Hacking stroke in women: towards aetiology-driven precision prevention

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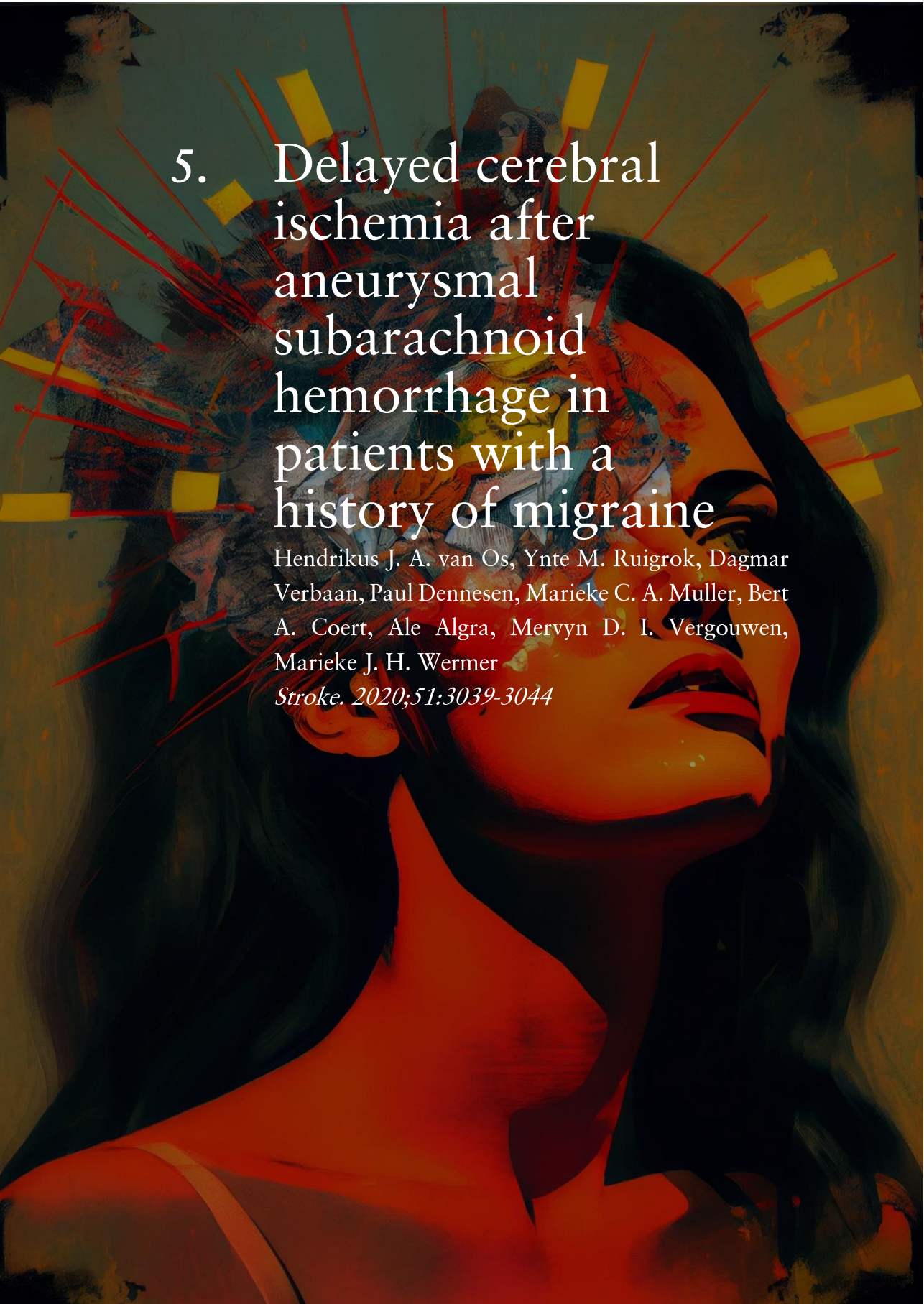

5. Delayed cerebral ischemia after aneurysmal subarachnoid hemorrhage in patients with a history of migraine

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Abstract

Background and purpose: Delayed cerebral ischemia (DCI) is a major contributor to the high morbidity in patients with aneurysmal subarachnoid hemorrhage (aSAH). Spreading depolarizations may play a role in DCI pathophysiology. Since migraine patients are probably more susceptible to spreading depolarizations, we investigated whether aSAH patients with migraine are at increased risk for DCI.

