Prognosis on recurrent stroke, functional outcome, and mortality : a comparative study of ischemic stroke subtypes

SUMMARY

In the *introduction* we discussed the importance of valid prognostic data for individual patient management. One of the aims of the study was to provide arguments to sustain the idea that separate ischemic stroke subtypes must be distinguished because of assumed, inherently differences in prognosis. Such distinctions could also be relevant for future study of possible genetic and molecular biological determinants of different types of underlying vascular pathology in stroke. Another goal was to try and distinguish separate clinical entities within the lacunar stroke type. Defining the clinical phenotype of a certain stroke subtype more accurately may facilitate future research into its vascular pathology.

In *chapter 2*, we described the Maastricht Stroke Databank (MSR), and the definitions and methods we used. This registry included 998 patients between july 1987 and march 1992 with a first ever ischemic brain infarction. Last follow-up was completed in may 1995. All patients were included prospectively and consecutively, including outpatients. Cerebral CT scanning was performed in 96 percent of all patients, and in 61 percent of all recurrent strokes. We are not aware of any other stroke registry that reported CT scan data in such rather high proportion in stroke recurrence following a first-ever brain infarct. In this chapter, we presented the baseline characteristics for the whole group, and data for mortality and stroke recurrence at 30 days, one year, and at the end of follow-up. Furthermore, we presented data on disability at stroke onset and at the end of the study.
This hospital based registry, with inclusion of outpatients, thus provided the opportunity to study an unselected series of patients, with every patient seen by a neurologist, and with most of them having a large array of ancillary investigations, whereas no patient was lost to our cross-sectional follow-up. Case ascertainment, therefore, especially in regard to subtype diagnosis and stroke recurrences, may have been more valid in this study than in other stroke registries.

In *chapter 3*, we compared the baseline characteristics of the Maastricht Stroke Registry with other, mostly Western registries. For reasons of comparison, we recalculated the data on distribution of ischemic subtypes in the other registries, as most of these were originally given as part of the whole stroke spectrum including PICH, SAB, and TIA. We found that our data on mortality and stroke recurrence, for both the whole group and the ischemic subtypes, were very

similar to those in the literature. This was an argument for the internal consistency and validity of our data.

In *chapter 4*, we presented data on mortality after first ischemic stroke, and the influence of different risk factors (predictors). We calculated mortality rates for 30 days, one year, and for the end of follow-up. To identify independent predictors, we used both logistic regression analysis and time dependent Cox analysis. Mortality was highest in the CE type and lowest in the LACI type at all points of measurement. Mortality was highest in the first year, and especially in the first month after stroke, for AT and CE. Kaplan-Meier analysis with log rank testing for significance showed a significant difference between the three stroke subtypes. In all patients, DM, high age, stroke subtype, and stroke severity were predictors for early mortality, whereas recurrent stroke just missed statistical significance. In LACI, DM and stroke severity were independent predictors. In AT, DM, high age, recurrent stroke, and stroke severity were predictors, while in CE high age and stroke severity were the only predictors for early mortality. Logistic regression analysis for one year mortality detected DM, IHD, high age, stroke subtype, stroke recurrence, and COPD as predictors, whereas ipsilateral carotid artery stenosis just missed statistical significance. In LACI, higher age and stroke recurrence were predictors, with hypertension just missing statistical significance. In AT, DM, high age, recurrent stroke, stroke severity and ICA stenosis were independent predictors of one year mortality, while in CE high age and stroke severity were predictors with DM just missing significance. In the time dependent analyses, stroke recurrence lost its significance in all types. In LACI, it added COPD as predictor. In AT, carotid stenosis lost significance. In CE, DM and COPD were added as predictors. So, in LACI, stroke severity was only a predictor of early mortality, whereas in AT and CE it remained an independent predictor over time. Recurrent stroke was an independent predictor of especially one year mortality in LACI and AT, but not in CE. DM was a significant predictor in AT but not in LACI, whereas its significance increased over time in CE. Our data indicate that a cerebral infarct significantly lowers life expectancy, not only early after stroke, but likely for the remaining survival period following stroke. Mortality rates and independent predictors of mortality vary significantly between ischemic stroke subtypes. This may reflect the difference in their underlying pathology, a difference that is consistent over time.

