А. Ф. Котельник, В. Я. Вартанов, Ю. Ф. Карауш, О. О. Орёл, А. Змеу

ANESTHESIA IN PREGNANT WITH NONSPECIFIC AORTOARTERITIS

Nicolae Testemitanu SUMPh, Chair of Anesthesiology and Reanimathology N 2, Mother and Child Institute, Chisinau, Republic of Moldova

АРТЕРИИТ ТАКАЯСУ — хронический идиопатический и гранулематозный васкулит, проявляющийся главным образом как панарит. Вероятно, это заболевание отвечает за аутоиммунный клеточный иммунитет. Воспаление начинается с адвенции, прогрессирует до интимы и приводит как у взрослых, так и у детей к сегментарному стенозу, окклюзии, дилатации и/или образованию аневризмы.

В статье приводится анализ литературных данных и клиническое наблюдение пациентки с артериитом Такаясу.

Ключевые слова: артериит Такаясу, родоразрешение, анестезия.

UDC 616.132-002
DOI 10.31379/2411.2616.11.1.5
A. F. Kotelnik, V. I. Vartanov, Yu. F. Karaush, O. O. Orel, A. Zmau

ANESTHESIA IN PREGNANT WITH NONSPECIFIC AORTOARTERITIS

Takayasu arteritis represents a chronic, idiopathic and granulomatous vasculitis, presenting itself mainly as panaortitis. Probably autoimmune cell-mediated immunity is responsible for the disease. Inflammation commences from the adventitia and progresses to the intima and leads to segmental stenosis, occlusion, dilation and/or aneurism formation both in children and adults.

The article contains literature analysis and data about clinical observation of a female patient with Takayasu arteritis.

Key words: Takayasu arteritis, delivery, anesthesia.

Introduction

Takayasu disease was described for the first time in 1856 by W. Savory and A. Kussmaer. In 1908, a Japanese ophthalmologist, M. Takayasu, noted changes in the central retinal artery and lack of pulse on the radial artery in a 21 year old female. In 1948, K. Shimuzu and K. Sano described in details the clinical features of the disease, that was further named Takayasu arteritis in 1954 [3]. Takayasu arteritis (pulseless disease, brachiocephalic arteritis etc.) — nonspecific aortoarteritis (NAA) is a chronic granulomatous arteritis that mainly affects the aorta and its main branches. More commonly it affects the aortic arch, carotid arteries, innominate artery, carotid and subclavian arteries; but it also may affect the celiac, mesenteric, renal, iliac, coronary and pulmonary arteries.

Granulomatous inflammatory changes start in the adventitia and external layers of the tunica media [1]. Histology findings are: clusters of lymphocytes, plasma cells and...
reticular cells, and in a lesser degree — neutrophils and giant cells. In late stages, the granulomas become fibrotic, minor tears appear, the tunica media becomes sclerotic with evident proliferation of the tunica intima that leads to narrowing of the vessel and promoting thrombosis [2]. The disease is considered to be rare, spread worldwide, but more commonly in Japan, where its signs are established in 0.03% of all pathophysiological researches. More than 80% of patients are females, aged between 15 and 40 years old [3].

Classification

Modern classification of the Takayasu arteritis is based on data received from angiographic investigation. Depending on the number of vessels involved, 5 types of the disease are described [4]:
- Type 1 — branches of the aortic arch;
- Type 2a — ascending aorta, aortic arch and its branches;
- Type 2b — type 2a + thoracic descending aorta;
- Type 3 — thoracic descending aorta, abdominal aorta and / or renal arteries;
- Type 4 — abdominal aorta and/or renal arteries;
- Type 5 — type 2b + type 4.

Etiology

Etiology of this disease is not fully discovered. Mycobacterium tuberculosis as well as viruses are incriminated as a possible causing factor. But tuberculosis vasculitis (aortitis) erosions of the vessel’s walls are characteristic, formation of true and false aneurisms, affecting the descending thoracic and abdominal aorta, that does not match the Takayasu vessel changes. Also, research [5] do not confirm a higher rate of infection with tuberculosis in patients with NAA.