Methods: We included aSAH patients from three hospitals in the Netherlands. We assessed life-time migraine history with a short screener. DCI was defined as neurological deterioration lasting >1 hour not attributable to other causes by diagnostic work-up. Adjustments were made for possible confounders in multivariable Cox regression analyses and adjusted hazard ratios (aHR) were calculated. We assessed the interaction effects of age and sex.

Results: We included 582 aSAH patients (mean age 57 years, 71% women) of whom 108 (19%) had a history of migraine (57 with aura). Patients with migraine were not at increased risk of developing DCI compared to patients without migraine (22% versus 24%, aHR: 0.89; 95% CI: 0.56–1.43). Additionally, no increased risk was found in migraine patients with possible aura (aHR: 0.74; 95% CI: 0.39–1.43), in women (aHR: 0.88; 95% CI: 0.53–1.45, $p_{interaction}$=0.859), or in young patients <50 years (aHR: 1.59; 95% CI: 0.72–3.49), although numbers in these subgroups were limited. We found an interaction between migraine and age with an increased risk of DCI among young migraine patients ($p_{interaction}$=0.075).

Conclusion: Patients with migraine are in general not at increased risk of DCI. Future studies should focus in particular on young SAH patients, in whom there might be an association between migraine history and development of DCI.

Introduction

Subarachnoid hemorrhage from a ruptured aneurysm (aSAH) results in death within three months of around one third of all patients, and more than half of all survivors make an incomplete recovery.[1] A major contributor to the high morbidity in patients who survive is delayed cerebral ischemia (DCI). DCI occurs in around 30% of SAH patients, mostly between day 4 and 10 after hemorrhage onset.[2] The mechanisms underlying DCI are still largely unknown. Several animal experiments suggest that spreading depolarisations (SDs) play a role in development of DCI, possibly induced by products of hemolysis.[3-6] SDs are the underlying mechanism of a migraine aura and are characterized by slowly spreading waves of intense neuroglial depolarizations followed by silencing of brain activity.[7, 8] Hemodynamically, SDs start with a short hyperemia which is followed by a prolonged period of oligemia.[9] In one study repetitively induced SDs resulted in neuronal death in the juvenile SAH rat brain, suggesting that spreading oligemia following SDs can in certain circumstances progress to tissue ischemia.[10] Additionally, valproate - which is an SD inhibitor - prevented SD related delayed brain injury in rats after experimental SAH.[11] In a small pilot study of aSAH patients with the aneurysms treated by clipping, SDs have been recorded directly with electrocorticography, and SD patterns seemed to be related to DCI development.[12, 13] Migraine with aura (MA) increases the risk of ischemic and hemorrhagic stroke approximately two-fold, especially in women.[14-16] This increased risk of ischemic stroke may be partly mediated by increased susceptibility to SDs.[7] One case-control study suggested that women with migraine might have an increased risk of developing DCI after aSAH compared with women without migraine. However, sample size was however limited and only women were included.[5]

In this study we investigated in a large prospectively collected cohort of aSAH patients whether patients with migraine are at increased risk of developing DCI compared with patients without migraine.

Methods

Patients

We included patients from two University hospitals (the University Medical Center Utrecht [UMCU] and the Amsterdam University Medical Center, University of Amsterdam [Amsterdam UMC]) and one large teaching hospital (Haaglanden Medical Center [HMC). In the UMCU, we included consecutive patients admitted for aSAH in the period from 2008 to 2018. In the Amsterdam UMC and UMCU, we included patients of the control arm of the ultra-early tranexamic acid after subarachnoid hemorrhage (ULTRA) study. The ULTRA study is a multicenter

prospective randomized open-label trial that investigates the effect of tranexamic acid on occurrence of rebleeds after SAH.[17] The ULTRA participants in our study did not receive the study medication and were included between 2011 and 2018. In the HMC, we consecutively included patients admitted for aSAH from 2014 to 2016. In all centers the following baseline characteristics were collected during admission: modified Rankin Scale (mRS) score before admission, age, sex, cardiovascular risk factors, history of cardiovascular disease, Glasgow Coma Score (GCS) at admission, location of aneurysm, and aneurysm treatment modality. Outcome was assessed via mRS score at discharge and after three (UMCU and HMC) or six months (Amsterdam UMC).

