the ganglionic biopsy. More complete investigations, including ganglionic biopsy, are to be performed on patients with localized adenopathy with systemic signs and those with generalized adenopathy of unknown cause.

### Patients and methods

The study was conducted on a group of 1,112 children with various diseases, who had peripheral adenopathy and needed hospitalization to identify the etiology. The cases were between 1 and 16 years of age and were 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 exam and biological investigations were performed. More complex investigations, including ganglionic adenopathy, were performed on patients with localized adenopathy and systemic signs.

### Outcome and discussions

In most cases, the cause of the adenopathy can be identified based on the anamnesis and clinical exam. In these situations, no additional investigations are required. In other cases, the etiological diagnostic cannot be established only based on the anamnesis and the clinical exam, although the latter may suggest a certain etiology; the paraclinical

investigations are not needed to identify the diagnostic. The paraclinical investigations aim to find the local or general cause of the ganglionic hypertrophy. These investigations must develop from simple to complex ones.

Although it is difficult to say which dimensions of the ganglions are pathological, most researchers believe that a ganglion exceeding 2 cm in diameter is surely pathological; those with 1 – 2 cm diameter need additional investigations if they are not solved after 2 weeks of treatment.

In the studied group, made up of children selected by the family doctory, who raised problems of differential diagnosis, the following paraclinical investigations were performed:

- ♦ A complete hemoleukogram, with a careful examination of the peripheral blood sample was performed in all the cases. The aim was to notice: the leukocytosis in the piogenic infections, the non-typical lymphocytes in the infectious mononucleosis, the infection with the cytomegalic virus, other viral infections, the eosinophilia in the hypersensitization reactions, the pancytopenia or thrombocytopenia in leukemia, HIV infection;

- ♦ the speed of hematias (VSH) is a non-specific, yet helpful test that was also performed in all the cases, as it was significantly high in bacterial infections, inflammatory and neoplastic diseases;

- ♦ the cultures in the ganglionic product were positive in 58 cases (18.5%), with pyogenic adenitis;

- ♦ the cultures in the pharyngeal exudate were positive in 40 cases (12.7%), and the skin lesion in 18 cases (5.7%) with pyogenic adenitis;

- ♦ the skin test in tuberculine, for the diagnosis of tubercular adenite was positive in 76 cases (87.3%); in the adenites with non-typical mycobacteria it was positive in all the 12 cases (100%).

- ♦ the serum tests: determining the IgG and IgM titre was performed in the 16 cases (100%) with toxoplasmosis, in the infection with citomegalic viruse in the 3 cases; determining the heterophilic antibodies was performed in the 36 cases with infectious mononucleosis, with 28 cases identified as positive (77.7%).

- ♦ the ELISA test to determine the HIV infection, positive in 184 cases (100%);

- ♦ antinuclear antibodies were present in 13 cases (37,1%) with ARJ and in the 4 cases with LES, while the

rheumatism factor was positive in 10 cases (28,5%) with ARJ;

The following *image explorations* were conducted:

- ♦ lung radiography that revealed mediastinal adenopathy in 12 children with tuberculosis adenitis, 6 cases of leukemia, 1 case of Hodgkin disease and 3 cases with non-Hodgkin lymphomas.

- ♦ abdominal ecography, computer tomography or nuclear magnetic resonance were sometimes needed to highlight associated abdominal adenopathy in lymphomas, abdominal tumors.

In patients with localized adenopathy, without other symptoms and specific anamnesis data, with normal clinical exam, the etiology is most likely benign, unspecific. In general, these patients were kept under observation, with the adenopathy being solved spontaneously.

The patients were informed to come back to the doctor for reassessment after 2 to 4 weeks or immediately, if the ganglions grow larger or other signs and symptoms appear. At the following examination, if the adenopathy was not in regression and no improvement was noticed, complementary investigations were conducted to set the diagnostic.

Some guideline criteria for ganglionic biopsy were the followings:

- abscesses;
- a significant increase in the ganglions after 2 weeks of proper antibiotic treatment;
- a significant adenopathy that failed to respond to the antibiotics therapy after 4 – 6 weeks or did not solve in 8 weeks;
- ganglions that grew rapidly, were conglomerated or fixed on the structures around them;
- ganglions localized in the rear triangle of the neck or in the over-clavicle region;
- other new signs and symptoms: astenia, weight loss, perspiration.

Ganglionic biopsy was conducted, during the 11 years of study of the 1,112 cases hospitalized with significant peripheral adenopathy, on 225 cases (21.2%).

Judging by the age of the children that needed ganglionic biopsy, the frequency of the cases needing biopsy increased with the age, reaching a maximum at the 10 – 16 years of age (42.6%). A slight predominance of the male cases was noticed (56.8%), as compared to the female cases (43.1%). Judging by the location of the adenopathy, most of the ganglionic biopsies were conducted on ganglions in the lateral-cervical region (45.3%).

