Zgodnja diagnoza velikoceličnega arteritisa - osnova za dober izhod

Early diagnosis of giant cell arteritis - the basis of good outcome

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Izvleček

Namen: *Nezdravljen gigantocelični arteritis lahko vodi v trajno slepoto ali možgansko kap. Namen raziskave je bil oceniti/ovrednotiti diagnostične postopke in zdravljenje temporalnega arteritisa na Oddelku za revmatologijo Univerzitetnega kliničnega Centra Maribor.*

Metode: *Opravljena je bila retrospektivna raziskava (od leta 2012–2017) pri bolnikih s temporalnim arteritisom. Pregledali smo epidemiološke podatke, čas do diagnoze in diagnostičnih postopkov. Rezultate smo obdelali s statističnim orodjem SPSS 22.0*

Glavni cilj: *Glavni cilj raziskave je bil ugotoviti čas med začetkom nastanka simptomov in sprejemom na Oddelek za revmatologijo in ugotoviti vzroke za zamudo pri postavitvi diagnoze.*

Rezultati: *V raziskavo je bilo vključenih 53 bolnikov (66% žensk) s temporalnim arteritisom starih 76,25 let*

Abstract

Purpose: *If untreated, giant cell arteritis can lead to blindness and stroke. The study objectives were to assess diagnostic procedures and treatment in early interventional clinic in University Clinical Centre Maribor in patients with temporal arteritis.*

Methods: *Retrospective study (from 2012 to 2017) of patients diagnosed with temporal arteritis. We assessed epidemiological data, delay of diagnosis, and diagnostic procedures. Results were assessed with statistical methods (SPSS 22.0).*

The main goal was to determinate the delay in days between symptom onset and admission to the interventional rheumatology clinic and to assess the causes of delay.

Results: *Fifty-three GCA (66 % female) patients with mean age 76.25 (from 63–89 years) years were included. Mean time duration of symptoms*

(od 63 do 89 let). Od začetka nastanka simptomov do sprejema na Oddelek za revmatologijo je v povprečju poteklo 33,74 dni (od 0 do 180 dni). Diagnostični postopek je bil zaključen v 2,04 dnevih od sprejema na oddelek. Biopsija temporalne arterije je bila opravljena pri 52 od 53 bolnikov v 2 dnevih s preliminarnim histološkim izvidom v 2 dnevih od sprejema na oddelek. Biopsija je bila pozitivna v 43 (81,1%) primerih. Ultrazvok velikih žil je bil opravljen v 2 dnevih pri 19 (35,8%) bolnikih in je bil v vseh primerih skladen z diagnozo arteritisa velikih žil. 16 (30,2%) bolnikov je imelo revmatično polimialgijo, 35 (66%) bolnikov motnje vida, trajno je oslepelo 12 (22,64%) bolnikov na eno oko in 2 (2,8%) bolnika na obe očesi.

Sedemnajst bolnikov (32,1%) smo začeli zdraviti z intravenoznimi pulzi metilprednizolona, povprečen odmerek peroralnega metilprednizolona je znašal 45,55 (± 15,54) mg. Vsi bolniki so prejeli nizek odmerek acetilsalicilne kisline.

***Zaključek:** Zgodnja diagnoza in zdravljenje gigantoceličnega arteritisa sta zelo pomembna, saj lahko napačno- ali ne-diagnosticirana bolezen vodi v popolno slepoto.*

Z boljšo edukacijo in obveščenostjo laične populacije ter z boljšim dostopom in profesionalno edukacijo primarnega nivoja ter zgodnjo napotitvijo v sekundarne intervencijske ustanove bi lahko preprečili usodne zaplete ter trajne okvare pri bolnikih s temporalnim arteritisom.

before admission to our early interventional clinic was 33.74 (0–180) days. The diagnostic procedure was completed in mean time of 2.04 days from the presentation at our interventional rheumatology clinic. The median time to the temporal artery biopsy (TAB) performed in 52 /53 patients was 2 days, with the median 2 days to the preliminary histological results from admission. TAB was positive in 43 (81.1%) of cases. The median time from admittance to colour Doppler sonography (CDS) of aortic arch branches was 2 days and it was positive in all 19 (35.8%) performed cases. 16 (30.2%) patients had polymyalgia rheumatica, 35 (66%) patients had visual disturbances, permanent one eye blindness occurred in 12 (22.64%) patients, and 2 (2.8%) patients experienced permanent blindness on both eyes.