Standard protocol approvals, registrations, and patient consents

In the UMCU, data for this study were collected within the context of the String of Pearls study. This study was approved by the Medical Ethical Committee, and informed consent was obtained from all patients for use of the data. In the Amsterdam UMC and the HMC data were collected in the context of the NIASH registration. Medical ethical approval was not required for this registration.

Migraine questionnaire

In all three participating centers research nurses recorded a migraine screener.[18] From this screener the following questions were used for this study: 1. 'Did you ever or do you still have migraine attacks?' 2. 'Did you ever suffer from attacks of severe headache that lasted several hours to days during which you had very low tolerance of light and noise?' 3. 'Did you ever experience periods that lasted between 5 to 60 minutes during which your sight was diminished or blurry at one side with possible flashes or glitters in the visual field, followed by headache?' A history of migraine was considered to be present when answers to both question 1 and 2 were positive. If answers to all three questions were positive, patients were classified as having migraine with possible aura. The migraine screener has been validated previously in a stroke population. For the combination of questions we used in our study, the positive predictive value for migraine was 0.78, and the negative predictive value was 0.97. For migraine with aura, the negative predictive value was 0.97 and the positive predictive value was 0.38.[18]

Assessment of delayed cerebral ischemia

DCI was defined as the occurrence of focal neurological impairment (such as hemiparesis, aphasia, apraxia, hemianopia, or neglect) or a decrease of at least 2 points on the Glasgow Coma Scale. The symptoms had to last for at least 1 hour,

were not present immediately after aneurysm occlusion, and could not be attributed to other causes after clinical assessment, CT or MRI scanning of the brain, and appropriate laboratory studies. DCI was assessed during hospitalization.[19]

Sample size calculation

To calculate the sample size needed we choose an alpha of 5% and a power of 80%. We expected DCI to occur in around 30% of unexposed patients.[2] Migraine prevalence was found to be around 17% in patients with aneurysmal SAH,[20] and one third of migraine patients were expected to have migraine with aura.[21] For our calculation we used the odds ratio from a previous observational study investigating the risk of developing DCI in migraine patients versus those without (OR: 2.68).[5] Based on these parameters a total sample size of 228 patients was needed to detect an association with overall migraine, and 551 to detect an association with migraine with aura.[22]

Statistical analysis

Because the development of DCI is time dependent we performed a survival analysis to investigate whether migraine (with and without possible aura combined or with possible aura only) is associated with occurrence of DCI. Adjustments were made for possible confounders (age, sex, GCS at admission) in a multivariable Cox regression analysis, and hazard ratios (HR) and adjusted HR (aHR) with 95% confidence intervals (CI) were calculated. Since migraine is more often active in young patients and in women, we stratified for age < 50 years and sex and we included the interaction terms age*migraine and sex*migraine in the analyses.[21] Statistical testing for interactions was done using an a-priori α=0.10. In addition, we constructed a Kaplan-Meier curve showing DCI-free survival of patients with and without a history of migraine. We calculated adjusted relative risks (aRR) for outcome with Poisson regression.

Results

In total, 879 patients were eligible for the study. Of these patients, 582 had complete data on both migraine and DCI and were included. Baseline characteristics of excluded patients were comparable with those of included patients (data not shown). Mean age of the included patients was 57 ± 13 (SD) years and 415 (71%) were women (Table 1). A history of migraine was reported in 108 (19%) patients, and 57 (10%) patients had migraine with possible aura. Patients with migraine were more often female. Clinical outcome at three months was available for 294 of 382 patients (77%) from the UMCU and HMC, and clinical outcome at six months for 185 of 200 patients (93%) from the Amsterdam UMC.

Delayed cerebral ischemia

Patients with a history of migraine were not at increased risk for developing DCI compared to patients without migraine (22% versus 24%, aHR: 0.88; 95% CI:0.53–1.45). In addition, no increased DCI risk was found in migraine patients with possible aura compared to SAH patients without migraine (20% versus 24%, aHR: 0.74; 95% CI: 0.39–1.43). After stratification for sex, we did not find an association between migraine and DCI development in women (aHR: 0.88; 95% CI: 0.53–1.45), and interaction between migraine and sex was not statistically significant ($p_{interaction} = 0.859$).