Pathogenesis

It is thought that auto-allergic reactions start with inflammation of the vasa vasorum. The antigen on the endothelium of vasa vasorum initiates immune reactions. The number of adhesive molecules on the endothelium rise quickly, large quantities of HLA-DR are expressed. Blood levels of IL-1, IL-6, TNF-α, IFN-γ [2]. The inflammatory infiltrate is due to CD4+, CD8+, macrophages, natural killer cells, granulocytes, dendritic cells, and less often due to B lymphocytes and even more seldom by giant cells. Blood levels of CD4+ and CD8+ T lymphocytes rise, cells that have high intracellular levels of calcium and high protein-kinase activity. In vitro, these lymphocytes are characterized with a high blast-transformation reaction and elevated toxicity against human endothelium [2]. Only in 50% of cases, granulomas are formed that consist of B and T lymphocytes, that have contact with dendritic cells, while granulocytes are placed outside the granuloma [1].

Neovascularization takes place in tunica media and intima. Tunica intima becomes thicker due to proliferation and migration of myocytes, fibroblasts and proteoglycan accumulation (mucopolysaccharides) [1]. Fibrotic processes of long duration deprive tunica media of muscular layers which are replaced by connective tissue that narrow the vessel. If the inflammatory process progresses faster — an aneurism is formed.

Clinical Findings

Clinical picture depends on the stage of the disease. If Takayasu arteritis starts to develop with the first stage, an acute course of the disease. In this case the disease starts with general inflammatory signs: low-grade or high-grade fever, joint pain, muscle pain, headaches, fatigue, weight loss.
1) First stage — pulse preserved (systemic or early):
— Malaise
— Weight loss
— Low-grade fever
— Joint pain

2) Second stage — active vessel inflammation:
— Pain over the affected vessel
— Subjective symptoms of vascular insufficiency
— Objective symptoms of vascular insufficiency

3) Third stage — stenotic lesions ("burned out disease", late or occlusive):
— Various symptoms related to vascular insufficiency

The disease may start with the second or the third stage. In such cases, it is thought that the disease is subacute and primarily chronic course of the disease. The most common symptoms associated with stenosis of arterial vessels are: increased weakness of the arms, headaches, head-spins. More than 50% of patients are diagnosed based on symptoms like: murmurs above subclavian and carotid arteries, abdominal aorta; weak or lack of the pulse on the radial artery; difference in systolic BP (more than 10 mmHg) between left and right arm. In 10–30% of cases a quite specific symptom is found: pain in the projection of the affected vessel [7]. Pain in the neck region is called carotidynia, and its irradiation to the lower jaw or processus mastoideus is possible. Stable burning pain between the scapulae (and lack of other cause) is referred to thoracic aortalgia, pain in the abdomen — abdominal aortalgia [6].

Half of the patients are found to have arterial hypertension. The pathogenetical explanation relies in the stenosis of the renal arteries, diminution of the baroreflex response from the carotid sinus, coarctation of the aorta and of its main branches, ischemia of the CNS. Renal hypertension develops in 33–83% of cases. The most frequent complications are: aortic regurgitation, heart failure, neurological symptoms (headaches, postural vertigo, fainting) and ophthalmologic disturbances (sight loss, amaurosis) [1].

More than 70% of patients have different heart lesions.

All types of renal lesions can be divided into 3 groups: ischemic nephropathy, glomerulonephritis and glomerulopathy, amyloidosis [1]:

— Ischemic nephropathy. Renal artery stenosis appears in type III, IV and V of Takayasu arteritis with a 25–75% frequency. Renal artery stenosis usually develops in its proximal fragment. Bilateral lesions are possible, this fact must be considered when prescribing ACE inhibitors. Intra-renal vessel involvement into the disease has been described. Kidney ischemia leads to diffuse atrophic processes in the glomeruli and tubules, interstitial fibrosis, focal inflammatory infiltration. The kidney gets smaller in size. However, as a rule, ischemia protects arterioles from significant increase of BP, that is why, arteriole sclerosis in an ischemic kidney is very expressed. In the other kidney we can observe signs of sclerosis and hyalinosis of arterioles. With time, ischemic nephropathy leads to chronic kidney disease [1].

