SMALL INFARCTIONS OF COCHLEAR, RETINAL AND ENCEPHALIC TISSUE (SICRET SYNDROME)

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ABSTRACT

Purpose: to report 3 new cases suggestive of SICRET syndrome.

Methods: case reports.
Three patients underwent clinical, laboratory and neuroradiological examination for recurrent retinal branch artery occlusions, encephalopathy and/or hearing loss.

Results:
In all 3 patients the laboratory tests were unremarkable for infectious or systemic disease.
All 3 cases showed retinal artery occlusions on funduscopy and fluorescein angiography. Visual acuity impairment and visual field defects were related to the retinal artery occlusion site. Variations in the presenting sign were noted in the 3 patients.

- The first patient (a 32 year old man) showed a documented association of small infarctions of the brain and the retina. The retinal occlusions were bilateral and 8 recurrences were observed.
- In the second case (a 26 year old woman) the brain was initially involved. Fluorescein angiography showed unilateral retinal artery occlusion. Cochlear manifestations were not reported.
- The third case (a 35 year old woman) showed initially bilateral recurrent branch artery occlusion and hearing loss without clinical signs of encephalopathy. Three recurrences were documented.

Conclusion:

SICRET syndrome is a microangiopathy that causes infarcts in the cochlea, retina, and brain of young patients, usually women. The aetiology is unknown. Clinically some infarcts may remain asymptomatic. Bilateral sensorineural hearing loss on low frequency on audiology, recurrent bilateral retinal branch artery occlusions on fluorescein angiography and small multiple areas of signal hyperintensity in white and gray matter on Brain MRI T2-weighted images are necessary for the diagnosis. Our 3 patients did not fulfill these criteria, but their disease was suggestive of SICRET syndrome.
SICRET syndrome should be included in the differential diagnosis of recurrent branch artery occlusions. The clinical course is self-limited and treatment options are not codified.

RÉSUMÉ

But: rapporter 3 nouveaux cas suggestifs du syndrome de SICRET.

Méthode:
Observation de cas. Une mise au point clinique, neuroradiologique et biologique a été réalisée chez les 3 patients.

Résultats:
Les résultats des tests biologiques n'ont pas mis en évidence une cause infectieuse ou systémique.
Les 3 patients ont présenté des occlusions de petites artérioles rétiniennes. Il y avait une corrélation entre la baisse d'acuité visuelle, la topographie du déficit du champ visuel et le site de l'occlusion. La

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présentation clinique était variable chez les 3 patients:

- Le premier, un homme de 32 ans, présenta 8 épisodes consécutifs d'occlusions des artérioles rétiniennes, associées à des petits infarctus cérébraux.
- La deuxième patiente, une femme de 26 ans, a présenté initialement une symptomatologie neurologique, suivie d'une occlusion d'une artériole rétinienne sans symptomatologie auditive.
- La troisième patiente, une femme de 35 ans, présenta 3 épisodes d'occlusions d'artérioles rétiniennes avec un déficit auditif pour les basses fréquences sans signes d'encéphalopathie.

Conclusion:

Le syndrome de SICRET est une micro-angiopathie idiopathique qui cause des petits infarctus cochléaires, rétiniens et cérébraux. Cette pathologie affecte avec prédilection la femme jeune et beaucoup de patients ne présentent pas la triade au début de la maladie.

La présence d'occlusions au niveau des petites artérioles rétiniennes à la fluoangiographie, l'observation de multiples petites zones hyperintenses au niveau de la substance blanche et grise sur les images de résonance magnétique pondérées en T1et T2, ainsi qu'une perte auditive bilatérale pour les basses fréquences à l'audiométrie sont nécessaires pour poser le diagnostic. Bien que nos 3 patients ne présentaient que 2 de ces 3 critères, leur affection était suggestive du syndrome de SICRET.

Aucun traitement médical n 'a encore prouvé son efficacité.