Table 1. Baseline characteristics of the participants

Characteristics	Migraine (n=108)	Migraine with aura (n=57)	No migraine (n=474)
Demographics			
Age, *mean years ± SD*	56 ± 12	58 ± 13	58 ± 13
Women, *n (%)*	90 (83%)	49 (86%)	325 (69%)
History, *n (%)*			
Hypertension	42 (40%)	22 (39%)	185 (40%)
Diabetes mellitus	4 (4%)	3 (5%)	20 (4%)
Hyperlipidemia	20 (19%)	14 (25%)	87 (19%)
Cardiovascular disease*	10 (9%)	6 (11%)	56 (12%)
SAH	4 (4%)	2 (4%)	13 (2%)
SAH in family history	2 (4%)	2 (6%)	5 (3%)
Intracranial hemorrhage	1 (1%)	0 (0%)	3 (1%)
Smoking: current**	54 (52%)	12 (20%)	217 (48%)
Smoking: past**	20 (19%)	30 (51%)	100 (22%)
Alcohol use**	51 (49%)	30 (55%)	277 (62%)
Medication on admission, *n (%)***			
Oral anticoagulation use	1 (2%)	1 (3%)	12 (5%)
Oral contraceptive use	7 (14%)	3 (10%)	17 (11%)
Platelet aggregation inhibitor use	9 (15%)	6 (16%)	29 (12%)
GCS at admission *(IQ range)*	15 (13 - 15)	15 (13-15)	15 (13-15)
GCS at admission < 13, *n (%)*	17 (18%)	7 (13%)	102 (23%)

**History of ischemic stroke, myocardial infarction and/or peripheral artery disease*
***Current smoking: within 6 months before admission; past smoking: quit smoking more than 6 months before admission; alcohol use: any use of alcohol*
****Medication at admission was assessed in the UMCU and the HMC only*

After stratification for age, we also did not find an association between migraine and DCI development in patients <50 years (aHR: 1.59; 95% CI: 0.72–3.49). However, the point estimate of the association changed from 0.70 in patients ≥50 to 1.59 in patients <50 years old, and we found an interaction between migraine and age ($p_{interaction}$ = 0.075). (Table 2) The Kaplan-Meier curve (Figure 1) showed no difference in time to DCI between patients with and without a history of migraine (Log Rank test p = 0.474).

Clinical outcome was comparable between patients with and without a history of migraine. At 3-month follow-up after SAH 83% patients with migraine versus 74% of patients without migraine had an mRS ≤ 2 (aRR: 1.02; 95% CI: 0.90–1.17; data from UMCU, HMC), and at 6-month follow-up 68% patients with migraine versus 79% patients without migraine had an mRS ≤ 2 (aRR: 0.82; 95% CI: 0.65–1.05; data from Amsterdam UMC).

Figure 1. DCI rate over time in patients with and without migraine

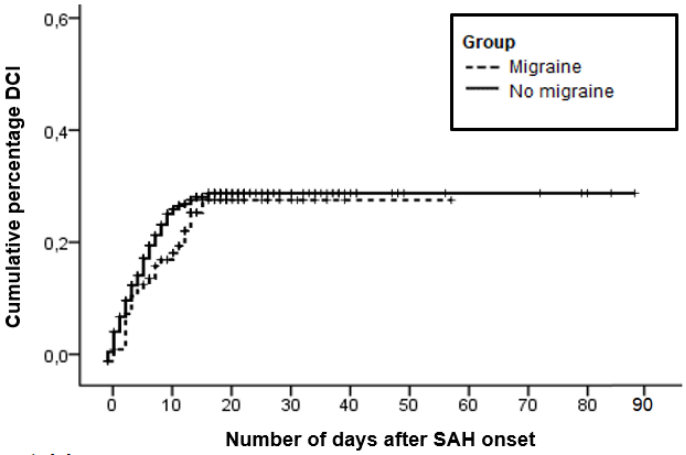

Table 2. Risk for delayed cerebral ischemia in patients with and without migraine, stratified by age and sex

Presence of DCI (n/N (%))	Migraine	MA	No migraine	Migraine vs. no migraine aHR (95% CI)	MA vs. no migraine aHR (95% CI)
All patients (n=582)	24/108 (22%)	11/55 (20%)	115/474 (24%)	0.89 (0.56–1.43)[1]	0.74 (0.39–1.43)[1]
Women (n=415)*	21/90 (23%)	10/47 (21%)	86/325 (27%)	0.88 (0.53–1.45)[2]	0.73 (0.37–1.46)[2]
Men (n=167)	3/18 (17%)	1/8 (13%)	29/149 (20%)	1.00 (0.30–3.36)[2]	0.81 (0.11–6.03)[2]
Age <50 years (n=151)	10/31 (32%)	4/13 (31%)	24/120 (20%)	1.59 (0.72–3.49)[3]	1.55 (0.53–4.57)[3]
Age ≥50 years (n=431)	14/77 (18%)	7/42 (17%)	91/353 (26%)	0.70 (0.39–1.26)[3]	0.56 (0.24–1.29)[3]