— Glomerulonephritis and glomerulopathy. This pathology is quite rare for this disease. But its appearance speaks for the activity of the immune process and a more advanced vessel inflammation [7]. More frequently, in Takayasu arteritis, cases of mesangial proliferative glomerulonephritis have been described. It is important to note that uremic syndrome is not characteristic for glomerulonephritis and may be a sign of arterial hypertension and/or ischemic nephropathy in Takayasu arteritis.
Amyloidosis. Development of secondary AA-amyloidosis is possible in Takayasu arteritis. For this specific kidney disease nephrotic syndrome is characteristic. Combinations between AA-amyloidosis and lung fibrosis, refractory arterial hypertension, aortic regurgitation have been described [1].

**Diagnosis**

**History and physical exam**
- Check if pulse is symmetrical on both arms above radial artery;
- Measure BP on both arms and legs;
- Auscultate common carotid arteries, subclavian arteries, abdominal aorta.

**Laboratory findings**
- Full blood count will most typically show anemia, thrombocytosis. Mild leukocytosis might be present in acute onset of the disease. In most of patients elevated ESR (erythrocyte sedimentation rate) is noted.
- Urine test is usually unremarkable (in case of renal injury, changes are noted characteristic for each type of disease).
- Biochemical and immunological test may be unremarkable, except C-reactive protein, which denotes the activity of the inflammatory process.
- An experimental test is appreciating the serum level of metalloproteinase 2nd type (sensibility and specificity is over 90%). Serum metalloproteinase 3 and 9, as well as IL-6 and RANTES pretend to represent new lab markers of the disease’s activity.

**Instrumental diagnosis**
- Chest X-ray performed during the 3rd stage of the disease may show nonspecific changes [1]:
  a) Irregular aortic arch;
  b) Calcification line of the aorta;
  c) Narrowing of pulmonary vessels;
  d) Dilation of ascending aorta;
  e) Cardiomegaly.
- Ultrasound. Duplex scan is one of the easiest way to diagnose vascular involvement in Takayasu arteritis. It is indispensable in early stages of the disease. In suspected cases of TA all patients should be performed a duplex scan of the neck vessels. One of the most characteristic changes is even and concentric vessel narrowing without signs of calcification.
- CT allows to see the thickness of the vessel, observe aneurisms, including dissecting aneurisms, calcification regions, formed thrombi. Transversal images offer a great precision. Spiral CT with contrast offer the possibility to recreate 2D and 3D images. CT is necessary in order to monitor the dinamics of intravascular changes of the aorta and pulmonary arteries. But CT has several flaws:
  a) High cost, especially spiral CT;
  b) Iodine-containing contrast and radiation;
  c) Bad visualization of medium size vessels (resolution of 1–2 mm).
- Magnetic resonance angiography allows us to see wall thickening of great vessels. Of great value is investigation with gadolinium. A drawback of this method is its high cost and poor visualization of vessels with calcification.
- Angiography remains a gold standard for Takayasu arteritis diagnostics. However, in the proximate future it might surrender in favor of new, more promising methods of investigations taking into consideration significant inconveniences of traditional investigations [1]:
a) Invasiveness;
b) Usage of large quantities of contrast material;
c) Impossibility to use in early stages of the disease and mild intravascular inflammatory process;
d) Impossibility to appreciate the type of vascular lesion (inflammatory lesion, calcification or intravascular thrombi);
e) Impossibility to differentiate acute vessel wall lesion and stenotic lesion;
f) The need of supplementary investigations in order to reveal coronary or pulmonary artery lesions.

— In order to decrease the amount of contrast used and to enhance image quality of small vessels — digital subtraction angiography is used [1]. In several abroad centers this method has replaced traditional angiography.