Le syndrome de SICRET doit être considéré dans le diagnostic différentiel des occlusions artérielles du sujet jeune.

SAMENVATTING

Doel: voorstelling van 3 gevallen, suggestief voor het SICRET-syndroom.

Methode:

Bij drie patiënten met recidiverende arteriële retinale takocclusies, encefalopathie en/of gehoorsdaling werden een klinisch onderzoek, labotesten en een neurologisch onderzoek uitgevoerd.

Resultaten:

De resultaten gaven geen aanwijzingen voor een infectieuze of systemische oorzaak.

De drie patiënten vertoonden retinale arteriële occlusies. De visusdaling en de gezichtsvelddefecten correleerden met de lokalisatie van de retinale arteriële occlusie. Het klinisch beeld was verschillend bij onze drie patiënten:

- Bij de eerste patiënt, een 32-jarige man, werden acht opeenvolgende, bilaterale retinale occlusies gedocumenteerd, in associatie met kleine infarcten ter hoogte van de hersenen.
- De tweede patiënte, een 26-jarige vrouw, had initieel hersenletsels. Op fluoresceïne-angiografie stelde men een retinale arteriële occlusie vast aan één oog. Er waren geen geassocieerde vestibulocochleaire symptomen.
- De derde patiënte, een 35-jarige vrouw, onderging 3 episodes van bilaterale retinale takocclusies en gehoorsdaling, maar zonder tekenen van encefalopathie.

Conclusie:

Het SICRET-syndroom is een idiopathische microangiopathie, die infarcten veroorzaakt ter hoogte van de cochlea, de retina en de hersenen van jonge patiënten, meestal vrouwen. Sommige van deze infarcten blijven asymptomatisch. Bilaterale neurosensorische gehoorsdaling voor de lage frequenties op het audiogram, recidiverende occlusies van retinale arteriolen op fluoresceïne-angiografie en talrijke kleine zones van verhoogte signaalintensiteit in de witte en de grijze stof op T2-gewogen beelden van de MRI hersenen zijn bepalend voor de diagnose. Onze 3 patiënten vertoonden slechts 2 van de 3 criteria maar hun ziektebeeld was zeer suggestief voor het SICRET-syndroom.

Men zou differentieel-diagnostisch steeds moeten denken aan het SICRET-syndroom bij recidiverende arteriële retinale occlusies. De aandoening is zelf-limiterend; er is geen algemeen aanvaarde behandeling.

KEY-WORDS

Branch retinal artery occlusion, encephalopathy, hearing loss, SICRET syndrome, Susac syndrome.

MOTS-CLÉS

Occlusion des artérioles rétiniennes, encéphalopathie, perte auditive, syndrome de SICRET, syndrome de Susac.

INTRODUCTION

SICRET syndrome is a microangiopathy of cochlear, retinal and encephalic tissue in which recurrent multiple retinal branch occlusions may be one of the presenting signs.
Multiorgan disease and recurrent multiple branch retinal occlusions are also observed in a number of systemic illnesses such as Behçet's disease and lupus erythematosus.
In 1973 Pfaffenbach and Hollenhorst (19) reported two patients with dementia, corticospinal tract signs and branch retinal occlusions without biological markers for systemic disease. These cases were considered as seronegative systemic lupus erythematosus.

In 1979 Susac et al. (22) described two young women who presented with multiple branch retinal artery occlusions in both eyes, hearing loss and neurological symptoms without clinical arguments for systemic disease. To characterize this entity Mass et al. (11) suggested in 1988 the acronym RED M syndrome (retinopathy, encephalopathy, deafness, associated micro-angiopathy syndrome).
In 1992, Schwitter et al. (21) proposed another acronym: SICRET (small infarcts of cochlear, retinal and encephalic tissues).
We report 3 new cases of presumed SICRET syndrome. The clinical features, fluorescein angiographic findings and available therapeutic modalities are discussed.