MA: Migraine with aura

Hazard ratio adjusted for age, sex and GCS at admission[1], for age and GCS at admission[2], and for sex and GCS at admission[3]

**Interaction between migraine and sex: 0.89 (0.24–3.26), p-value = 0.859; interaction between migraine and age (continuous): 0.93 (0.94 - 1.00), p-value = 0.075.*

Discussion

This study shows that patients with a history of migraine are in general not at increased risk of developing DCI. However, a possible association could not be excluded in the subgroup of patients <50 years since a statistically significant interaction was found between migraine and age. The subgroup of patients <50 years had a limited sample size leading to larger confidence intervals.

In one other study the association between DCI and migraine in aSAH patients was investigated. In that study migraine patients more often developed DCI (OR: 2.68; 95% CI: 0.99–7.29).[5] The study differed from our study on several important points. First, the study had a case-control design and included 36 young, female aSAH-patients who had developed DCI as cases and 36 age-matched female aSAH patients without DCI as controls. The women were younger (mean age 42 years) and more patients had a history of migraine (36%) than the participants of our study. Additionally, assessment of migraine was different (open questionnaire based on ICHD-criteria versus our migraine screener). Both studies used the same definition of DCI. Although we found no association between migraine and risk of DCI in our entire population, the interaction between migraine and age suggests that young migraine patients may have an increased risk of DCI, supporting the conclusion of the previous case-control study.[5] The association between young age and risk of DCI in migraine patients may be explained by a higher attack frequency and therefore more active migraine status in young patients.[21] Migraine activity may be related to an increased susceptibility to SDs, which could lead to increased risk of DCI development.

A study in mice with the mutation for familial hemiplegic migraine showed that development of ischemia may be facilitated by an increased susceptibility to SDs. These mice were studied between an age of 2–6 months, which is biologically equivalent to human young adult age.[23] The risk increase of ischemic stroke risk in migraine patients is also highest in patients under 45 years, and has clearly been associated with a high attack frequency. These findings may also be related to an increased susceptibility to SDs in these patient subgroups.[16, 24] However, also other pathophysiological processes may be underlying the potential relation between migraine and risk of DCI. Migraine has been linked with endothelial dysfunction, an association that appears to be particularly strong in young women.[25] In aSAH patients endothelial dysfunction also plays an important role in the development of DCI, thus aSAH patients with migraine – especially those of younger age – may be more susceptible for the pathophysiological cascade of events leading up to DCI.[26]

Several shortcomings of our study must be considered. First, our study population had a better clinical outcome than the average SAH patient population. This reflects the problem that the migraine screener could only be assessed in patients in a well enough condition to answer the questions during admission. Therefore, we cannot generalize our results to a more severe SAH population. Second, our migraine screener had several limitations. In a validation study the negative predictive value was found to be high and the positive predictive value moderate. For migraine with aura, negative predictive value was high but positive predictive value was low, hence we used the term 'possible aura'.[18] The potential misclassification bias in migraine diagnosis and aura symptoms might have diluted the effect sizes we found in our study. Further, because the questionnaire relates to history of migraine, patients who did not experience attacks for a long time may have forgotten information leading to recall bias. However, the migraine prevalence of 19% in our cohort was in line with the prevalence of 17% found by a previous study in patients with aneurysmal SAH.[20] Additionally, the majority of our study population consists of women, and migraine prevalence in women in the general population is found to be around 17%.[21] Unfortunately we did not have information about current attack frequency of migraine patients.

Strong points of this study include the relatively large sample size and the detailed and uniform assessment of DCI. The multi-center design including two academic and one large teaching hospital and the inclusion of men and women of all ages increases the generalizability of our study.

Conclusion

In the overall SAH population we found no association between DCI development and history of migraine. However, we found an interaction between migraine and age suggesting that young migraine patients may have an increased risk of DCI. Future studies with a larger number of young SAH patients are needed to further study the association between migraine and DCI in this particular subgroup.

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