— One of the most promising instrumental investigations is positron emission tomography. This noninvasive method offers the possibility to reveal, with great precision, outbreaks of vessels with granulomatous inflammation, fact that might have fundamental importance for appreciation of the effectiveness of immune treatment.

Diagnostic Criteria

Takayasu arteritis diagnostics is based on criteria developed by Ishikawa (1988) and modified by Sharma (1996).

1) Major criteria.
— Involvement of left mid-subclavian artery — most prominent stenosis or occlusion of the mid part of the vessel (1 cm from the proximal orifice of the left vertebral artery till 3 cm distal to this anatomic region), which can be diagnosed through angiography.
— Involvement of right mid-subclavian artery — most prominent stenosis or occlusion of the mid part of the vessel (1 cm from the proximal orifice of the left vertebral artery till 3 cm distal to this anatomic region), which can be diagnosed through angiography.
— Objective and subjective characteristic symptoms in the first month of the disease — limb limping, lack of pulse or pulse differences in arms, undetectable BP or significant differences between BP measured in both arms (systolic differences > 10 mmHg), shivers, neck pain, transitory amaurosis, foggy sight, fants, dyspnea, palpitations.

2) Minor criteria.
— Elevated ESR — elevation > 20 mm/h with no other reason at the moment of diagnosis or proven to happen in anamniss.
— Tenderness of the carotid artery — unilateral or bilateral pain of the common carotid artery, revealed through palpation (lack of muscle pain).
— Arterial hypertension — persistent elevated BP > 140/90 mmHg above brachial artery or > 160/90 mmHg above popliteal artery in patients younger than 40 y. o. or signs of this type of changes in anamniss at ages less than 40 y. o.
— Aortal regurgitation — revealed in auscultation, Doppler investigation or angiography; or annuloaortic ectasia — revealed through angiography or 2D echocardiography.
— Lesion of pulmonary artery — lobar or segmental artery occlusion, or its equivalent, found through angiography or perfusion scintigraphy; stenosis, aneurism, uneven vessel diameter or any combination of the above mentioned changes in pulmonary vessels, in one or both pulmonary arteries, found at angiography.
— Lesions of left mid-carotid artery — presence of a more pronounced stenosis or occlusion in the middle part of the artery, of a 5 cm length, localized 2 cm distal from the orifice of the artery, found at angiography.

— Lesions of the distal brachiocephalic trunk — presence of a more pronounced stenosis or occlusion in the distal third part of the trunk, found at angiography.

— Lesions of descending thoracic aorta — stenosis, dilation or aneurism, uneven diameter or any combination of the above mentioned changes, found at angiography; presence only of an uneven diameter is not accepted.

— Lesions of the abdominal aorta — stenosis, dilation or aneurism, uneven diameter or any combination of the above mentioned changes.

— Lesions of the coronary arteries — proven at angiography in patients younger than 20 y. o., in absence of any risk factors (hyperlipidemia and diabetes mellitus).

Presence of 2 major or 1 major and 2 minor criteria, or 4 minor criteria allows to diagnose Takayasu arteritis (sensitivity and sensibility is over 85%).

**Treatment of Takayasu Arteritis in Pregnant Women**

Treatment aims to suppress inflammation and exclude vascular insufficiency:

— Glucocorticosteroids;

— Cytostatic agents (if hormonal therapy is ineffective);

— Drugs that aim to dilate vessels and prevent thrombi formation;

— Surgical treatment — in cases of vessel occlusion > 70%. Performed only in non-active phase of the disease (and absence of clinical features).

**Complications and Consequences of Takayasu Arteritis in Pregnant Women**

The following complications are possible:

— Preeclampsia — a pregnancy complication, characterized through elevated BP, proteinuria, high seizure risk;

— Post-partum hemorrhage;

— Stroke (acute blood flow disturbance in the brain that leads to brain cell death);

— Sepsis — acute dysfunction of multiple organs, caused by bacteria in the blood flow.

