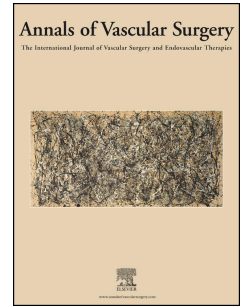# Journal Pre-proof

Carotid artery aneurysm in HIV. A review of case reports in literature

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1 Title : Carotid artery aneurysm in HIV. A review of case reports in literature.

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18 **Abstract**

19 **Background :**

20 HIV infection may affect   cardiovascular system through different physio pathological patterns

21 including viral vasculitis, thrombophilia induction, opportunistic infection,   major HIV vasculo-

22 tropic coinfections and secondary effects of antiretroviral therapy. Vessel pathology may

23 manifest as obstructive disease, dissection or aneurysm conditions that may involve major ,

24 medium or small vessels, in different arterial branches.

25   Rarely reported in HIV negative patients , aneurysms involving   carotid artery have been

26 described for the first time in seropositive patients in 1989. Since then, sporadic case reports

27 and monocentric experiences have been published on the subject until nowadays ;

28 unexpectedly, in some of the cases aneurysms have occurred notwithstanding the efficacy

29 of antiviral treatment in chronic viral suppression and restoration of the immune function.

30 As a potential aetiological cause of stroke, and because a complete understanding of

31 physiopathology in this setting hasn't been reached, studies are needed, to improve

32 management of patients affected by this highly morbid-high mortality non-AIDS related

33 comorbidity.

34 **Aims :** in our study we have focused on aneurysm pathology affecting carotid arteries in HIV

35 patients , analysing clinical and surgical presentation, management and outcome, through a

36 review of cases published in literature. The cases retrieved were additionally analysed

37 according to the segment of carotid artery involved (extra cranial or intracranial carotid

38 artery) with regard to anagraphic details, aneurysm type, presentation, treatment and

39 outcome, to analyse potential differences due to the two main different localization of the

40 lesion.

41 Because of the availability in literature of only scattered information on this clinical subject

42 (fragmented in case reports or small monocentric reports), and of the lack of a previously

43 published overview, our work was conceived to fulfil this actual and necessary clinical need.

44 **Methods :** Medline(www.ncbi.nlm.nih.gov/pubmed) database was reviewed for "carotid artery

45 aneurysm AND HIV OR AIDS OR immunodeficiency. Research was restricted to English

46 language. Only case reports were included. Data on patients age, sex, traditional risk factors,

47 timing from HIV diagnosis, pharmacological details, coinfection (syphilis, HCV HBV), anatomical

48 localization of lesion (intra or extra-cranial), neurological presentation and, when available,

49 details on cerebral imaging findings (such as subarachnoid haemorrhage or cerebral

50 infarction) surgical treatment , surgical outcome and overall mortality were collected and

51 summarised in tables.

52 **Results:** 19 articles including a total of 46 case were included in our report. Mean age of

53 patients was 30.6±14.2; 30 patients were male (65.2%). Smoke and hypertension were the

54 most frequently reported traditional cardiovascular risk factors (in 13% and 10.9% of cases).

55 Diagnosis of carotid artery aneurysm may occur in previously undiagnosed HIV patients

56 (56.5%), but also in children with vertically acquired infection or years after HIV diagnosis.

57 They have been described in patients with a CD4+ leucocyte count < 200, but also in patients

58 with a higher count. Previous infectious conditions reported in patients included

59 tuberculosis (19.6%) and herpes virus (13%). In 17.4% of cases a pathogen agent was

60 isolated from peripheral colture . Aneurysms were localized in intra-cranial carotid artery

61 (41.3%) or in extra-cranial localization (58%); the majority were pseudo aneurysms (44%)

62 while fusiform aneurysms occurred in 23.9%. In 39.1% of cases aneurysms involved

63 additional arterial branches. Presenting features at diagnosis included symptoms due to

64 compression of neck structures, as painful cervical mass (52.2%) , dysphonia or dysphagia .

65 Positivity for neurological symptoms occurred in 36.9%: cranial nerve palsies, hemiparesis,

66 hemiplegia , monoplegia , aphasia, headache , impaired consciousness and seizures. Ischemic

67 lesions were reported in 5 cases (10.9 %) and subarachnoid haemorrhage in 3 (6.5%). For

68 19 cases a colture of surgical specimen was available; in 63% of patients no infectious

69 agent was identifiable . Patients were managed surgically in 58.7% of cases, in 26% of

70 cases with a conservative pharmacological treatment, 15.2% of cases (7 patients) no

71 treatment was reported . Of these, 4 cases (8.6%) were left untreated because of exitus at

72 presentation (subarachnoid haemorrhage, generalized seizures, hydrocephalus, airway

73 obstruction waiting for surgery); in the other 3 cases no details on specific treatment were

74 reported; in these cases exitus occurred at a later stage (ranging from 25 days to 2

75 months) as a final event complicating a pre-existing heart failure in one case, a bacterial

76 pneumonia complicating a major stroke in another case, and for a not-specified reason in

77 the third. Surgical options included open surgery (74%) and endovascular interventions

78   (22.2%). Overall surgical morbidity and mortality were both high, 22.2% and 7.4 %

79   respectively, but when considering separately morbidity and mortality for different surgical

80   approaches, endovascular treatment carried the highest rates : 57.1 morbidity ; 14.7 %

81   mortality vs 10% and 5% for open surgery.

82   Finally, the overall mortality in surgically treated and untreated HIV patients with carotid

83   artery aneurysm was 26.1% .

84   The independent sample t-test carried out for further analysis of cases according to

85   two main different aneurysm locations (extra-cranial and intracranial carotid artery), has

86   shown that the majority of common carotid artery involvement was observed in men

87   (81.5%) while 57.9% of intracranial aneurysms were diagnosed in female patients. In

88   paediatric patients (<18 years old) only intracranial district involvement was reported.

89   Vertical transmission was concerned preponderantly in patients with intracranial

90   aneurysms; previously unknown HIV infection occurred in 85.2% of patients with common

91   carotid artery involvement (even though this may occur according to the origin of patients

92   from lower income countries). Intracranial aneurysms presented more frequently central

93   neurological symptoms or signs while in cervical location peripheral nerve impairment

94   was more frequent . Extra-cranial aneurysms appeared to be more frequently saccular in

95   shape, intracranial fusiform. Occasional diagnosis of aneurysm in other arterial districts

96   occurred more frequently in patients with intracranial involvement. According to

97   management of patients, a surgical approach was most frequently reported in common

98   carotid artery aneurysm management (24 of 27 patients, 88.8% vs , 3 of 19 patients, 15.8%)

99   while for intra-cranial lesions a conservative approach (either pharmacological (11 cases) or

100 of no treatment (3 cases) or lack of data (2 cases) was mainly observed . In 3 untreated

101 cases, this occurred because of fatal outcome on presentation. As for surgical management ,

102 in the majority of cases carried out to treat extra-cranial lesions, a high complication rate

103 was observed for endovascular procedures, including stent occlusion , endo-leak and post-

104   operatory myocardial infarction. Surgical reconstruction was complicated in 1 case by major

105   post-operatory stroke. A higher mortality was reported for patients with intracranial

106   aneurysms (42.1% vs 14.8% p< 0.02). Follow up was brief in the majority of cases (1 to 10

107   months), and a long term outcome can't be assessed from available data.

108

109   **Conclusions** : aneurysms may occur in both extra and intracranial carotid artery in patients

110   with HIV at younger age than in non-HIV patients and are linked to a high morbidity and

111   mortality . Because of associated comorbidities (coinfections, thrombophilia, inflammatory

112   burden, immunosuppression) both medical and surgical management have a high morbidity

113   and mortality, even higher for endovascular treatment. Carotid aneurysm may occur as a

114   first manifestation of HIV, and must be suspected whenever this rare vascular condition

115   may occur in the absence of a more likely aetiology. Carotid artery aneurysm must be

116   suspected in HIV patients presenting with compressive symptoms of the neck, neurological

117   impairment or in differential diagnosis for stroke. Two different physiopathology patterns

118   may be suggested for extracranial and intracranial carotid artery aneurysms, suggesting

119   a complex entanglement of factors that may combine differently to lead to lesion

120   formation in both districts. Further studies are needed to better understand

121   physiopathology and to improve treatment and patients outcome.

122

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124

125   **Introduction**

126   The epidemiology of HIV has changed significantly over the past 2 decades. Antiretroviral

127   therapy, by controlling viral burden and restoring immune function, has transformed HIV

128   infection into a chronic disease, improving patient's survival [1].