Case 1:

A 32 year old man with a medical history of malaria, developed in October 1987 in Mauritania a period of diarrhea followed by blurred vision, headache and vertigo.
On November 17, 1987, he was admitted for neurological and ophthalmological evaluation. On admission, positive findings included left hemiparesis with paresthesia and unsteady gait, left hyperactive tendon reflexes, cognitive dysfunction, memory loss, hearing loss and confusion.
On ophthalmological examination the VA was 0,9 in RE and 1,0 in LE. Severe visual field defects were documented in both eyes.
Fundoscopy revealed bilateral retinal arterial occlusions of the superotemporal retinal arteries in both eyes. There were no cells in the vitreous. Blood tests including erythrocyte sedimentation rate, C-reactive protein level, glucose tolerance test,VDRL, serologic tests and culture for infectious agents in blood and CSF, protein C, S, ATIII, cryoglobulin, serum complement, homocystein blood levels were within normal limits. Muscle biopsy, echography, Holter, chest XR, CT abdomen were all normal. The audiogram was also considered as normal. The cerebrospinal fluid examination showed elevated protein content (1,87 g/l with 100 % lymphocytosis). The electrophoretic analysis was normal.
EEG showed diffuse slowing and the MRI showed multiple focal areas of high signal intensity on T2 weighted image in the periventricular, thalamic and cerebellar regions (fig 1). The initial diagnosis was multifocal idiopathic demyelinating disease. The initial treatment included steroids and dipyridamol.
In May 1988 he was readmitted for depression. The neurologic and ophthalmologic examinations showed stable findings. The hypothesis of a viral encephalitis (enterovirus) was

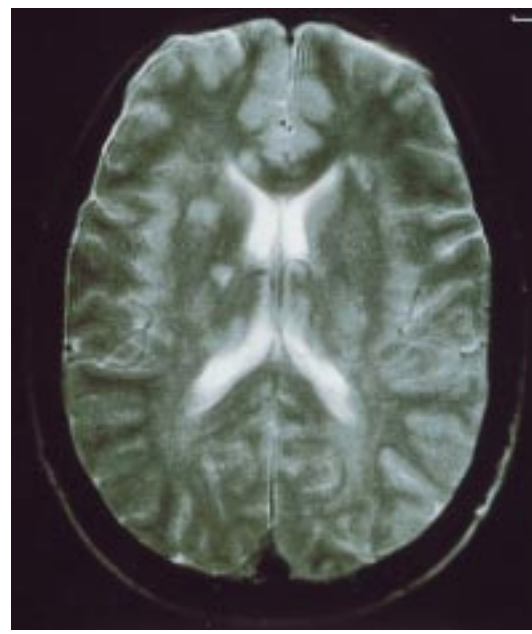

Fig 1. Case 1: Axial T2-weighted magnetic resonance imaging showing multiple hyperintense lesions scattered troughout the periventricular white matter and involving the right thalamus.