**Clinical Case**

Female patient V., 26 y. o., is routinely admitted on 23.06.2017. Diagnosis: pregnancy 38–39 weeks, second pregnancy, first delivery, complicated obstetrical anamnesis (1 pregnancy termination due to medical indications), asymmetrical fetus hyptrophy. Nonspecific aortoarteritis (Takayasu disease), high activity, type III with lesions of the ascending aorta, aortic arch, common carotid artery, left subclavian artery, brachiocephalic trunk, right renal artery. Hypertension 2nd–3rd degree, iron deficiency anemia of 1st degree.

Dynamics of BP. (Table 1).

<table>
<thead>
<tr>
<th>Date</th>
<th>Time</th>
<th>BP right arm</th>
<th>BP left arm</th>
</tr>
</thead>
<tbody>
<tr>
<td>24.06.2017</td>
<td>7.45</td>
<td>150/60</td>
<td>110/80</td>
</tr>
<tr>
<td></td>
<td>16.00</td>
<td>150/40</td>
<td>100/80</td>
</tr>
<tr>
<td>25.06.2017</td>
<td>8.00</td>
<td>150/60</td>
<td>80/50</td>
</tr>
<tr>
<td></td>
<td>20.00</td>
<td>180/60</td>
<td>80/50</td>
</tr>
<tr>
<td>26.06.2017</td>
<td>7.00</td>
<td>140/50</td>
<td>90/60</td>
</tr>
<tr>
<td></td>
<td>18.00</td>
<td>140/35</td>
<td>90/60</td>
</tr>
<tr>
<td></td>
<td>22.00</td>
<td>140/50</td>
<td>90/60</td>
</tr>
<tr>
<td>27.06.2017</td>
<td>7.30</td>
<td>150/50</td>
<td>110/80</td>
</tr>
<tr>
<td></td>
<td>14.30</td>
<td>150/50</td>
<td>100/60</td>
</tr>
<tr>
<td>28.06.2017</td>
<td>7.40</td>
<td>150/50</td>
<td>110/80</td>
</tr>
<tr>
<td></td>
<td>16.00</td>
<td>150/50</td>
<td>100/60</td>
</tr>
<tr>
<td></td>
<td>20.00</td>
<td>155/50</td>
<td>100/60</td>
</tr>
<tr>
<td>29.06.2017</td>
<td>8.00</td>
<td>160/45</td>
<td>80/50</td>
</tr>
<tr>
<td></td>
<td>22.00</td>
<td>160/80</td>
<td>80/60</td>
</tr>
</tbody>
</table>
**Delivery plan:**
Taking into consideration extra-genital pathology (Takayasu arteritis), high risk of maternal death, abdominal delivery has been proposed.

**24.06.17 Cardiology consult:**
The patient has no complaints. Takayasu arteritis has been discovered for the first time in 2015, during previous pregnancy (which has been terminated at 17–18 weeks due to medical considerations). Second pregnancy has been monitored by the family doctor starting with 22nd week. During all pregnancy the patient received:
- Tab. Methylpred — 4 mg;
- Tab. Concor — 2.5 mg;
- Tab. Indapamide — 1.5 mg;
- Tab. Cardiomagnil — 15 mg.

Patient addressed to the Institute of Mother and Child for the first time on the 35 week of pregnancy for consultation and a delivery plan. Patient claims she has been informed about the high risk of severe cardio-vascular complications, including death, but refused to terminate the pregnancy.

Patient has monitored her BP at home, on her right arm, BP has not exceed levels of 140–145/60 mmHg; left arm BP — 80–60/40 mmHg. Physical exam: fair medical state, no oedema. Weight — 69 kg; height — 167 cm. Lung auscultation: normal breath sounds, no crackles. Heart sounds are rhythmic, clear, systolic murmur above the aortic arch. HR 84 bpm. BP on right arm — 150/60 mmHg, on left hand — 80/60 mmHg.

**Diagnosis:** Nonspecific aortoarteritis (Takayasu disease), high activity, type III with lesions of the ascending aorta, aortic arch, common carotid artery, left subclavian artery, brachiocephalic trunk, right renal artery. Hypertension 2nd–3rd degree. Iron deficiency anemia of 1st degree. Pregnancy 38–39 weeks.