129   According to a recently published meta-analysis, patients living with HIV may have a

130   relative risk of 2 for cardiovascular conditions when compared to other high

131   cardiovascular risk groups such as diabetes mellitus [2], due to traditional cardiovascular risk

132   factors, but also to disease-specific factors such as inflammation, immune activation and effects

133   of HIV medications; traditional charts may be insufficient in quantifying risk in this setting [3].

134   Cardiovascular comorbidities may manifest in many different ways in HIV patients, including

135   myocardial infarction, stroke, aortitis, aortic aneurysms or dissections or peripheral vascular

136   disease. Among arterial branches that may be affected by aneurysm lesions, carotid

137   artery is not the most frequently involved. This may seem not the case for aneurysm

138   pathology in HIV patients. Even though carotid aneurysms are still only reported in

139   sporadic case reports and monocentric experiences, according to a previously published

140   monocentric experience including 28 HIV patients with aneurysm pathology in different

141   arterial branches, carotid district appeared the most frequently involved vessel [4]. Apart

142   from compression symptoms in the neck caused by lesions in extra-cranial region, intra-cranial

143   aneurysm may be complicated by neurological impairment, ischemic stroke or

144   subarachnoid haemorrhage .

145   An overall increased incidence of cerebrovascular events has been reported in patients

146   with HIV, with a relative risk of 1.34, increasing to 2.44 in women (data of Spanish Cohort of

147   adult people living with HIV of the AIDS Research Network-CoRIS) [5]. Many different

148   aetiologies have been reported for ischemic stroke in persons living with HIV, including large-

149   artery atherosclerosis, small-vessel disease, cardio-embolism, infection-related stroke,

150   coagulopathy and HIV-associated vasculopathy, in the form of stenosis or aneurysm [6].

151   Aneurysm pathology in patients with HIV may involve major arteries , such as thoracic or

152   abdominal aorta [7], but also may affect medium sized vessels, more frequently the carotid

153   artery district. As a potential aetiological cause for events of neurovascular interest , the

154   understanding of carotid artery pathology in HIV patients is of pivotal importance to

155 ameliorate differential diagnosis process, patients management and treatment in this

156 specific field, which yields a high morbidity and mortality rate.

157 This considered, our study will focus on carotid artery aneurysm pathology in patients with

158 HIV, through a review of cases in literature.

159

160 **Materials and methods**

161 Literature has been systematically searched using Medline(www.ncbi.nlm.nih.gov/pubmed)

162 database with the keywords "carotid aneurysm" AND "HIV" OR "AIDS" OR "immunodeficiency"

163 Retrieved articles were selected if they included a case report of carotid artery aneurysm in a

164 patient with HIV, involving either extra-cranial or intracranial portion of this vessel. The case

165 was selected if details on patient's age, sex , and carotid artery aneurysm involvement were

166 specified; HIV infection had to be clearly stated; among papers reporting monocentric

167 experiences, we included only reports which specified separate data for each patient. One

168 monocentric experience was included because anagraphical data and details on aneurysm

169 type, symptoms and treatment were singularly considered, even though complications and

170 mortality were reported as referred to the whole group [8]. Research was restricted to

171 English language publications.

172 Data on age, sex, and presence of traditional cardiovascular risk factors were registered in an

173 electronic data base.

174 Disease specific data , including time from HIV diagnosis, viral load, CD 4+ cell count, years of

175 antiretroviral treatment, were added when available. The infectious clinical state has been

176 better described by including coinfections at the time of carotid artery diagnosis or cultural

177 positivity of surgical samples ; previous infections of interest were also signalled when

178 described.

179 Details on clinical presentations of carotid artery involvement were registered; specifically,

180 data of neurological interest were singularly analysed , including ischemic lesions and /or

181 subarachnoid haemorrhage on imaging , seizures, headache, focal neurologic signs and cranial

182 nerve palsies.

183 Data of specific surgical vascular interest included at which level carotid artery segment

184 was involved by aneurysm lesion (intra or extra-cranial) ; aneurysm subtype (fusiform,

185 saccular-irregular or pseudo-aneurysm) and histologic report (when available) ; the

186 occurrence of aneurysm pathology involving other vascular districts, was additionally

187 specified if signalled.

188 Pharmacological or surgical treatment of carotid artery lesion was specified; details on

189 interventional procedure and its outcome have been analysed, assessing surgical morbidity

190 and mortality as a whole and specifically for endovascular and open procedures.

191 Patients mortality was reported, specifying, when available, cause and timing of death after

192 carotid aneurysm diagnosis.

193 Finally, data were furtherly analysed with an independent sample t-test comparing the

194 two main different aneurysm locations : extra-cranial carotid artery and intracranial carotid

195 artery , in order to analyse any occurrence of statistically significant difference in

196 anagraphical data , aneurysm type , clinical presentation, surgical treatment and outcome

197 which may suggest two different physio pathological patterns according to district involved.

198 Due to the large heterogeneity of cases sporadically reported, data could not be quantitatively

199 combined and analysed.

200

201 **Results**

202 23 articles were initially retrieved. After reading the full text , 3 papers were discarded, 2

203 because they were monocentric experiences focusing on multiple district aneurysm

204 pathology, reporting pooled data on eventual carotid lesions [4,9] and 1 because not all

205 necessary data were reported singularly for each patient , being the report an overview on

206 multidistrict aneurysm pathology in HIV [10].

207   19 articles and a total of 46 case reports have been included in our review; 17 were

208   single case reports, 1 was a monocentric experience including 3 suitable cases ; finally we

209   added 1 polycentric retrospective experience of HIV-infected patients with cerebral vasculitis

210   and vessels ectasia from 4 different tertiary centres (25 cases) [Table 1].

211   The mean age of patients was 30.6 ± 14.2 ; 30 of the 46 patients (65.2%) were male.

212   The most frequently reported traditional cardiovascular risk factors were smoke (in 6

213   cases, 13%) and hypertension (5 cases, 10.9%); obesity (1 case) , dyslipidaemia (1 case) ,

214   diabetes (1 case) have been also reported. In three cases a history of previous pathological

215   conditions of cardiovascular interest was reported: dilated cardiomyopathy associated with

216   heart failure (2 cases)and in 1 case a previous deep venous vessel thrombosis event. In 14

217   cases (30.4%)   anamnesis was clear for either traditional cardiovascular risk factors or

218   previously known pathologies or events of cardiovascular interest [Table 1].

219   As for HIV status, a vertical transmission was reported in 7 cases (15.2%). In 6 patients

220   aneurysm occurred years after HIV infection, while in 1 case it developed 2 months

221   after viral diagnosis and start of treatment. In 4 cases HIV was diagnosed in occasion of

222   the hospitalization due to carotid artery condition; this was the case in 3 paediatric

223   patients and in one 24 year old girl in Sub-Saharan context. In the other patients data

224   weren't specified .

225   Antiretroviral treatment (HAART or unspecified antiretroviral regimen), had been prescribed

226   previously in 12 cases (26 %), but in 7 (15.2%) cases a poor adherence to treatment was

227   signalled. The majority of patients (24, 52%) wasn't in treatment when aneurysm occurred, or

228   data on previous treatment wasn't reported.

229   Previous infectious events were reported in 18 cases (39.1%) . Herpetic infection was

230   reported in anamnesis in 6 cases (13%) and included 1 case of labialis Herpes Simplex Virus

231   (HSV) infection; 1 case of anal HSV infection; 1 varicella case and Herpes Zoster in 3 cases.

232 In 9 cases (19.6 %) previous tuberculosis infection was reported. Pneumocystis Carinii

233 occurred in 4 patients (8.6%).

234 Syphilis was reported in 2 cases (4.3%), and hepatotropic viruses infection in 3 (2 HBV+

235 and 1 HCV+ patient).

236 In 8 cases cultural tests positivity on peripheral biologic samples was reported during

237 hospitalization for carotid condition: Salmonella Choleraesuis , Klebsiella , Bacillus sp ,

238 pulmonary active tuberculosis, Staphylococcus Epidermidis, Varicella-Zoster virus and

239 Streptococcus Pneumoniae were among isolated agents, while positivity of surgical specimen

240 was reported in 7 cases and included isolation of Aspergillus fumigatus, Mycobacterium

241 avium cellular, Mycobacterium Tuberculosis, Enterococcus and Staphylococcus and

242 Streptococcus Pneumoniae. In 12 of the 19 available samples (63.1%) no coltural positivity

243 was signalled.