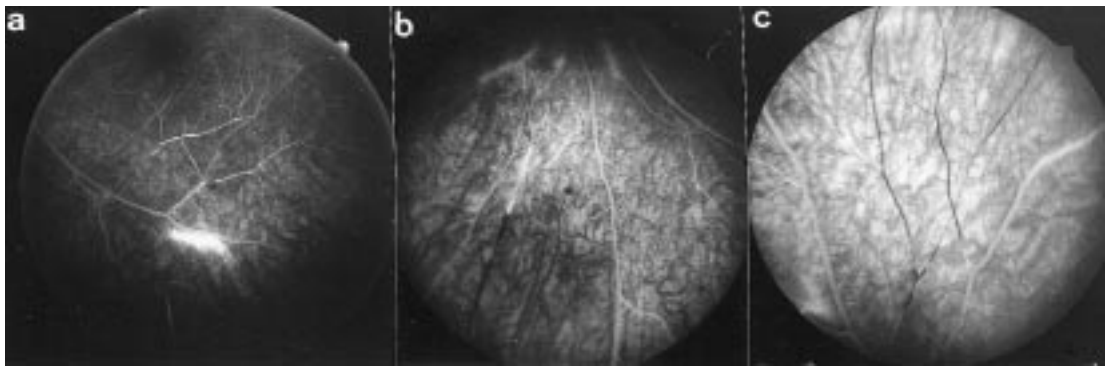

Fig 2. Case 1 (a): fluorescein angiogram of the right eye on 20/1/89. Note arterial branch occlusion from the inferotemporal retinal artery. Hyperfluorescence of the vessel wall and leakage are observed proximal to the site of obstruction.
Case 1 (b): Fluorescein angiogram of the right eye on 24/11/89 showing an inferotemporal arterial occlusion and multiple areas of segmental vessel wall hyperfluorescence elsewhere.
Case 1 (c): Fluorescein angiogram of the left eye on 23/03/90. Note multiple superotemporal retinal arteriolar obstructions.

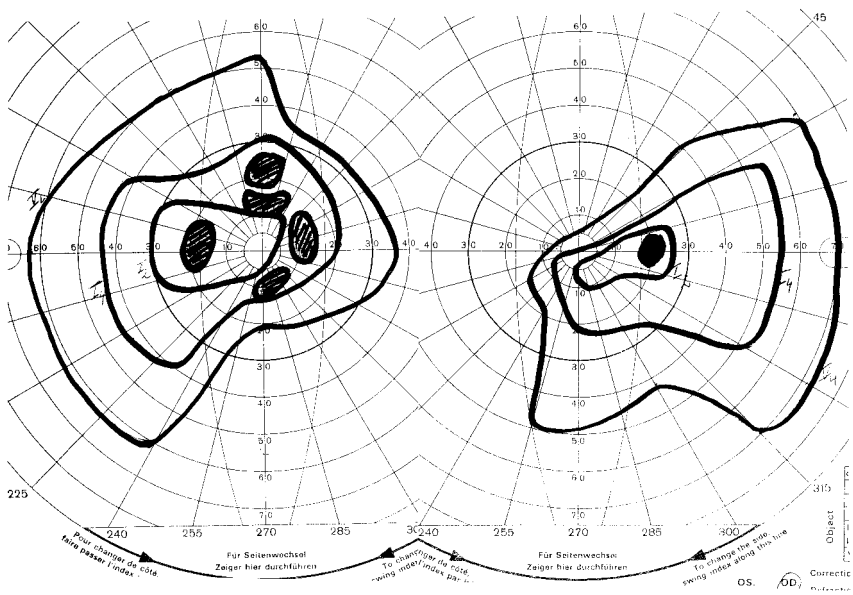

Fig 3. Case 1: Goldmann visual field showing bilateral visual field defects.

considered and the patient remained on the same medication.
Recurrent branch retinal artery occlusions located in the retinal midperiphery of both eyes were observed in January 1989 (fig. 2a), July 1989, November 1989 (fig. 2b), March 1990 (fig. 2c), January 1991, March and November 1992, with corresponding visual field defects. Fortunately central vision was spared.
Since December 1992 the patient did not experience any new symptoms and neurological and ophthalmological examinations showed stable findings with a VA of 0,9 in RE and 1,0 in LE and severe visual field defects (fig. 3).

Case 2:

A 26 year old woman, with a past history of reversible hemiparesis in 1989 and deprivation amblyopia due to congenital cataract in the left eye, complained suddenly in November 1992 of photopsia followed by a superior scotoma in the RE.

On admission the general examination was normal. No cutaneous rash, nor hearing loss were reported. VA was 1,0 in RE and 0,05 in LE.
Funduscopy and fluorescein angiography showed an inferotemporal retinal branch artery occlusion. On visual field a superonasal field defect was found, sparing the fixation point.
The only positive finding on blood test was a decreased protein S, confirmed after serial control test. Repeated MRI and audiogram were considered as normal.
Initial treatment included daily aspirine. Since December 1992 no recurrence was noted.
The VA is 1,0 in the affected eye with a persistent nasal superior visual field deficit.