Seventeen patients (32.1%) were initially treated with intravenous methylprednisolone pulse. The mean initial dose of oral methylprednisolone was 45.55 (± 15.54) mg. All patients received low dose Aspirin.

***Conclusions:** Early diagnosis and treatment of giant cell arteritis are very important as miss- or non-diagnosed GCA can lead to permanent blindness of the patient.*

With better education and public awareness, better access and better professional education of primary care physicians, and early admission to secondary interventional clinics we might spare these patients from the devastating consequences of the GCA.

INTRODUCTION

Temporal arteritis – giant cell arteritis (GCA) the most common form of primary vasculitis is an inflammatory vasculopathy that can affect medium and large sized arteries mostly branches of the carotid arteries (1). In the United States population, the lifetime risk of developing GCA has been estimated at approximately 1 percent in women and 0.5 percent in men (2). The disease occurs after age 50 with the incidence peaking between the ages 70–79 (3). The highest incidence is found in Scandinavian countries and among Americans of Scandinavian descent (3). The female: male ratio is 1:3 (3). In approximately 40–50 percent GCA is accompanied by polymyalgia rheumatica (4). It mostly involves superficial temporal branch, but other arteries may be affected as well (5). Symptoms are caused by local vascular ischaemia often combined with cytokine–mediated features (6). Headache, jaw claudication, transient visual loss, scalp tenderness, and limb claudication are most often observed (7). In untreated disease permanent visual loss or stroke may occur (8). Aortic aneurysms, dissections and ruptures were also described (9). Systemic symptoms associated with GCA include fever, fatigue, and weight

loss (10). A characteristic high erythrocyte sedimentation rate (ESR) and C–reactive protein (CRP) are observed in patients with GCA (11).

Hallo sign, reduction in lumen width, increased blood flow velocity and, absence of colour Doppler signal are typical ultrasound signs in patients with temporal arteritis (12). Granulomatous inflammation consists of mononuclear cell infiltrates and formation of giant cell within the vessel wall (13). High dose of glucocorticosteroids are a highly effective treatment in GCA. Visual loss may occur in 15–20% of patients before treatment is started, while blindness after the first 1–2 weeks of treatment is very rare (14). Early diagnosis and treatment are of the most importance as miss– or non–diagnosed GCA can lead to permanent blindness or stroke.

Diagnosis of GCA in primary care remains difficult because of relative rarity of the disease, and frequently non–specific nature of many early symptoms of GCA (6). Delay to diagnosis is therefore not unusual. Delay may also occur because patients may not be aware of the significance of GCA symptoms, such as jaw claudication and temporal artery abnormalities, and therefore do not seek healthcare promptly (15).

For GCA, a secondary care "fast–track" referral pathway, combined with general practitioner education, reported a significant reduction in the number of patients experiencing permanent sight loss compared to those going through usual care.

Our aim was to present our work in early interventional clinic on Department of Rheumatology in UMC Maribor in the past five years. This is the tertiary centre in the region who serves population of 350 000.

MATERIAL AND METHODS

This is a retrospective, observational, cohort study. Our material represents Caucasian referral cohort from mostly north eastern Slovenian mixed rural and urban areas. Patients with suspected vasculitis are referred to the hospital department, but the choice of referral department may vary depending on the presenting clinical features of each case. All rheumatologists in the region are hospital based. This is the only department in the region with population approx. 350 000.

We collected data of patients referred to our department. The International Classification of Disease–10 (ICD–10 – (M31.6) coding system was used to identify patients from the hospital's electronic administrative patients records. A consultant rheumatologist reviewed the patients' records and recorded clinical details on a standardized form. We excluded patients if their GCA diagnosis originated prior to the beginning of our study, if data were unavailable, if the review of records concluded that GCA was an implausible diagnosis or if the American College of Rheumatology (ACR) 1990 classification criteria for GCA were not fulfilled.