244 Carotid artery aneurysms occurred in the extra-cranial segment of carotid artery (mainly

245 common carotid artery) in 27 cases (58%) or in the   intra-cranial portion, from cavernous

246 segment to the origin of cerebral arteries, in 19 cases (41.3%). In the majority of cases lesion

247 had pseudo aneurysm features (20 cases, 44%) or saccular , lobulated or irregular shape (7,

248 15.4%); in the 11 cases left (23.9%) the aneurysm was fusiform.

249 When analysing cases according to clinical presentation at diagnosis, symptoms due to

250 painful cervical mass were reported (24 cases, 52.2%). Also compression of cervical

251 structures was described, and among these, dysphonia (due to recurrent laryngeal nerve

252 compression) occurred in 5 (10.9%) and dysphagia in 3 cases (6.5%). In 2 (4.3%) of the 4

253 patients in which cavernous segment of the internal carotid artery occurred, epistaxis was

254 among presenting symptoms, intractable in one case. One case of visual impairment

255 occurred, as a result of retinal necrosis.

256 Fever was reported as one of the presenting symptoms in 2 cases; in which death

257 occurred. In   2 cases carotid aneurysm has been diagnosed as an incidental finding.

258 As for neurological presentation, patients were positive for neurological symptoms or signs

259 in 26 cases (56.5%). Specifically, headache was reported in 6 patients (13%), ischemic lesions

260 in five cases (10.9%); seizures were reported in 5 patients; subarachnoid haemorrhage

261 was reported in 3 (6.5%) and cranial nerve palsies (VII, IX,X,XI and XII) in 11 (23.9%). Lethargy

262 and confusion were reported in association with neurological clinical pictures in 6 cases

263 (13%).

264 Co-occurrence of aneurysm lesions in other arterial branches was reported in 18 cases

265 (39.1 %). Cerebral arteries were the most involved (12 cases, 48%), but aneurysms also

266 occurred in subclavian artery (in 1 of 2 cases bilateral), vertebral artery, abdominal aorta,

267 contralateral carotid and ophthalmic artery.

268 Management of carotid artery aneurysm varied between no therapy, pharmacological

269 management (for which details were frequently poorly specified, but when available,

270 consisted mainly in antiretroviral treatment prescription or optimization, antiplatelet

271 treatment for ischemic or associated carotid artery obstructive condition or antibiotic

272 treatment for infectious comorbidities) and surgical treatment, either with open or

273 endovascular approach. Among the 7 patients which hadn't received any treatment (or for

274 whom details on treatment were formally lacking), this has occurred because of exitus on

275 hospitalization in 5 cases; in the other 2 cases exitus occurred after discharge, respectively

276 1 and 2 months after aneurysm diagnosis, for unspecified reasons. In latter cases a

277 supportive treatment for the comorbidity finally leading to death must have been

278 prescribed without clinical success.

279 Among the pharmacologically managed patients (12 cases, 26.1%), 1 death occurred in a

280 poorly compliant 29 year old patient with intra-cranial carotid aneurysm and history of

281 recurrent herpes zoster infection, which developed subarachnoid haemorrhage 3 weeks

282 after first hospitalization for aphasia; another death occurred 4 months after hospital

283 discharge in a 6 year old patient with intra-cavernous fusiform aneurysm presenting with

284 seizures and salmonellae Coleraesuis sepsis, conservatively managed with antibiotic

285 treatment. No other death has occurred in patients managed conservatively. Aspirin was

286 part of pharmacological management in three cases.

287 Surgical treatment has been reported in 27 cases (58.7 %). 20 of the 27 surgically treated

288 patients were managed by open approach (74%) ; surgical procedures included

289 aneurysmectomy and carotid jugular fistula repair; carotid-ophthalmic saphenous vein fistula

290 repair; carotid-subclavian PTFE bypass, carotid artery/middle cerebral artery reconstruction

291 with fenestrated aneurysm clips; unspecified by-pass (8 cases) and carotid artery ligation (8

292 procedures). The other 7 patients were managed by endovascular approach, with covered

293 stent implant (6 cases) or intra-cavernous aneurysm embolization (1 procedure) (25.9%) .

294   Surgery complications were reported for 6 cases, 22.2% of the 27 surgically managed

295 patients, specifically :

296 Complications for open surgery were reported in 2 of the 20 open surgery treated cases

297 (10%) and included :

298 – 1 Transitory III nerve palsy (carotid ophthalmic bypass for intracranial aneurysm

299   treatment) ;

300 – 1 middle cerebral a. haemorrhagic infarct (3 days after artery ligation for a common

301   carotid aneurysm).

302 Reported complications were more frequent for endovascular treatment (4 of the

303 7 endo-vascular treated patients 57.1 %). In this case they included :

304 – 1 myocardial infarction (fatal) 24h post covered stent implant (common carotid);

305 – 1 early stent occlusion (in common carotid artery, uneventful);

306 – 1 stent occlusion (1 month) initially uneventful but at 10 month ophthalmic artery

307   thrombosis (common carotid artery treatment);

308   – 1 stent endo-leak with active bleeding (4 months after surgery for common

309   carotid aneurysm). Carotid ligation performed to stop the acute bleeding led to

310   middle cerebral artery infarct with dense paraplegia.

311   The reported overall surgical mortality was of 2 /27 treated cases (7.04%). Mortality

312   was higher for endo-vascular treated patients (1 case out of 7 , 14.2%) than for open

313   cases (1 case/20, 5%).

314   Overall mortality in HIV patients with carotid aneurysm amounted to 26% (12

315   cases).

316   Additional causes of death, including surgical complications were:

317   – 1 myocardial infarction 24 hours after endovascular stenting of common carotid

318   artery aneurysm;

319   – 1 fatal stroke 2 days after carotid ligation (common carotid aneurysm);

320   – 1 hydrocephalus a few hours after admission to hospital , unsuccessfully drained, in a

321   13 year old boy with an intra-cranic carotid artery aneurysm;

322   – 1 death in a 6 year old patient with bilateral intra-cranial carotid aneurysm ,

323   with subarachnoid haemorrhage and seizures, and autoptic positivity for varicella

324   zoster virus on carotid artery specimen;

325   – 1 subarachnoid haemorrhage at 3 weeks in a 29 year old female patient with

326   intracranial involvement, not compliant with therapy;

327   – 1 heart failure (34 days after hospitalization , in a patient with common carotid

328   aneurysm , not treated surgically, hospitalized for sespsis due to staphylococcus

329   aureus);

330   – 1 death for AIDS related causes 2 years after endovascular embolization of a intra-

331   cavernous carotid aneurysm);

332   – 1 death caused by bacterial pneumonia 25 days after pharmacological treatment of an

333   ischemic stroke in a patient with intracranial carotid aneurysm;

334 − dyspnoea and cough 4 months after treating a 6 year old girl with antibiotic

335 therapy , for salmonellae coleraesuis sepsis and intracranial cerebral artery

336 aneurysm and seizures ;

337 − generalized seizures in a 7 year old patient with internal cerebral carotid aneurysm

338 and subarachnoid haemorrhage (12 hours);

339 − 1 non specified (at 2 months) of a 12 year old girl previously hospitalized for

340 seizures, with concomitant intra-cranic aneurysm;

341 − 1 case of airway obstruction by compressive cervical aneurysm, occurred in a 52 year

342 old male patient, hospitalized because of compressive mass and XII nerve palsy.

343 Where specified, follow up was usually brief; in the majority of patients who survived,

344 a 1 month up to 10 month follow up was reported; only one monocentric

345 experience reported a longer follow up, from 1 to 17 years.

346 Summary of data of cases included in review have been given in Table 2.1 (anagraphic data

347 and infectivology details) ; Table 2.2 (carotid aneurysm pathology details) and Table 2.3

348 (outcome and mortality).

349 In our review we have included both extra-cranial and intracranial carotid artery

350 aneurysm in order to have an overview on the subject. Still, even though the number of

351 retrieved cases was not consistent, a statistically significant difference in terms of age

352 at onset, symptoms, comorbidities , treatment and outcome has been observed,

353 suggesting that two different patterns may be involved in physiopathology of extra-

354 cranial carotid artery aneurysm or intra-cranial aneurism condition.

355 The mean age of patients with intracranial aneurysm was significantly lower than the

356 one of patients with extra-cranial involvement (22.5 vs 36.3, p<0.001).

357 While the majority of common carotid artery involvement was observed in men (

358 81.5%), on the contrary 57.9% of intracranial aneurysms were diagnosed in female

359 patients. In paediatric patients (<18 years old) only intracranial district involvement

360   was reported. Vertical transmission of the infection was concerned preponderantly in

361   patients with intracranial aneurysms; while previously unknown infection occurred in

362   85.2% of patients with common carotid artery involvement.

