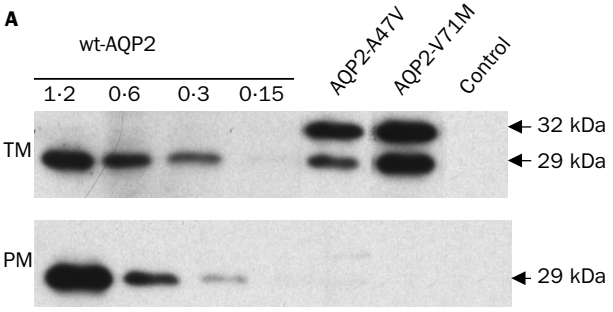

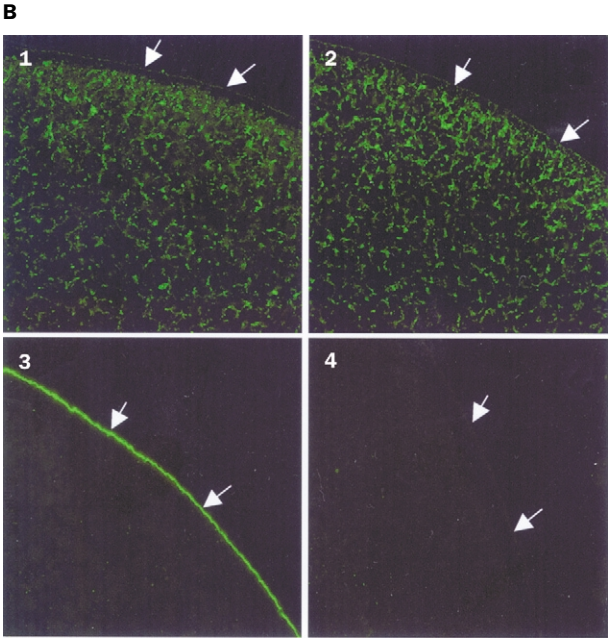

Figure 2: **Effect of the *AQP2* gene mutations on AQP2 function**
(A) Immunoblot of expressed AQP2 proteins. Total membranes (TM) or plasma membranes (PM) of 12 non-injected oocytes or those expressing AQP2-A47V, AQP2-V71M, or wt-AQP2. Unglycosylated (29 kDa) and high-mannose glycosylated (32 kDa) AQP2 are shown.
(B) Immunocytochemistry of oocytes expressing AQP2 proteins. Oocytes expressing AQP2-A47V (1), AQP2-V71M (2), wt-AQP2 (3) or non-injected oocytes (4). Arrows: plasma membranes.

receptors such as V1R or V2R, might be the proteins activated by desmopressin in treatment of primary nocturnal enuresis. This central effect of desmopressin is also supported by the fact that use of tricyclic antidepressants and the bell pad are as effective as desmopressin in treatment of primary nocturnal enuresis.

Our clinical and experimental data show that a major action of desmopressin to resolve primary nocturnal enuresis might reside outside the kidney and we suggest the central nervous system as the alternative site. Such action would account not only for the pathophysiological but also for the pharmacological basis of desmopressin treatment.

Contributors
The first two authors contributed equally to the study. D Müller made the clinical diagnosis of the affected families and wrote the report. N Marr did the functional investigations on the mutant AQP2 proteins. T Ankermann and P Eggert participated in the clinical and biochemical investigations of the patients. P Dean set up the techniques to investigate AQP2 function, supervised the cell biology, and wrote the report.

Conflict of interest statement
None declared.

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Merkel cell carcinoma and HIV infection

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Merkel cell carcinoma (MCC) is a rare skin cancer that occurs more frequently after organ transplantation or B-cell malignancy, conditions of suppressed or disordered immunity. To assess further whether immune suppression increases MCC risk, we studied its occurrence in a cohort of 309 365 individuals with acquired immunodeficiency syndrome (AIDS) by using linked AIDS and cancer registries. We identified six cases of MCC, corresponding to a relative risk of 13·4 (95% CI 4·9–29·1) compared with the general population. These results suggest that immune suppression induced by the human immunodeficiency virus increases MCC risk.