Case 3:

A 35 year old woman was admitted in February 1979 because of a sudden scotoma in RE, tinnitus and hearing loss.
On admission VA was 1,0 in RE and 0,9 in LE. There were no aqueous or vitreous cells.
Fundoscopy and fluorescein angiography showed a retinal branch artery occlusion of the inferotemporal artery in the LE and multiple occlusions of the peripheral branches of the temporal and inferior nasal arteries. Elschnig's spots were observed in the superior temporal quadrant in the RE. Small retinal haemorrhages were present.
The Goldmann VF test showed corresponding visual field defects.
Neurological clinical examination was normal but a discrete slowing on EEG was noted.
CT brain with and without contrast was considered as normal.
Normal findings on blood test included: erythrocyte sedimentation rate,C reactive protein level, protein C, S, AT III, auto-antibodies (ANF, ANCA, RF), lupus anticoagulant, complement level, cryoglobulin, serologic tests and culture for infectious agents.
The audiogram showed bilateral hearing loss for low frequencies.
Initial therapy included: IV papaverin and IV steroids for 3 days followed by oral steroids.
Subsequent new retinal artery occlusions were noted in September 1979 in the LE and in September 1980 in the RE.
The patient is lost for follow-up since 1981.

DISCUSSION

SICRET syndrome is a microangiopathy of the brain, retina and cochlea, which affects usually young women with a mean age of 25 years (15, 22, 23), although it can occur in older patients (2). These patients develop multiple, often bilateral, branch retinal occlusions, progressive hearing loss and encephalopathy.
Our 3 patients showed a heterogeneous mode of onset of the disease:
- The first case had the association with encephalopathy and recurrent retinal branch artery occlusions.
- The initial symptom in the second case was hemiparesis followed by retinal artery occlusions whereas hearing loss was not reported.
- The third patient initially presented branch artery occlusions and hearing loss, but no clinical manifestations of encephalopathy.

In all 3 cases there was no evidence of a systemic disease.

Similar observations have been reported (3-6, 12, 20, 21). Some patients may present an incomplete form of the SICRET syndrome. Analyzing the subclinical cases Petty et al. (18) found that 97 % of the patients did not have the clinical triade at the time of onset. In some patients the triade became complete after a delay of weeks up to more than 2 years.
Fluorescein angiography showed multiple bilateral branch retinal occlusions in 2 of our 3 patients. None of our 3 cases had evidence of emboli on fundoscopy and no embolic sources were identified on systemic evaluation.
Vessel wall hyperfluorescence was documented and has been reported at sites distant from and unassociated with those with retinal occlusions, sometimes noted before the occurrence of the retinal arterial occlusion (14).
Some authors suggest that the vessel wall hyperfluorescence on fluorescein angiography has to be considered as an indicator of active disease (14, 15).
In our 3 cases none showed evidence of ocular inflammation or venous involvement. The number of retinal recurrences were 8 for the first case, 3 for the second case whereas the third patient had only one episode. The interval between 2 attacks can be variable and no pre-

cipitating factor has been detected. The number of recurrences seems to decrease with time. In all 3 patients the final VA was at least 0,9 in the affected eye with variable permanent visual field defects.
Hearing loss in SICRET syndrome is often acute, bilateral and asymmetric and may be the presenting feature. Associated symptoms include vertigo, unsteady gait, tinnitus, nausea and vomiting.
In some patients hearing loss may remain subclinical and is only detected on audiogram which indicates hearing loss for low frequency tones. This deficit is thought to result from microinfarction of the apical turn of the cochlea supplied by an end arteriole of the inner ear (12,25).