363   Diagnosis of carotid artery aneurysm was contextual to HIV diagnosis in the majority of

364   patients with common carotid artery involvement (23 cases of 27, 85.2%) , while in

365   patients with intra-cranial presentation it occurred in patients with known vertical

366   transmission in 6 of 19 cases (31.6%); years after diagnosis in 6 cases or as a

367   diagnosis concomitant with the vascular one in 3 (15.8%) (p<0.001). Intracranial

368   aneurysms were more frequent in patients with vertical transmission (p<0.004).

369   Patients with intra-cranial artery involvement more frequently (but not significantly)

370   manifested neurological impairment, in the form of ischemic lesions (4 cases, 21.1% vs 1

371   case, 3.7% p=0.06) , hemiparesis, monoplegia or hemiplegia (5 cases 26.3% vs 2 cases,

372   7.4% p= 0.08). Cranial nerve palsy was reported more frequently in cervical involvement

373   (9 cases, 33.3% vs 2 cases , 10.5%; p =0.07). Seizures, headache, consciousness

374   impairment and subarachnoid haemorrhage occurred only in patients with intracranial

375   involvement, while painful cervical mass, dysphonia, dysphagia were exclusively reported

376   for cervical involvement. Aneurysms involving other arterial districts were more

377   frequently reported in patients with intracranial carotid aneurysm (68.4 vs 18.5%

378   p<0.001). A difference in aneurysm type has been observed (fusiform aneurysm being

379   more frequent in patients with intracranial involvement (52.6% vs 3.7% p < 0.001);

380   saccular aneurysm or pseudo-aneurysm were more frequent in cervical artery vessels

381   (88.9 % vs 15.8%; p<0.001). Mortality was higher in patients with intracranial

382   involvement (42.1% vs 14.8% p=0.02).

383   According to management of patients, a surgical approach (including artery

384   reconstruction, ligation , or endovascular stenting) was most frequently reported for

385   common carotid artery aneurysm management , while for intra-cranial lesions a

386   conservative approach or lack of data on pharmacological management was   frequently

387   observed. In 3 cases this occurred   because of fatal outcome on presentation. As for

388   surgical management , in the majority of cases carried out for e extra-cranial lesions,

389   endovascular procedures were found to carry a high complication rate, including stent

390   occlusion , endo-leak and post-operatory myocardial infarction. Surgical reconstruction

391   was complicated in 1 case by major post-operatory stroke. A higher   mortality was

392   reported for patients with intracranial aneurysms (42.1% vs 14.8% p< 0.02) [Table 2.4].

393

394   Discussion

395   If we consider   data related to studies on the general population, aneurysms of the extra-

396   cranial carotid artery are rare and account for less than 1% of all arterial aneurysms. The lesion

397   most   frequently involves the common carotid artery near the bifurcation. Atherosclerosis ,

398   trauma , fibromuscular dysplasia, prior surgery, congenital defects, radiation and infections are

399   among   described aetiologies for aneurysm in carotid artery [11].

400   Carotid artery aneurysm may occur in patients with HIV. Our review of literature has

401   retrieved 46 cases for which data on aneurysm location, surgical procedure and

402   outcome had been singularly reported for each patient, or for which data corresponding to

403   a case series could be sufficiently precise for a descriptive analysis of the group. More

404   cases have been reported in monocentric experiences of developing countries, but had to

405   be discarded not fulfilling inclusion criteria , even though they included very interesting

406   considerations.

407   Traditional cardiovascular risk factors were reported in patients and included hypertension,

408   dyslipidaemia , obesity , smoke and diabetes . Vascular pre-existing pathologies in anamnesis

409   have also been reported , including previous femoral deep vein thrombosis and dilated

410   cardiomyopathy associated with   heart failure. A higher prevalence of traditional risk factors

411   has been observed previously in HIV patients, due to the infection itself (which may lead to

412   early decreases in HDL cholesterol and elevations in triglycerides) and to HAART's effects on the

413   incidence of traditional risk factors and dis-metabolic features, which promote atherosclerosis

414   [12].

415   Mean age of patients included in our review was 30.6 , lower than the one reported in a 15

416   year monocentric experience of patients treated for extra-cranial carotid artery aneurysm,

417   which was 67 [11]; when considering only intracranial aneurysms, an even lower mean age

418   was reported (22.5 vs 36.3 for patients with common carotid artery involvement).

419   Furthermore in 9 HIV patients carotid aneurysm occurred in paediatric age; in 5 of these

420   cases they had led the patient to exitus. HIV status was unknown at the time of carotid

421   artery aneurysm diagnosis in 4 of the 5 deceased patients [13-16]. Interestingly, in all

422   paediatric cases aneurysms had developed in the intracranial segment of carotid artery. In

423   three of the paediatric cases that presented with carotid aneurysm and a confirmed newly

424   diagnosis of HIV , a concomitant history of severe infection was reported; the three cases

425   all presented with fatal subarachnoid haemorrhage and seizures; in one, diagnosed with

426   intra-cavernous aneurysm, salmonellae Coleraesuis sepsis occurred; varicella virus sepsis

427   was reported in the other case of bilateral carotid artery involvement, while in the third

428   patient a recent history for abdominal tuberculosis was recorded.

429   In paediatric cases with documented vertical transmission, a poor compliance to

430   antiretroviral treatment was reported in two patients, which presented with fusiform

431   intracranial aneurysm symptomatic for stroke in one case and subarachnoid haemorrhage in

432   the other. A favourable outcome was reported with conservative management

433   (antiretroviral therapy and aspirin) in the former case and with surgical aneurysm repair in

434   the latter. We can speculate that even when a vertical transmission was not previously

435   known and specified, a lifelong unknown and so untreated HIV infection may be responsible

436   of the vascular involvement in paediatric age: bacterial mycotic aneurysms, along with

437 viral arteritis (either by HIV itself or varicella virus) appear to be a likely pathological

438 cause.

439 A clinical incidence of 1.3% per year and a 24% autopsy-incidence for cerebrovascular disease

440 has been previously reported in literature for children with HIV; cerebrovascular disease

441 may manifest as arteritis and formation of fusiform aneurysm. A link with increased mortality

442 six months after diagnosis of a cerebral aneurysm condition has been suggested [14] and it

443 has been proposed that in children with fusiform aneurysm of intracranial vessels, HIV-induced

444 vasculopathy should be considered, as it may be the initial manifestation of clinical AIDS [13] .

445 Details on patients medical history given in most of the cases included in review referred to

446 previous infectious events. It is known that degradation of the arterial wall by bacteria or

447 septic embolization may cause mycotic aneurysms. Additionally, previous findings from case-

448 control studies in literature have shown an association between systemic infection (acute,

449 chronically persistent or anamnestic) and stroke (odds ratio ranging from 2 to 14·5), likely due

450 to inflammatory response to the infectious agent and consequent endothelial damage ,

451 which also predispose patients to intracranial haemorrhage [14].

452 Previous infections , acute sepsis or cultural positivity of surgical specimens from carotid

453 wall have all been described in our reviewed cases of patients with carotid artery

454 aneurysm.

455 Mycobacterium Tuberculosis was the most frequently reported infectious agent (9 cases,

456 19.6%); followed by Herpes Virus (6 reported cases; 13%); positivity for Syphilis and for

457 hepatitis viruses (HBV, HCV), cytomegalovirus has also been reported [Table2].

458 All of these agents are known to potentially induce vasculitis, even though with different

459 mechanisms, including immune complexes deposition (HBV), crioglobulinaemic vasculitis

460 (HCV), viral direct damage to the vessel's wall (cytomegalovirus); bacterial and fungal

461 infection may affect vessels through direct invasion of endothelial cells, extension of a localized

462 focus of infection or septic haematogenous embolization.

463   In 2 cases of our review previous syphilitic infection has been reported. In one case an

464   intra-cavernous carotid aneurysm symptomatic for headache was diagnosed in a 59 year

465   old male patient, successfully managed conservatively [18]; in the other case a common

466   carotid artery aneurysm was reported in a 47 year old male patient also affected by

467   chronic heart failure. In this case Staphylococcus aureus sepsis and subsequent exitus

468   were reported [19]. In both cases no histologic report was available, and a syphilitic

469   vasculitis component couldn't be ascertained, but it is useful to keep in mind that HIV and

470   Treponema Pallidum coinfection is relatively common and accounts for about 25% of primary

471   and secondary syphilis. A rapid progression to tertiary syphilis may occur in HIV patients which

472   results in earlier onset of cardiovascular and neurologic sequelae [20].