Table no. 1 – Characteristics of the group of children requiring ganglionic biopsy (N=225)

Characteristics		No.	%
<i>Gender</i>	Male	128	56,8
	Female	97	43,1
<i>Age groups</i>	0 – 1 year	3	1,3
	1 – 3 years	27	12
	3 – 6 years	41	18,2
	6 – 10 years	58	25,7
	10 – 16 years	96	42,6
<i>Location of adenopathy</i>	Lateral-cervical	102	45,3
	Axillary	43	18,1
	Submandibulary	41	18,2
	Inguinal	23	1,2
	Over-claviculary	11	4,8
	Lateral-thoracic	2	0,8
	Preauricular	3	1,3

The cases in which ganglionic biopsy was conducted were divided in two main categories, based on the hysto-pathological exam: reactive adenopathies in 200 cases (88.9%) and malignant adenopathies in 25 cases (11.1%).

The reactive adenopathies were classified in 5 characteristic patterns: inter-follicular pattern (50.2%),

follicular pattern (25.8%), mixed pattern (8%), sinus pattern (2.7%), diffuse pattern (2.2%).

We noticed changes characteristic to the *follicular pattern* in 58 cases (25.8%), out of which: 46 cases (20.4%) with unspecific follicular hyperplasia, in response to some infectious diseases, 3 cases (1.3%) with Castleman disease and 9 cases (4%) with HIV infection.

Table no.2 – Hystopathological Types of Adenopathies (N=225)

Types of adenopathies	No.	%
<i>Reactive Adenopathies</i>	200	88,9
▪ Follicular pattern	58	25,8
<b>Non-specific follicular hyperplasia</b>	46	20,4
Rheumatoid arthritis / Sjögren syndrome	0	0
Syphilis	0	0
Angiofollicular hyperplasia (Castleman disease)	3	1,3
AIDS	9	4
Progressive change of germinating centers	0	0
▪ Inter-follicular pattern	113	50,2
Non-specific inter-follicular hyperplasia	36	15,5
Dermatopathic lymphadenitis	1	0,4
Histiocytary necrosing lymphadenitis (Kikuchi disease)	1	0,4
Granulomatous lymphadenitis	75	33,3
▪ Mixed follicular and interfollicular pattern	18	8,0
Toxoplasmosis	7	3,1
Cat claw disease	11	4,8
Venereum lymphogranulomatosis	0	0
Mesenteric lymphadenitis	0	0
Kimura disease	0	0
▪ Diffuse pattern	5	2,2
Infectious mononucleosis and other viral adenites	4	1,7
Angioimmunoblastic adenopathy	0	0
Drug-induced adenopathy	1	0,4
Systemic Lupus erythematous	0	0
Kawasaki disease	0	0
▪ Sinus pattern	6	2,7
Sinus hystiocytosis	3	1,3
Hemophagocytic syndrome	0	0
Sinus hystiocytosis with massive adenopathy	3	1,3
Whipple disease	0	0
<i>Malingant Adenopathies</i>	25	11,1
Non-Hodgkin lymphomas	14	5,7
Hodgkin disease	7	3,1
Ganglionic metastases	4	1,7

There were 113 cases (50.2%) showing the *inter-follicular pattern* in which the germinating centers are small, with the change of the para-cortex by the proliferation of the T lymphocytes. The followings are included in this pattern:

- ♦ unspecific inter-follicular hyperplasia was noticed in 36 cases (15.5%);
- ♦ dermatopathic lymphadenitis associated to chronic dermatitis in 1 case (0.4%);
- ♦ hystiocytary necrosing lymphadenitis (the Kikuchi disease) in 1 case (0.4%);
- ♦ specific granulomatous adenitis (tuberculosis, non-typical mycobacteria) were noticed in 68 cases (30.2%), while non-specific granulomatous adenitis were noticed in 7 cases (3.1%).

The *mixed pattern*, characterized from the hystologic viewpoint by areas of the follicular pattern type and areas

similar to the difuse pattern was noticed in 18 cases (8%): 7 cases (3.1%) of toxoplasmosis and 11 cases (4.8%) with the cat claw disease. No cases of venereum lympho-granulomatosis and the Kimura disease were noticed. This study does not focus on mesenteric lymphadenitis, but on peripheral adenopathies.

The *diffuse pattern* was noticed only in 5 cases (2.2%): 2 cases (0.8%) of infectious mono-nucleosis, 2 cases (0.8%) of post-vaccine adenitis, and one case (0.4%) with adenopathy induced by chronic intake of anti-convulsives.

In this pattern, the ganglionic architecture is generally diffuse, and the modifications may often be mistaken for lymphomas.

No cases of either angioimmunoblastic adenopathy or the Kawasaki disease were noticed in this study.

The LES was noticed in 4 cases, but no ganglionic biopsy was conducted on them.

In the *sinus pattern*, the ganglions kept their architecture, but the sinuses were widened and infiltrated with histiocytes.