In *chapter 5*, we presented our data concerning stroke recurrence after first cerebral infarction, with the influence of different risk factors (predictors). There were no statistically significant differences in stroke recurrence rates between stroke subtypes at 30 days, one year, or at the end of follow-up. Log rank testing of survival free of recurrent stroke showed a difference between CE and both AT and LACI, but no difference between AT and LACI. The recurrence rates were higher in the first year, and especially in the first month for AT and CE. For LACI however, we found a more evenly distributed recurrence rate in time. Logistic regression analysis detected IHD and COPD as significant predictors in the whole group for early recurrence. When we analyzed the three subtypes separately, various point estimates indicated increased risk of recurrent stroke, but these were not statistically significant, probably due to the small numbers of events involved. At one year, IHD and COPD were independent predictors in the whole group. In the subtypes, DM was a strong predictor in LACI and CE. Time dependent analyses in the whole group showed DM, IHD, COPD and LA as independent predictors. In LACI, DM, asymptomatic lacunar lesions on CT, and LA were significant predictors. For the AT type, IHD, COPD, and an ipsilateral carotid artery stenosis were predictors, whereas in CE only DM was a predictor. The association of ASLA and LA in lacunar stroke points to a kind of coherence in underlying vascular pathophysiology, which is small vessel disease in most lacunar patients.

In *chapter 6* we investigated functional outcome after stroke, using the modified Rankin scale. At the end of the follow-up period, significantly more patients in the LACI type were functionally independent, compared to both AT and CE. There was no significant difference however between AT and CE. In stroke survivors, higher age, stroke subtype, degree of neurological deficit at first stroke, ASLA, LA, and stroke recurrence were independent predictors of unfavourable functional outcome. More severe neurological deficit was the most powerful predictor of unfavourable outcome, and lacunar stroke subtype the most powerful predictor of favourable functional outcome. In LACI, high age, stroke severity, and recurrent stroke were independent powerful predictors of unfavourable outcome. In AT, high age, severity, and recurrence predicted unfavourable outcome, and in CE: initial severity and ASLA. The classical vascular risk factors had hardly any effect on functional outcome. Therefore, unfavourable

functional outcome in stroke survivors is not very likely influenced by treatment of these classical risk factors. Attempts to lower the initial degree of stroke severity seem more promising in this respect.

In *chapter* 7, we explored the relationships between subtype and location of first brain infarction on one hand, and subtype of recurrent stroke (including PICH), and location of recurrent stroke on the other hand. We found that 57% of LACI, 83% of AT, and 94% of CE (as recurrent strokes) were of the same type as the first stroke. Of "true to type" lacunar recurrences, 70% occurred in the same brain territory as the first stroke. For "true to type" AT recurrences, this percentage was 79%. However, in CE only 39% of "true to type" recurrences were in the same brain territory as the first stroke. First stroke subtype was an independent predictor of lacunar versus nonlacunar recurrent stroke subtype. Hypertension also predicted a lacunar type recurrence. In the same way, first AT type predicted an AT recurrence, but here however, hypertension was inversely related to AT stroke subtype recurrence. So, in this chapter we found further evidence for the existence of pathophysiologically different vasculopathies underlying different brain infarction subtypes, as stroke subtype manifestation, measured by recurrent stroke subtype, and the area of recurrent stroke occurrence, were consistent over time.

In *chapter 8*, we provided further evidence for the existence of two separate subtypes of lacunar stroke: LACI with asymptomatic lacunar lesions on CT versus LACI without such lesions (LACI+ versus LACI -). As for baseline characteristics, LA was significantly more frequent among LACI+. The LACI+ type also had a significantly higher mortality rate and a significantly higher recurrence rate at the end of the follow-up period. LACI+ versus LACI- was an independent predictor for stroke recurrence, but not for mortality. LACI+ survivors had worse functional outcome, but not statistically significant so. Prognosis for major handicap or death however was significantly worse for LACI+. LACI+ versus LACI- however, was not an independent predictor for unfavourable functional outcome (or unfavourable functional outcome or death), despite the numerically strong association. When we restricted the analysis to lacunar patients with both ASLA and LA, hypertension was a significant predictor for the +/+ versus $^{-}/^{-}$ type. Furthermore, five of the six PICH recurrences occurred in

the LACI+/+ type, being almost one third of all recurrences in this subgroup. Time interval between index and recurrent stroke was shorter in the LACI −/− group. Our findings support the existence of two lacunar entities, with different underlying risk factors, association with LA, and prognosis for mortality, (type of) recurrence, functional outcome and underlying vasculopathy: small vessel atheromatosis in patients with a single symptomatic lacunar stroke, and arteriolosclerosis in those with one or more silent lacunar lesions.