473   Positivity for HCV has been reported in 1 case, in a 29 year old female patient presenting

474   with status epilepticus and bilateral internal carotid artery aneurysm, extending to cerebral

475   arteries and associated with ophthalmic and vertebral aneurysm, successfully managed

476   conservatively. In this case an additional history of Herpes Zoster, along with the possible

477   vasculitic involvement of arteries by HIV probably had played an synergic action on

478   vessels; unfortunately no coltural or histological report were available in this case [21].

479   HIV/HCV coinfection which may occur in up to 15%-30% of HIV patients may have an increased

480   relative risk for cardiovascular disease of 1.24, probably due to persistent inflammatory

481   responses of both viruses [22].

482   During hospitalization microbiological haemoculture was found positive for Salmonella

483   Choleraesuis in one case , and in another case Staphylococcus Epidermidis was isolated.

484   Additionally one CVC positivity for Klebsiella and one case of pulmonary active tuberculosis

485   were reported, that could suggest a potential mycotic aetiology for the aneurysm [23].

486   It is of interest that Varicella-Zoster virus (VZV) was isolated during autopsy in brain vessels, in

487   a case of a 6 year old patient with unknown HIV positivity, which presented with a fatal

488   subarachnoid haemorrhage and bilateral internal carotid aneurysm involvement [13] ;

489 additionally a history for recurrent herpes zoster infections has been reported in a fatal

490 case of a 29 year old African woman presenting with left carotid artery involvement,

491 symptomatic for aphasia and subarachnoid haemorrhage. Evidence from coltural data

492 were not available in this case [24]. Even though uncommonly, VZV vasculopathy can present

493 as aneurysms with subarachnoid haemorrhage due to viral reactivation from sensory and/or

494 autonomic ganglia, viral spreading to cerebral vessels adventitia through corresponding nerve

495 fibres, and induction of adventitial cellular and cytokine inflammatory response; vasculopathy

496 may cause transient ischemic attacks and ischemic or haemorrhagic strokes [25]; according to

497 meta-analysis data , a relative risk for stroke up to 2 has been reported in patients 3

498 months after infection [26].

499 Unfortunately colture of a surgical or autoptic specimen that could confirm the mycotic

500 aetiology of aneurysm was only available in 19 cases; surprisingly, while in 6 cases (36.8%)

501 colture was positive (Aspergillus fumigatus, Mycobacterium avium cellular, Enterococcus,

502 Staphylococcus, Streptococcus pneumonia and Varicella-Zoster), in 12 cases (56%), negativity

503 was reported for cultured vessel's wall.

504 Interestingly, also in the excluded paper by Chetty et al, microbiological assessment of

505 surgical specimen was found to be negative in 6 out of 7 samples of carotid artery wall

506 [10]. As reported in our previous review of literature of aortic pathology in HIV [7], in some

507 cases HIV was considered to be the main or the only agent explaining vascular lesions, and

508 viral vasculitis could be considered as the only alternative aetiological hypothesis for the

509 clinical picture.

510 Analysing carotid artery segment involved by aneurysm lesion, two different locations have

511 been described : extra-cranial carotid involvement , mainly of common carotid artery, in 27

512 cases (58%) and intra-cranial carotid artery in 19 (41.3%). A different pathogenesis for the

513 two locations has been proposed. The pathogenesis of intracranial aneurysms has been

514 suggested to involve immune activation in response to trans-endothelial migration of HIV with

515   tropism for cerebral mononuclear cells; additionally circulating cytokines and growth factors,

516   produced in response to both HIV and coinfections, concur to vascular remodelling,

517   increasing elastases and leading to the fragmentation and thinning of the internal elastic lamina,

518   early histological finding in the development of fusiform aneurysms.

519   As for extra-cranial aneurysms in HIV-positive patients, a different pathogenesis has been

520   proposed, which may involve vasculitis of the vasa vasora, absent in the intracranial arteries

521   [9].

522   Where available , histologic findings were in line with previous reports, and with what has

523   been previously described for aortic aneurysms [7] showing the presence of vascular and

524   perivascular acute inflammation, inflammatory cells (lymphocytes, plasma cells, eosinophils,

525   multinucleated giant cells, hystiocytosis), focal elastic lamina calcification, rarefaction or

526   rupture; intimal thickening or medial fibrosis [13,27,28] ; luminal thrombosis with

527   neutrophil infiltration of thrombus and concentric intimal fibrosis was reported in an autoptic

528   case of bilateral carotid artery aneurysm symptomatic for left ischemic lesion [9]. These

529   features overlapped active tuberculosis vascular findings in 3 cases [8], confirming that

530   aneurysm features may be a result of the additional action of different aetiological

531   agents, that must be suspected even in presence of a negative blood-colture.

532   The pathogenesis of vessel's wall inflammation during HIV infection has not been fully

533   understood. The proposed mechanisms include direct invasion of HIV to the artery wall, release

534   of cytokines from inflammatory cells causing vessel injury, vasoconstriction induced by viral

535   proteins, or the decreased ability of the immunocompromised host to clear out pathogens

536   coexisting in HIV-positive patient [29].

537   Several types of vasculitis have been described previously in literature in HIV patients, such as

538   leucocytoclastic vasculitis, granulomatous angiitis , angiitis associated with lymphoproliferative

539   syndromes [30], along with a higher arterial uptake on 18-fluorodesossiglucose PET examination

540   in HIV-infected patients compared with controls, independently by the CD 4 count, viral load,

541   duration of HIV infection, the use of and duration of HAART, and gender [31].

542   A very interesting remark has been reported by Chetty et al. who have compared HIV

543   vasculitis findings to lesions described for Takayasu's disease . Specifically, they have

544   observed that the temporal sequence of events leading to active and healing stages, and the

545   absence of an obvious causative agent can be considered as common features of HIV and

546   autoimmune condition and that also in HIV vasculitis two patterns may be described: an acute

547   or active phase (leukocytoclastic vasculitis of the vasa vasora and ischemia of the media) and a

548   chronic or healed/healing phase (less obvious leukocytoclastic vasculitis and fibrosis in the

549   media) ultimately leading to weakening of the vessel wall and aneurysm formation [10].

550   Shared features between autoimmune conditions and HIV abnormal findings on vessel wall,

551   which may be found also in the absence of   an infectious cause, is of striking interest, and

552   it may suggest a   central role of lymphocyte physiology and its haltered homeostasis in

553   causing vascular damage, prior to the effects of antiretroviral treatment or of

554   opportunistic infection on the vessel wall. An abnormal low number of T regulatory cells

555   has been reported in HIV patients [32]. T regulatory cells are the counterpart of effector T

556   cells and play a major role in the regulation of memory immunity for antigen. Physiology

557   underlining T regulatory cells and their function in immune memory are still being defined,

558   but, in a totally speculative way, it is intriguing to hypothesize that some sort of

559   impairment of their function due to HIV infection, not restored by antiretroviral therapy and

560   immune reconstitution, could lead to an imbalance of effector memory and regulatory

561   memory finally leading to the observed unregulated chronic inflammatory burden that

562   occurs also in the absence of active infectious conditions in HIV.

563   Coming back to carotid aneurysms, considerations on HAART treatment can be added. HAART

564   may have different effects on vessels , and understanding it's role in vascular pathology in

565   HIV patients is a challenging issue. Interestingly, aneurysm resolution with pharmacologic

566 therapy has been described in a case of a 12 year old female patient with perinatal

567 acquired HIV, presenting with generalized headache, transient left hemiparesis and decreased

568 visual acuity in the left eye. Aneurysm involved the intracerebral portion of the right internal

569 carotid artery and was associated with intracranial arteritis and total obstruction of

570 contralateral internal carotid artery. Because of low risk of rupture, the patient was treated

571 with aspirin (325 mg/day), to decrease the risk of infarction due to the vascular inflammatory

572 response, and antiretroviral therapy. A favourable immunologic response and undetectable viral

573 load was found on follow up. Magnetic resonance imaging performed 15 months later

574 showed aneurysm resolution and no subsequent ischemic events; neurologic recovery was

575 complete [33]. One case of regression of aneurysm lesion has been reported also among

576 aortic aneurysms, analysed in our previous review [7]. In that specific case it was noticed

577 that because the patient's absolute CD4+ count remained above 500/µl and viral load remained

578 undetectable throughout the course of observation, the patient was in HAART previously to the

579 event, antiviral therapy may not be the only factor influencing changes in arterial wall [34].