STATISTICAL ANALYSIS

Descriptive methods were used to characterize the sample. The t test was used for comparing continuous variables and Mann Whitney U test for comparing categorical variables. The computing was done using the IBM Statistical Package for the Social Sciences (SPSS) software version 22.0 (IBM Corp, Armonk)

RESULTS

We included 53 patients who fulfilled ACR classification criteria for GCA and were hospitalised in time span of 5 years (1.1.2012–31.12.2017); 18 (34.0 %) male and 35 (66 %) female patients. Mean age all over at disease onset was 76.25 ± 11 years ranging from 63 years to 89 years, mean male age was 73.5 ± 6.36 years, ranging from 68 years to 87 years, mean female age was 79.0 ± 4.24 years ranging from 66 years to 89 years, without age difference between sexes p 0.709. (Table 1)

Mean time duration (standard deviation – SD) of symptoms before admission to our early interventional clinic was 33.74 (42.96) days, with minimum 0 and maximum 180 days.

The diagnostic procedure was completed in mean time 2.04 days from the presentation at our early interventional clinic. The median time to the temporal artery biopsy (TAB) was 2 days, with the median 2 days to the preliminary histological results. TAB was performed in 52 (98.1%) patients and was positive in 43 (81.1%) of

Table 1. *Characteristics of study population*

Clinical characteristic	Overall	female	male	p value for differences between sexes
Mean age at onset of GCA, years (SD)	76.25 (11)	79 (4.24)	73.5 (6.36)	0.709
ACR criteria fullfield, persons, n (%)	53 (100)	35 (100)	18 (100)	1.0
Age > 50 years at disease onset, n (%)	53 (100)	35 (100)	18 (100)	1.0
New onset headache, n (%)	47 (88,67)	32 (91.42)	15 (83.33)	0.383
Temporal artery tenderness, n (%)	26 (49.05)	17 (48.57)	9 (50.0)	0.922
ESR > 50 mm/h, n (%)	44 (83)	29 (82.85)	15 (83.33)	0.965
Biopsy showing vasculitis, n (%)	43 (81,1)	31(88.57)	12 (66.66)	1.0
US signs of vasculitis, n (%)*	19/21	12 (92.3)	7 (87.5)	1.0
Jaw claudication, n (%)	26 (49.1)	18 (51.43)	8 (44.44)	0.564
Polymyalgia rheumatica, n (%)	16 (30.2)	13 (37.14)	3 (16.66)	1.0
Visual disturbance, n (%)	35 (66.0)	26 (74.29)	9 (50.0)	0.080
Permanent blindness, n (%)	10 (18.9)	8 (22.86)	2 (11.11)	0.305
Blindness in one eye, n (%)	12 (22,64)	9 (25.71)	3 (16.67)	0.460
Blindness in both eyes, n (%)	2 (3,8)	2 (5.71)	0	0.306
Mean ESR, mm/h (SD)	77.36 (29.31)	76.06 (4.37)	79.89 (8.4)	0.657
Mean CRP, mg/L (SD)	83.74 (54.9)	77.09 (52.14)	96.67 (59.26)	0.222

Legend: GCA–giant cell vasculitis, n–number, SD–standard deviation, ACR–American college of rheumatology, ESR – Erythrocyte Sedimentation Rate–Westergreen, CRP–C reactive protein.

Table 2. *Time to diagnostic procedures and initiation of therapy /delay in diagnostic procedures and initiation of therapy*

	Mean	Median	Minimum	Maximum
Duration of symptoms, d (SD)	33.74 (42.96)	21	0	180
Time to biopsy, d (SD)	2.83 (2.61)	2	0	14
Time to ultrasound, d (SD)	2.95 (2.96)	2	0	10
Time to diagnosis, d (SD)	2.04	1	0	10
Time to treatment, d (SD)	1.59 (3.33)	0	0	17

Legend: d-days, SD- standard deviation

cases. The median time to colour Doppler sonography (CDS) was 2 days and it was positive in all 19 (35.8%) performed cases. We initiated ultrasound examination in 2015. (Table 2)

16 (30.2%) patients had polymyalgia rheumatica, 35 (66%) patients had visual disturbances, permanent one eye blindness occurred in 12 (22.64%) patients, but only 2 (2.8%) patients experienced permanent blindness on both eyes.