**Recommendations:**
- Rheumatology consult.
- Ultrasound. Duplex scan of the upper limb vessels and great arteries.
- Examination of the fundus of the eye.
- Echocardiography.

**Treatment:**
- Tab. Bisoprolol — 5 mg;
- Tab. Methylpred — 4 mg;
- Tab. Cardiomagnil 75 mg;
- Tab. Valerian — t. i. d.;

**27.06.17. Rheumatology consult:**
Stop bisoprolol administration (5 mg) 48–72h prior delivery. 27.06.17 — BP 150/50 mmHg on the right arm, 100/60 mmHg on the left hand, HR 96 bpm.

Recommendations: Continue treatment with metoprolol 25 mg twice or three times a day, under BP and HR control, and dose correction if necessary.

**27.06.17. Anesthesiology consult:**
General state of the patient — medium severity, no complaints at the moment. BP on right arm 150/100 mmHg, left arm — 100/60 mmHg. Have been informed about lab tests, investigations, rheumatology and cardiology consults. Total intravenous anesthesia is planned. Patient has been informed about possible risks and complications. Anesthesia risk ASA IV.

**27.06.17. Echocardiography conclusion:** heart chambers not enlarged. Valves are intact, mitral and aortal valve insufficiency of first degree.
Scheduled C-section was performed.

Prior induction, table 15. tilt was performed for prophylaxis of aorto-caval compression.

Premedication: Atropine 0.1% — 0.5 ml; Sol. Dexamethasone 8 mg iv.

Induction: Propofol 100 mg, Ketamine 100 mg, Suxamethonium 100 mg.

After myorelaxation oro-tracheal intubation was performed with N7 tube, no technical deficiencies. Patient connected to artificial ventilation in VCV regimen, FiO₂ — 4%, VT = 5550 ml, SpO₂ = 99–100%, RR = 12/min, PEEP = 2 cm H₂O.

Anesthesia maintenance: Acurmil — 30 mg, Ketamine 50 mg, Propofol 100 mg, Phentanyl 0.3 mg in titrated doses, Dexamethasone — 8 mg, Diazepam — 10 mg, Sevoflurane 3–2.5–1.5–1–0.8–0.4–0 vol %, Morphine 10 mg, Ceftazidime — 1g before umbilical cord clamping, Proserine — 10 mg, Dexketoprofen — 1000 mg.

Perioperative infusion of 1000 ml of Sterofundin, 5 units of oxytocin. Blood loss was equivalent to 700 ml. Length of surgery was 85 minutes. Intubation was performed during adequate spontaneous breathing, after neurologic regain, muscle force return. Postoperative period evolved without any complications. Following general treatment considerations were applied: infusion therapy, symptomatic treatment (uterotonsics, analgesia), deep vein thrombosis prophylaxis (2500 UA of Zibor), antibacterial therapy (ceftazidime 1–2 g per day), intestinal stimulation (proserine 0.05% — ml twice per day).

Lab tests revealed results within normal ranges. No complaints regarding cardio-vascular system have not been documented during the entire postoperative period. On day 6, patient was discharged in satisfactory state with recommendations of cardiology and rheumatology follow-up.

Conclusions

Depending on the type of Takayasu arteritis, vessel lesion might be both unilateral and bilateral, which is why BP monitoring is mandatory on both arms, and in some cases even on lower limbs.

Hypotension should be avoided until baby extraction.

Taking into consideration high anesthesiological risk — general anesthesia is preferred.

Ключевые слова: артериит Такаясу, розродження, анестезія.

ЛІТЕРАТУРА

1. Симитченко И. О. Артериит Такаясу: клинические варианты, оценка активности и прогноз. 2012. C. 58
REFERENCES


5. Hall S., Barr W., Lie J.T., Stanson A.W., Kazmier F.J., Hunder G.G.


Submitted 18.01.2018
Reviewer prof. Yu. Yu. Kobelyatskyy, date of review 26.01.2018