580 On the contrary, the starting of HAART therapy was reported to anticipate aneurysm

581 occurrence in some cases. Bonkosky et al have reported the case of a 12 year old male

582 patient with perinatal acquired HIV , not compliant with treatment, in which internal carotid

583 aneurysms and recent signs of cerebral infarction were a result of immune reconstitution

584 syndrome, after starting HAART 10 days previously. Authors consider that immune

585 reconstitution arteriopathy contributes the complex to spectrum of arterial disease in HIV-

586 infected children and adults, suggesting the need for secondary prevention of stroke events in

587 cases of restored immunity complicating chronic endothelial infection [35].

588 Because carotid artery aneurysm are rarely reported in literature, no specific guidelines are

589 available for surgical treatment.

590 According to a retrospective review of 132 patients treated for extra-cranial carotid artery

591 aneurysm in Mayo clinic between 1998 and 2012, indications for intervention were based

592   on symptoms, suspected infection, increasing aneurysm size, location, morphology and

593   aetiology, without strict size cut-off. Differently from our findings in the HIV specific

594   setting, mean age of patients was higher, 61 years; 52% of patients were men, in 81 % of

595   cases internal carotid artery was involved, only in 8 cases aneurysm occurred in common

596   carotid artery. Aneurysms were symptomatic in 52% of cases while only in 2 of our cases

597   carotid finding was incidental; symptoms included painless mass, transient ischemic attacks,

598   vision symptoms ruptures, stroke [11].

599   Indications for treatment were in agreement with what reported above . In patients for

600   which indication for surgery was proposed (27 cases), options include both open (bypass

601   or ligature) or endovascular options (covered stent insertion or embolization) ; an hybrid

602   approach has been uses to resolve technical challenges in open surgery, as reported by

603   Pradachy , who has used angioplasty balloon to control the inflow in the proximal CCA while

604   repairing aneurysm with a prosthetic graft; the proximal extent of the aneurysm would have

605   otherwise necessitated a thoracotomy for proximal control [8].

606   Ligation has been proposed as an option wherever technical difficulty in reaching a satisfactory

607   site for a distal anastomosis occurred, in presence of a thrombosed artery or in case of

608   preoperative deterioration of patients clinical conditions, to minimize surgical time [8]. Ligation

609   was well tolerated; complications occurred in two cases: one patient had an haemorrhagic

610   stroke 3 days after procedure, while in the other case major stroke occurred during

611   reintervention for treatment of an endoleak after primary endovascular treatment of

612   common carotid aneurysm [8].

613   Morbidity for vascular interventions on carotid aneurysm in HIV resulted high (22.2%

614   morbidity and 7.4% mortality; both immediate and late complications for surgical

615   procedures were reported. Complications included post operatory fatal cardiac event, intra-

616   operatory or late carotid stent occlusion, the late one followed by mono-lateral blindness due

617   to thrombosis of ophthalmic artery , stent endo-leak from external carotid with

618 development of neck haematoma, stroke after carotid artery ligation performed as urgent

619 secondary procedure, and transitory nerve palsy.

620 Higher morbidity and mortality were reported for endovascular treatment , (57.1%

621 morbidity and 14.2 % mortality).

622 The reasons for the poor outcome after stenting are not known. It has been suggested that

623 clot embolization from the aneurysm may be one explanation; additionally it has been

624 observed that vasculitis involves the bifurcation and challenges the sealing at this area,

625 increasing likelihood of an endo-leak ; furthermore, because the artery is not biopsied, other

626 pathologies are missed which may contribute to the development of complications later on [8].

627 There have been no comparative studies, to date, on surgery versus endovascular intervention

628 in patients with HIV vasculopathy [36].

629 Finally, the exitus of one patient with common carotid artery aneurysm and compressive

630 symptoms, occurred in the ward from sudden airway obstruction while awaiting surgical

631 intervention [8] underlies the importance of prompt management of patients in which

632 these kink of lesions occur in this particular setting, because of the potential rapid and

633 life-threatening evolution of clinical picture.

634 Mortality reported for the 46 patients included in the study was 26.1%. Mortality cause

635 included post-operatory myocardial infarction, post operatory haemorrhagic infarction,

636 subarachnoid haemorrhage occurrence 3 weeks after hospitalization and medical treatment,

637 heart failure, infectious causes or AIDS related causes , seizures. As occurs in other

638 conditions such as autoimmune disease, the presence of a vascular lesion and not only

639 the severity of its presentation, may be linked with an increased mortality , reflecting a

640 more broad, advanced impairment of patients general conditions.

641 Data on follow up was not available for all reports, and in patients were no exitus was

642 reported, it ranged for 1 to 10 month in the majority of cases; Only one monocentric

643 experience, by Law Ye, reported a 17 years follow up for 2 intracranial aneurysms

644   pharmacologically treated with HAART. In one of the two cases, even though no

645   complication was reported for carotid aneurysm, the patient underwent a surgical

646   correction of a vertebral aneurysm causing compression to contiguous structures [21],

647   underlining the importance of long follow up in these patients, not only in the directly

648   involved arterial segment, but also in other branches that may be prone to developing

649   aneurysm conditions.

650

651   Conclusions : aneurysms may occur in both extra and intracranial carotid artery in patients

652   with HIV . Mean age of patients is lower than in non-HIV patients in witch carotid

653   aneurysm have been reported, and carry a high morbidity and mortality.

654   Because of associated medical and surgical comorbidities (coinfections, thrombophilia,

655   inflammatory burden, immunosuppression or associated aneurysm involving other districts)

656   management can be challenging, with high rate of surgical complications, higher for

657   endovascular treatment. Aneurysm lesions may occur in previously undiagnosed HIV patients,

658   and may require specific management such as integrating stroke prevention therapy,

659   antiretroviral management, assessment and treatment of infectious comorbid conditions

660   and a more frequent follow up.

661   HIV diagnosis must be suspected whenever this rare vascular condition may occur in the

662   absence of a more likely aetiological cause.

663   In patients with a known HIV a carotid artery aneurysm aetiology must be included in

664   differential diagnosis of compressive symptoms in the neck, neurological impairment or,

665   more specifically, in differential diagnosis of stroke.

666   Further studies are needed in this specific field of vascular surgery, to better understand

667   physiopathology behind this condition, improve treatment options and patients outcome.

668

669

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671

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Author Year	Ref	Age	Sex	Risk Factors	Years from diagnosis	CD4 + cells /mm3	Viral load copies/ml	Neurological symptoms/signs	*previous infections*, coltural investigations* surgical specimen	segment involved	other aneurysms	carotid treatment	surgical outcome	Mortality Follow-up
Sinzhobamvia 1989	[19]	24	M	Hypertension	new diagnosis	-	-	none	klebsiella (urine) bacillus sp (CVC); staphilococcus epidermidis	common carotid *saccular*	none	carotid-succlavian ptfe bypass	uneventfull	Alive No follow-up
		29	F	-	ns	-	-	none	pulmonary active tuberculosis	common carotid	abdominal aorta	pharmacological (tuberculosis treatment +steroids)	-	Alive No follow up
		47	M	Dilated cardiomiopathy; Congestive heart failure	ns	-	-	none	*syphilis.* staphilococcus epidermidis (blood)	common carotid *fusiform*	none	no surgery	-	exitus *heart failure (34 days after hospitalizaton)*
Destian 1994	[28]	38	M	-	ns	-	-	none	*mycobacterium avium cellulare(gastrointestinal); pneumonia (2 episodes) chronic sinus infection*micobacterium avium cellulare; anaerobic enterococcus; staphilococcus (aneurysm wall)	intracavernous carotid *lobulated*	-	carotid-ophtalmic saphenous vein bypass	transitory III nerve palsi; graft patency; no evidence of cerebral ischemia	Alive 6 weeks follow up
Shah 1996	[2]	12	F	-	from birth	-	-	seizures	-	internal cerebral carotid	cerebral arteries	no surgery	-	exitus *2 months after hospitalization, unknown cause*
Fulmer 1998	[13]	6	F	None	new diagnosis	-	-	subharacnoid haemorrhage; seizures; headache; III cranial nerve palsy; lethargy	varicella-zoster virus (vessels brain parenchyma)	internal cerebral carotid (bilateral) *fusiform*	cerebral arteries	no surgery (exitus)	-	exitus *subharachnoid hemorrhage*
Bonkowsky 2002	[35]	12	M	Mild obesity	from birth	257	<50	ischemic lesion;VII-XII cranial nerve palsie	*pneumocisti carinii (1998)* stereptococcus pneumoniae pneumonia (2000)	internal cerebral carotid	cerebral arteries	pharmacological (antiretroviral + aspirine)	-	Alive 12 months follow-up