Headache has been reported to be the most common prodromal symptom that may appear several months before the development of the encephalopathy. Most patients have abnormalities in cognition, memory and behaviour, leading to psychiatric hospitalization, as our first patient.
Corticospinal tract signs include hemiparesis as in our second patient or hyperreflexia with Babinsky sign as observed in our first patient.
In previously reported cases (1, 9, 11, 17, 23) patients had variable degrees of dysarthria, paresthesia, hyperesthesia, dysmetria, cranial nerve palsies (III,VI,VII), seizures and myoclonus.

MRI is the neuroradiological procedure of choice and reveals small multifocal areas of hyperintensity throughout the white and gray matter of the cerebrum and the infratentorium structures. These lesions are predominant in the white matter and often misinterpreted as related to multiple sclerosis.
Cerebral angiography has been reported to be normal in most cases (18).
CT scan of the brain, with or without contrast is usually normal in the acute and subacute phase.
Electroencephalography showed diffuse slowing in 2 of our 3 patients as in most reported patients with SICRET syndrome (18, 19).
Markers for infectious agent, autoimmune disease or coagulopathy are negative. However cases of SICRET syndrome associated with protein S deficiency and factor V Leiden mutation have been reported (1, 24), suggesting that SICRET syndrome in some patients may be associated with abnormalities in the coagulation pathway.
Increased CSF protein content with lymphocytic pleocytosis has been frequently reported (10, 11, 17, 22, 23). As in our first case no oligoclonal bands on electrophoretic analysis are found, CSF tests for syphilis, Lyme disease, virus, fungus, bacteria, parasites are negative.

The diagnosis of SICRET syndrome will be suspected on clinical grounds in the presence of visual symptoms combined with hearing and neurological symptoms mainly in young women. Documented retinal artery occlusions on fluorescein angiography, bilateral sensorineural hearing loss for low frequency tone on audiogram and multiple areas of increased signal scattered throughout white and gray matter on MRI-T2 weighted image will confirm the diagnosis. In some patients one or two features of the triade may remain subclinical (5, 6, 8, 12, 13, 17, 18).
The differential diagnosis of SICRET includes causes of confusional state, sudden hearing loss and/or retinal artery occlusions in young women. It has been covered extensively elsewhere (5, 12, 13, 17, 18). Briefly it includes: multiple sclerosis, systemic lupus erythematosus, transient ischaemic attacks, complicated migraine and in addition primary CNS lymphoma, multifocal CNS infections (Borrelia, syphylis, fungi, tuberculosis), neurosarcoidosis, polyarteritis nodosa, Wegener granulomatosis, neuro-Behçet, Cogan syndrome, embolic disease, thrombophilic disorders, angiofibrodysplasia.
Because the pathogenesis of SICRET syndrome is still unknown and its clinical course is self-limiting, it is difficult to determine whether there is an effective treatment.
Many authors have observed improvement or stabilization under immunosuppressive therapy or a combination of immunosuppressive and anticoagulant treatment (4, 10, 11, 13).
Some patients deteriorate despite steroid or immunosuppressive treatment (12, 16, 17, 19).
Improvement or deterioration has been observed with patients on anticoagulation or antiplatelet (aspirine, dipyridamole) treatment combined with calcium antagonists (7, 25).
Some patients recover without any therapy (3).

More recently hyperbaric oxygen has been used with documented visual field recovery in patients with SICRET syndrome (3, 9).

The prognosis is variable. Blindness, deafness and neurological sequelae are rare.
No deaths have been reported.
Brain MRI abnormalities may disappear after the acute phase, elevated protein content in the CSF and lymphocytic pleocytosis both return to normal after a few weeks.
Fluorescein angiography shows repermeabilization of previously occluded retinal arterioles with surrounding granular aspect of the retinal pigment epithelium.
Permanent visual field defects and hearing loss are the main sequelae. Retinal neovascularization may result from the retinal vascular occlusion (8).
Long term follow-up of SICRET syndrome has to include visual field testing, fluorescein angiography, audiogram and brain MRI to detect subclinical recurrences.

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