Seventeen patients (32.1%) were initially treated with intravenous methylprednisolone (MP) pulse either with 1000, 500 or 250 mg respectively. The mean initial dose (Standard deviation) dose of oral MP was 45.55 (15.54) mg.

DISCUSSION

In our cohort we observed typical GCA population of patients over 50 years old with female predominance and no differences between sexes considering demographic characteristics. These findings are in concordance with the study of Norwegian group (16). The incidence of polymyalgia rheumatica was lower as previous reported (4). The number of patients in our study is relatively small what might explain the low number of patients with polymyalgia rheumatica. We found higher percentage of visual disturbance and permanent visual loss comparing to Brekke's group Reports from the historical cohorts showed 15–20% of permanent visual loss in GCA. (17, 18). By visual disturbances were meant all transient visual losses (amaurosis fugax and blurred vision as well). Permanent visual loss (22.64%) is in concordance with previously published studies (15–20%). A lot of patients in our study are enrolled from Department of ophthalmology what might explain the predominance of patients with visual disturbance. We found diagnostic delay of nearly 5 weeks in GCA with maximum of 25 weeks and minimum 0 weeks from the symptoms onset. The longest delays were due to nonspecific non–cranial syndromes (fever, anorexia or polymyalgia) what is in concordance with published meta–analysis from Prior et al who found delay of 9 weeks and 18 weeks for non–cranial syndromes, respectively (19). No other characteristic had been reported often enough, included an appropriate comparator group or were from a unique dataset to allow further meta–analysis (19). When patients present to the clinician with mainly constitutional symptoms (fever, malaise) diagnosis is more challenging as these symptoms occur in other more prevalent disorder (19). There might be different reasons for delayed diagnosis for example it could be related to the time taken for the patient to consult healthcare after symptom onset, the patient to be given an appointment, the primary care clinician to refer the patients to secondary care and the patient to receive a secondary care appointment (19). There may be also more specific reasons for delay, for example, varying test availability (i.e. ultrasonography) due to different service provision. Future research should make the distinction between "consultation delay" (the period from symptom onset to receiving a consultation) and "diagnostic delay" (the time between first consultation and final diagnosis) (19, 20). We found a great "consultation delay" and hardly any "diagnostic delay" in our study especially due to good collaboration with department of plastic surgery and

department of pathology. Mostly we perform biopsy of temporal artery on the day of admission or the day after and the preliminary pathologic results are reported by pathologist to rheumatologist on the same day. We start to treat patients immediately after histology is available, or sometimes even before if the vision disturbance is in question. In spite of our quick diagnostic procedure we still, unfortunately, found patients with permanent visual loss but all of them were from the so called "consultation delay" group. The main problem is the disease recognition and delayed referral to rheumatologic centre. GPs in Slovenia usually do not start treatment with corticosteroids due to easy accessibility of rheumatologic centres for patients with urgent rheumatic diseases. The primary limitation of our review is a relatively small number of patients in our cohort. We also could not completely define every single reason for late admission of the patients to our department. We also started to use ultrasound for diagnostics of GCA in the last two years, so not all of the patients had this examination.

The strength of this study is that it provides the first systematic overview of our cohort with GCA over 5 years time span with a delay in diagnosis as a main outcome.

CONCLUSION

The mean delay from symptoms onset to diagnosis of GCA was, despite quick diagnostic procedure in our early interventional clinic too long. Even when the patient experienced the typical cranial presentation, delay from the onset of symptoms to the presentation to the early interventional clinic is too long and there are still some patients experiencing permanent visual loss resulting in higher overall cost in healthcare. With better education and public awareness, better admittance to the primary care physicians, and to secondary early interventional clinics we might spare these patients from the devastating consequences of the GCA.

ABBREVATIONS

1. GCA – giant cell vasculitis
2. ESR – Erythrocyte Sedimentation Rate–Westergreen
3. CRP – C reactive protein
4. ICD – International Classification of Diseases
5. ACR – American College of Rheumatology
6. TAB – Temporal artery biopsy
7. CDS – Colour Doppler sonography
8. MP – Methylprednisolone

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