Desai 2002	[27]	28	M	-	ns	-	-	vocal cord palsy	-	common carotid+jugular fistula	-	aneurysmectomy and fistula repair	uneventfull-voice hoarseness persistence	alive
Visrutaratna 2002	[14]	6	F	-	new diagnosis	-	-	seizures	Salmonella choleraesuis (blood)	intracavernous carotid *fusiform*	cerebral arteries	pharmacological (antibiotics)	-	exitus *respiratory crisis (4 months)*
Petropoulou 2003	[37]	12	M	None	ns	24	139	none	*candidiasis (oral ; esofagus) HBV; multiple pneumonia episodes; recurrent tonsillitis*	internal cerebral carotid *saccular*	cerebral arteries	pharmacological	-	Alive No follow-up
Crevits 2004	[18]	59	M	Dyslipidaemia; prior deep vein thrombosis	18	-	-	headache	*HBV;parotitis; HZV; herpes labialis; syphilis*	intracavernous carotid	none	pharmacological (aspirine)	-	Alive 6 weeks follow-up
Martinez Longoria 2004	[33]	12	F	None	from birth	-	-	headache; transient hemiparesis	*respiratory infections; varicella; gastroenteritidis*	internal cerebral carotid	cerebral arteries	pharmacological (aspirine)	-	Alive 24 months follow-up
Ake 2006	[24]	29	F	Hypertension	9	15	191.429	aphasia	*recurrent HZV; herpes simplex (anal)*	internal cerebral carotid	cerebral arteries	pharmacological (non compliant)	-	exitus *subharachnoid hemorrhage (3 weeks)*
Dhawan 2006	[15]	7	M	-	new diagnosis	-	advanced stage	subharacnoid haemorrhage; seizures	*abdominal TBC (4 y before)*	internal cerebral carotid	cerebral arteries	no treatment (exitus)	-	exitus *generalized seizures (12 hours)*
Tipping 2006	[9]	27	F	-	ns	-	-	ischemic lesions; hemiparesis	negative surgical specimen	internal cerebral carotid *fusiform*	none	no treatment (exitus)	-	exitus *bacterial pneumonia (25 days after hospitalization)*
Wang 2007	[38]	41	M	-	10	8	-	none	*opportunistic infections-pneumocistis mycobacterium avium complex (2 w before)* aspergillus fumigatus	intracavernous carotid proximal arterial stenosis *irregular shape*	-	endovascular embolization	uneventfull, no further epistaxis.	exitus *AIDS related (2 years)*

Pradachy 2009	[8]	33	M	none		904		hemiparesis	no growth in 11 patients;TBC in 2. Streptococcus Pneumoniae in 1 surgical report available for 14 patients; 11 no growth; 2 of the 6 positive histhology for TB were positive for TB; 1 streptococcus pneumoniae	common carotid artery or bifurcation *3 saccular aneurysms; 19 pseudoaneurysms*	in 4 cases: bilateral succlavian and vertebral artery (1) succlavian artery (1), controlateral carotid aretry (1) abdominal aorta (1)	bypass	1 death after evar for miocardial infarction 24 h after surgery; 1 carotid artery ligation had right middle c erebral arteryintracerebral hemorragic infarct day 3 (exitus) ; 1 aneventful stent occlusion; 1 stent endoleak with active bleeding at 4 month from surgery trated with cartid ligation, developed middle cerebral artery infarct with dense paraplegia (histology confirmed HIV vasculitis and active TB ; 1 stent thrombosed at 1 month (aneventful occlusion) but at 10 months after surgery came with blindness of one eye because of ophtalmic artery, managed with long term anticoagulation	3 cases of exitus*1 exitus for airway obstruction waiting for urgency treatment; 1 miocardial infartion 24 h after endovascular repair (covered stent); 1 fatal major stroke 3 days after carotid ligation* 1 to 10 months follow up, less that satisfactory for socio-economical reasons
		52	M	ex smoker		-		CN XII palsy				died waiting for surgery (sudden airway obstruction)		

	30	F	none		113		none				bypass
	34	F	none		190		CN XII palsy				bypass
	53	M	dibetes mellitus		220		none				bypass
	47	M	hypertension		339		none				ligation
	53	M	smoker		343		none				bypass
	27	M	prev tbm		74		none	TBC			ligation
	47	M	hypertension		219		RCL palsy				ligation
	30	F	ptb		355		none	TBC			ligation
	45	M	smoker		387		none				bypass
	27	M	none		-		CN XII palsy				bypass
	24	M	none		-		CN XII palsy				ligation
	56	M	none		211		none				ligation
	38	M	prev tpb smoker		193		CN XII palsy	TBC			ligation
	31	M	none		-		none				stent
	26	F	smoker		407		none				stent
	30	M	none		520		none				stent
	33	M	hypertension		-		CN IX + RCL palsy				stent

		24	M	none		316		none				stent		
		25	M	smoker		118		CN IX, X, XI, XII palsy				bypass		
		44	M	prev tpb		400		monoplegia	TBC			ligation		
Sastri 2011	[16]	13	M	None	ns	-	-	ischemic lesions; hemiplegia; aphasia	-	internal cerebral carotid fusiform	-	no surgery (extraventricular drainage)	-	exitus hydrocephalus (few hours)
Bakhaidar 2015	[39]	7	M	None	from birth	-	310798	subharacnoid haemorrhage; headache	pulmunary TBC (2 years before)	internal cerebral carotid fusiform	-	ICA/MCA reconstruction fenestrated aneurysm clips	uneventful	Alive No follow-up
Saraf 2017	[40]	43	M	-	2 months	-	-	none	miliary TBC (2 weeks before)	common carotid pseudoaneurysm	-	endovascular covered stent (Fluency)	uneventfull-patent stent, swelling reduction	Alive 2 months follow-up
Law-Ye 2018	[21]	29	F	-	7	90	48.925	status hepilepticus	Multimetameric herpes zooster; Pneumocystosis; Perianal condyloma; HCV	bilateral internal carotid artery; termination extending to anterior+middle cerebral arteries fusiform	ophtalmic; vertebral	pharmacological (HAART)	-	alive 17 years follow- up (surgery for vertebral aneurysm)
		23	F	-	5	205	28.548	headache	CMV retinitis; HIV meningoencephalitis	internal carotid termination to anterior + middle cerebral arteries fusiform	cerebral	pharmacological (HAART)	-	alive 17 years follow-up
		47	F	-	11	-	-	seizures, hemiparesis (left lenticular infarct)		internal carotid termination to anterior + middle cerebral arteries fusiform	cerebral	pharmacological (HAART)	-	alive 1 year follow-up
		25	F	-	from birth	3	190	none	Mouth and vaginal candidosis; Thoracic Pneumocystosis; CMV; colitis; toxoplasmosis; Esophagus candidosis H1N1 influenza; Haemophilus pneumopathy	internal carotid termination to anterior+middle cerebral arteries fusiform	cerebral	pharmacological (HAART)	-	lost to follow up

| | | 23 | F | Myocarditis + heart failure; Adrenal insufficiency; Interstitial pneumopathy | from birth | - | - | psychomotor retardation | *Tuberculosis; EBV; Mycotic esophagitis; Intercostal Herpes zoster* | internal carotid termination to anterior+middle cerebral arteries *fusiform* | cerebral | pharmacological (HAART) | - | alive 3 years follow up |

Table 1 Summary of cases. Data from Pradachy's case series have been given as a summary where no specific data for each patient was available (type of aneurysm, surgical intervention, outcome). Data of infectivology interest, as previous infections, coltural positivity during hospitalization (other that surgical specimen, and coltural positivity for surgical specimen have been distinguished in the same column using cursive (past infection) ; normal typing, for coltural samples, and underlined (surgical findings).

Anagraphic data		
Mean age	30.6±14.2	
	N cases (N tot=46)	**N cases (%)**
Male	30	65.2%
Female	16	34.8%
Cardiovascular risk factors		
None	14	30.4%
Smoke	6	13%
Hypertension	5	10.9%
Cardiac insufficiency	2	4.3%
Mild obesity	1	2.2%
Dyslipidaemia	1	2.2%
Diabetes	1	2.2 %
Deep venous thrombosis	1	2.2%
Not specified	13	28.3%
HIV specific details		
Timing from diagnosis		
▪ At birth (vertical transmission)	7	15.2
▪ New diagnosis (on admission)	26	56.5 (%)
▪ 2 months before vascular event	1	2.2 (%)
▪ More than 5 years	6	13 (%)
▪ Not specified	7	15.2 (%)
HIV status (CD4+ < 200)		
no	14	30.4 (%)
CD4+ < 200	10	21.7 (%)
Not specified	22	47.8 (%)
Previous other infections		
Tuberculosis	9	19.6 (%)
Herpes virus	6	13 (%)
Pneumocystis carinii	4	8.6 (%)
Syphilis − Negative (6) 13% − Positive (2) 4.3% − Not specified (38)	2	4.3(%)
HBV	2	4.3 (%)
HCV	1	2.2(%)
Positive microbiological culture (samples other than surgical)		
Positive microbiological culture (samples other than surgical) − Salmonella choleraesuis (blood) (1) − klebsiella (urine) bacillus sp (CVC) (1) − tuberculosis (5) − staphilococcus epidermidis (blood) (1)	8	17.4 (%)

Table 2. 1 Summary of data from cases included in review.