3 cases (1.3%) of hystiocytosis with Langerhans cells and 3 cases (1.3%) of sinus hystiocytosis with massive adenopathy (the Rosai – Dorfman disease) were noticed in this group of reactive adenopathies. No case with either hemophagocytic syndrome or the Whipple disease was found.

*Malignant adenopathies* were found in 25 cases (11.1%) of the total ganglionic biopsies, out of which: 14 cases (5.7%) with non-Hodgkin malignant lymphomas, 7 cases (3.1%) with the Hodgkin disease, and 4 cases (1.7%) with ganglionic metastases.

In a study conducted by Moore and fellows (1999) on 1,332 cases under 16 years of age, for a span of time of 23 years (1976 – 1999), in which the cervical lymphatic ganglions were excised, the results were the followings: normal ganglions in 1.5% cases, non-specific reactive hyperplasia in 637 cases (47.8%), chronic granulomatous modifications in 484 cases (36.3%). In cases of granulomatous diseases, the tuberculosis adenitis was confirmed in 332 cases (25%), the Rosai Dorfman disease in 3 cases, syphilis in 4 cases, toxoplasmosis in 1 case. The neoplasia was confirmed in 154 cases, out of which lymphomas in 108 cases, acute leukemia in 10 cases.

Bases on two retrospective studies, Pangalis and fellows developed (1993) a useful algorithm to select the patients with adenopathies of nonspecified etiology requiring ganglionic biopsy. Three variables with predictable value were identified in the first study, for patients aged between 9 and 25 that needed to undergo biopsy: the size of the lymphatic ganglions of over 2 cm and the modifications of the thoracic radiography had a positive prediction value; the signs of recent infection in the ORL area had a negative prediction value. In the second study conducted on adults, the followings had positive prediction value: age over 40, the size of the ganglions of over 1.5 x 1.5 cm, the over-clavicle location, the hard texture of the ganglions and the lack of sensitivity or ganglionic pain. The followings had a negative prediction value: ages under 40, the size of the ganglions under 1 x 1 cm, the elastic ganglionic texture and sensitive ganglions presenting pain when touched.

If a ganglionic biopsy is decided, the largest ganglion or the ganglion that has recently increased and shows abnormal clinical characteristic will be excised. If a lymphoma is suspected, it is useful to conduct biopsy on more than one ganglion, because the specific modifications may not be present in all the ganglions. One should avoid conducting biopsy on the axillary or inguinal ganglions if the adenopathy is generalized, as the ganglions in these regions often show only reactive hyperplasia. The ganglion on which the biopsy is to be performed will be completely excised, with intact capsule (Twist and fellows, 2000).

In his studies, Ferrer (2003) underscores that the definitive diagnostic can be established only in 40 – 60 %

cases, for the following reasons: improper size of the sample, unsuitable restoration, and an unsuitable choice of the ganglions for the biopsy. If, after the biopsy, one cannot set a diagnostic, it is recommended to repeat the biopsy when the problems persist or grow.

The histological examination of the ganglionic product is often not enough. The flowcytometry and the imunohistochemical genetic exams can bring additional information.

In case an infectious mononucleosis or a hypersensitivity to drugs is suspected, one should avoid performing a biopsy, because the histological changes are very similar to those in lymphomas and can be misinterpreted (Pangalis, 1993).

The FNA is primarily used for adults, because the tissue obtained is not enough for complete investigations and does not enable the examination of the ganglionic architecture. The main difficulty is to establish a differential diagnosis between the lymphomas having a low degree of malignancy and the reactive hyperplasia (Lioe and fellows, 1999). So, at an early stage, the diagnostic of lymphoma may be omitted (Moore, 2001). In a study conducted on 157 patients, dummy-negative results at the FNA were obtained in 3.5% patients, when the cases of lymphoma were excluded; when included, the percentage of fake-negative was 12.5%. So, the overall precision of the diagnostic was 24.4%, the sensitivity was 85.4% and the specificity 100%.

The FNA is recommended in infections located at the level of the ganglions, in ganglionic metastases, in order to assess the thyroid nodule or to investigate some ganglions that were not accessible to the biopsy, such as the retro-peritoneal ones.

In association with the flowcytometry, the FNA allows a better assessment of the development of lymphomas under treatment.

The material vacuumed out through the FNA will be sent to the lab to perform the Gram and Ziehl-Nielsen colorations and for cultures to highlight the aerobe and anaerobe bacteria, the mycobacteria and the fungi (Umpathy and fellows, 2003).

### Conclusions

1. Ganglionic biopsy was conducted in 225 cases (21.2%), particularly at the children aged 10 – 16 (42.6%) that run a higher risk of having serious diseases.
2. The hystopathological exam showed that most of them were reactive adenopathies (88.9%), with the malignant adenopathies being present in 11.1% cases.
3. Within the reactive adenopathies, the most frequently noticed were the granulomatous adenitis (33.3%), followed by nonspecific follicular hyperplasia (20.4% and nonspecific inter-follicular hyperplasia (15.5%).

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