SAMENVATTING

De hypothese dat de gebruikelijke indeling van ischemische herseninfarcten, als deze is gebaseerd op verschillen in onderliggende vasculaire pathofysiologie, ook tot uiting zou moeten komen in de prognose van patiënten met een herseninfarct, lag ten grondslag aan de onderzoeken in dit proefschrift. Een tweede doel was het leveren van aanvullend bewijs voor het bestaan van een onderverdeling binnen het lacunaire herseninfarct: patiënten met een of meerdere asymptomatische lacunaire laesies, tegenover patiënten zonder een dergelijke laesie. Vanuit dit perspectief onderzochten we het optreden van eventuele recidief herseninfarcten of hersenbloedingen, functionele uitkomst en sterfte in een groep van 998 patiënten met een eerste herseninfarct, geregistreerd in de Maastricht Stroke Registry.

We vonden een grote mate van overeenkomst tussen het subtype van het eerste herseninfarct en een tweede beroerte, infarct of bloeding. Dit wijst in de richting van een consistentie in onderliggende vaat pathologie in de tijd in de onderscheiden typen herseninfarcten: lacunaire, atherothrombotische en cardioembole infarcten. Deze verschillende vormen van vaat pathologie sluiten elkaar echter niet uit, en meer dan één type vaat pathologie kan bij een individuele patiënt voorkomen. Recidief beroertes komen significant meer voor bij cardioembole dan bij lacunaire of atherothrombotische herseninfarcten. Er bestaat een vroege clustering van recidief beroertes in atherothrombotische en cardioembole herseninfarcten, passend bij de theorie van een in de tijd geclusterde embolische aktiviteit van een ziek groot vat of van een cardiale emboliebron. Bovendien komen recidieven bij lacunaire en atherothrombotische infarcten vooral voor in hetzelfde hersengebied als het eerste infarct, in tegenstelling tot recidieven bij cardioembole infarcten. Opvallenderwijs vonden we chronisch obstructieve longziekten als onafhankelijke predictor van recidief beroerten, mogelijk als arrhytmogene bijwerking van vaak bij deze patiënten gebruikte medicatie, of als gevolg van de bij deze patiënten vaak optredende infecties.

Ten aanzien van sterfte hadden lacunaire infarcten een betere prognose dan de beide andere typen. De atherothrombotische infarcten hadden een betere prognose dan de cardioembole. Het subtype van een eerste herseninfarct, en de mate van initiële neurologische uitvalsverschijnselen waren de krachtigste voorspellers van sterfte. Uit deze onderzoeken volgt dat de beste manier om de sterfte na een eerste herseninfarct terug te dringen, bestaat uit het verminderen van de initiele

uitvalsverschijnselen. Methoden om dit te bereiken zijn opname op een stroke unit, thrombolyse, en mogelijk in de toekomst neuroprotectie.
Patiënten met een lacunair herseninfarct hadden ook de beste prognose voor de uiteindelijke mate van functionele onafhankelijkheid. Ook in dit opzicht bleken de initiële mate van uitvalsverschijnselen en het infarct subtype de krachtigste voorspellers. De klassieke vasculaire risicofactoren bleken nauwelijks enig effect op de uiteindelijke mate van invaliditeit te hebben.
Binnen het lacunaire subtype hadden de patiënten met een of meer asymptomatische lacunaire laesies de slechtste prognose voor sterfte, recidief beroerte en functionele uitkomst. Bovendien bleek een grote meerderheid van de recidief hersenbloedingen in deze groep patiënten voor te komen, wijzend op een specifieke onderliggende aandoening van de kleine hersenvaten (arteriolosclerosis of lipohyalinosis), in tegenstelling tot microatheromatose bij patienten zonder asymptomatische lacunaire infarcten.
Concluderend hebben onze studies nieuwe argumenten gevonden voor het bestaan van verschillende typen herseninfarcten met verschillende onderliggende vasculaire pathofysiologie, en een hierop berustende verschillende prognose ten aanzien van het tijdstip van voorkomen en het type van recidieven, functionele uitkomst en sterfte.
Bovendien vonden we nieuwe argumenten voor het bestaan van een onderverdeling in de lacunaire herseninfarcten.