Carotid aneurysm pathology details n patients ; n (%) N tot = 46	n patients	n% (N tot = 46)
Carotid aneurysm location		
Intracranic	19	41.3 (%)
Extracranic	27	58(%)
Aneurysm type		
Fusiform	11	23.9 (%)
Saccular, lobulated, irregular	7	15.4(%)
Pseudoaneurysm	20	44 (%)
Not specified	8	17.4 (%)
Associated aneurysm in other districts		
Cerebral arteries	12	48 (%)
Abdominal aorta	2	4.3(%)
Ophthalmic	1	2.2 (%)
Contralateral carotid	1	2.2 (%)
Vertebral	2	4.3 (%)
Succlavian (in 1 of 2 cases bilateral)	2	4.3 (%)
None	22	47.8 (%)
Present	18	39.1 (%)
Not specified	6	13 (%)
Signs and symptoms		
Painful cervical mass	24	52.2%
Dysphonia	5	10.9 (%)
Dysphagia	3	6.5 (%)
Fever	2	4.3 (%)
Epistaxis	2	4.3 (%)
Asyntomatic	2	4.3 (%)
Visual impairment	1	2.2(%)
Neurological signs/symptoms		
Positive for neurological symptoms	26	56.5 (%)
Neurologically negative	20	43.4 (%)
Specific neurological symptom/sign		
Cranial nerve palsies	11	23.9 (%)
Hemiparesis, hemiplegia, monoplegia	7	15.2 (%)
Headache	6	13 (%)
Consciousness impairment	6	13 (%)
Seizures	5	10.9 (%)
Ischemic lesions	5	10.9 (%)
Subarachnoid haemorrhage	3	6.5 (%)
Aphasia	2	4.3 (%)

Table 2.2 Summary of data from cases included in review. Carotid aneurysm pathology details.

Carotid aneurysm management		
Surgical	27	58.7(%)
Pharmacological	12	26.1 (%)
No treatment	7	15.2 (%)
Open/endovascular approach (of 27 surgically managed patients)		
Open	20	74 (%)
Endovascular	7	25.9 (%)
Overall surgical morbidity	6	22.2 (%)
Overall surgical mortality	2	7.4 (%)
Surgical procedure and complications		
Open surgery	20	74%
Reconstruction	12	44.4%
Ligation	8	29.3%
Morbidity for open procedures	2	10%
Mortality for open procedures	1	5%
Reported complications for surgical procedures	− Transitory III nerve palsy (carotid ophthalmic bypass) − 1 middle cerebral a. haemorrhagic infarct (3days after ligation)	
Endovascular procedures	**7**	**25.9 %**
Endovascular covered stent	6	22.2 %
Endovascular embolization	1	3.7%
Morbidity for endovascular treatment	4	57.1%
Mortality for endovascular treatment	1	14.2 %
Reported complications	− 1 myocardial infarction (fatal) 24h p.o − 1 early stent occlusion (uneventful) − 1 stent occlusion (1 month) initially uneventful but at 10 month ophthalmic a.thrombosis − 1 stent endo-leak with active bleeding (4 months).Carotid ligation → middle cerebral artery infarct with dense paraplegia	
Surgical specimen or autoptic microbiological data (18 samples)		
Positive colutural surgical specimen − Aspergillus fumigatus (1) − Mycobacterium avium cellular (3) − Enterococcus (1) − Staphylococcus (1) − Streptococcus pneumonia (1) − varicella-zoster virus (vessels and smaller vessels brain parenchyma) (1)	6	33.3%
Negative	12	66.6%
Mortality		
Alive	33	71.7 (%)
Exitus	12	26.1 (%)
Lost to follow up	1	2.2 (%)
Causes of death		
Postoperatory myocardial infarction	1	
Post operatory middle cerebral artery haemorragic infarct	1	
Subarachnoid haemorrhage (3 weeks in 1 case)	2	8 (%)
Heart failure (34 days)	1	4 (%)
AIDS related causes (2 years)	1	4 (%)
Bacterial pneumonia (25 days)	1	4 (%)
Dyspnoea and cough (4 months)	1	4 (%)
Generalized seizures (12 hours)	1	4 (%)
Hydrocephalus (few hours)	1	4 (%)
Non specified (at 2 months)	2	8 (%)

Table 2.3 Summary of cases included in review. Surgical details and outcome.

Anagraphic data	Common C.A	%	Intracranial C.A	%	p
N patients	N= 27	%	N=19	%	
Mean age	36.3 ±10.5		22.5±15.2		<0.001
Sex					**<0.005**
Male	22	81.5%	8	42.1%	
Female	5	18.5%	11	57.9%	
Pediatric age (< 18 y)	0	**0%**	**9**		**P<0.004**
Adult age (≥18y)	**27**	**100%**	**10**		
HIV specific details					
Timing from diagnosis					**P<0.001**
▪ At birth (vertical transmission)	1	3.7%	6	31.6%	
▪ New diagnosis (on admission, 1 case 2 months previously to carotid diagnosis)	23	85.2%	3	15.8%	
▪ More than 5 years	0	0%	6	31.6%	
▪ Not specified	3	11.1%	4	21.1%	
Previous other infections					**P<0.2**
Tuberculosis	4	14.8%	5	26.3%	
Neurological symptoms/signs					**P<0.2**
None	15	55.6%	4	21.1%	
Positive	12	44.4%	15	78.9%	
Cranial nerve palsies	9	33.3%	2	10.5%	P<0.07
Hemiplegia mono-paresis monoplegia	2	7.4%	5	26.3%	P<0.08
Ischemic lesions	1	3.7%	4	21.1%	P<0.06
Aneurysm type					**P<0.001**
▪ saccular/irregular /pseudo	24	88.9%	3	15.8%	
▪ fusiform	1	3.7%	10	52.6%	
▪ Missing	2	7.4%	6	31.6%	
Aneurysms in other branches					**P<0.001**
None	20	74.1%	2	10.5%	
Present	5	18.5%	13	68.4%	
Not specified	2	7.4%	4	21.1%	
Treatment details					**P<0.001**
No treatment	2	7.4%	5	26.3%	
Morbidity or mortality in patients in unspecified or no treatment	– 47 y, Common aneurysm pulsatile cervical mass, Congestive Heart failure 34 days – 52 y, Common carotid- fatal airway obstruction waiting for surgery		– 12 y, fusiform intracranial aneurysm, seizures +hemiplegia– exitus 2 months for unspecified cause – 6 y, subarachnoid haemorrhage on bilateral fusiform intracranial aneurysm – 7y, generalized seizures- 12 h after hospitalization – 27y, fusiform intracranial Ischemic lesions+ hemiparesis, died after 25 days for pneumonia – 13 y hemiparesis and ischemic stroke –exitus due to hydrocephalus in few hours		
Pharmacological	1	3.7%	11	57.9%	
			– 6 y, intra-cavernous with seizures-antibiotics for salmonellae – 29y, intracranial , subarachnoid haemorrhage 3 weeks , not compliant with HAART		
Surgical reconstruction	10	37%	2	10.5%	
			1 III n palsy after carotid ophthalmic graft		
Surgical ligation	8	29.6%	0	0	
	– Fatal major stroke 3 days after carotid ligation				
Endovascular	6	22.2%	1	5.3%	
	– 1 case uneventful stent occlusion – 1 case stent occlusion at 1 month+ ophthalmic a. thrombosis+ blindness 10 month later – 1 stent endo-leak with active bleeding at 4 month from carotid artery ligation , developed middle cerebral artery infarct + paraplegia – EVAR Myocardial infarction 24 h		– 41 y, intra-cavernous aneurysm embolization+ epistaxis;exitus for AIDS related cause 2 years later		
Mortality					**P<0.02**
Alive	23	85.2%	10	52.6%	
Exitus	4	14.8%	8	42.1%	
Lost to follow up	0	0%	1	5.3%	

Table 2.4 common carotid artery aneurysm vs intracranial lesions : comparison of anagraphic data , presentation features, treatment and outcome statistically significant difference.