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Merkel cell carcinoma (MCC) is a rare skin cancer thought to be of neural crest derivation. In the USA, MCC occurs predominantly among elderly men (85% of cases arise after age 60 years). The cancer is especially uncommon in black people and, as with other skin cancers, exposure to ultraviolet sunlight may be a risk factor.[1] Suppression or dysregulation of the immune system might also have a role. MCC occurs more commonly in organ transplant recipients than in the general population. In the Cincinnati Transplant Tumor Registry, Penn and First[2] found 41 cases of MCC, comprising 0·9% of incident skin cancers. MCC also arises in excess in individuals with B-cell lymphoid neoplasms.[1] These observations prompted us to look for an excess of MCC in individuals with human immunodeficiency virus (HIV) infection and acquired immunodeficiency syndrome (AIDS).

We linked data from population-based AIDS and cancer registries in 11 geographical locations in the USA for the period 1978–96.[3] We used the cancer registries to find and classify malignancies in individuals who had been identified in corresponding AIDS registries. The cohort consisted of 309 365 individuals with AIDS (mean age 37 years; 83% male; 43% white, 36% black, 20% Hispanic). We counted

Case	Sex, race	HIV risk group	Age at MCC (years)	Time from AIDS to MCC (months)	MCC site
Present report					
1	Male, white	Homosexual/bisexual male	51	–13	Unknown
2	Male, white	Homosexual/bisexual male	42	–10	Upper limb
3	Male, Hispanic	Heterosexual	59	–7	Face
4*	Male, Hispanic	Intravenous drug use	48	–2	Lower limb
5	Male, white	Unknown	40	0	Trunk
6	Male, white	Homosexual/bisexual male	44	4	Trunk
7†	Male, NS	Homosexual/bisexual male	47	MCC before AIDS	Buttock
8‡	Male, white	NS	40	MCC before AIDS	Inguinal node
9§	Male, white	Homosexual/bisexual male	48	MCC before AIDS	Scalp
10¶	Male, white	Intravenous drug use	60	MCC before AIDS	Nasal bridge

Abbreviations: MCC=Merkel cell carcinoma; NS=not stated. *This individual also had Hodgkin's disease, diagnosed 33 months before MCC.
†*V A Med Q* 1992; **119:** 256. ‡*Southern Med J* 2000; **93:** 920. §*Diag Cytopath* 2001; **24:** 186. ¶*J Am Acad Dermatol* 2001; **45:** 309.

Characteristics of individuals with HIV infection and Merkel cell carcinoma (MCC)

MCC cases occurring in the period from −60 months to +27 months relative to AIDS onset. We then calculated the relative risk (RR) in patients with AIDS compared with the general population, as the ratio of observed to expected cancer cases. The number of expected MCC cases was derived from sex, age, race, and year-specific incidence rates applied to person-years under follow-up. We recognised that we could have missed MCC occurring in HIV-infected individuals who died before developing AIDS. To account for this effect of MCC-related mortality in our risk analyses, we adjusted the expected rates for person-years before AIDS, as described elsewhere.[3] Exact two-sided CIs and p values were calculated for risk estimates. The research was approved by ethical committees at the National Cancer Institute and participating registries.

We identified six individuals with AIDS who developed MCC in the period of observation (RR 13·4 [95% CI 4·9–29·1]; p<0·0001; table). All were men (four white, two Hispanics). Ages at MCC diagnosis ranged from 40 to 59 years, and individuals with MCC were older at the onset of AIDS than other cohort patients (mean age 48 *vs* 37 years; p=0·01). Excluding black people and individuals younger than 40 years old (groups with low MCC risk) did not materially change the effect of HIV/AIDS (RR 17·4 [95% CI 6·4–37·8]).

Our data add evidence that weakened immunity increases MCC risk.[1,2] With only six cases, we could not examine quantitatively whether MCC risk increased over time relative to AIDS onset or with depletion of CD4 lymphocytes, which could have provided additional evidence regarding the effect of immunosuppression.[3] Nonetheless, it is striking that three of our cases occurred more than 6 months before AIDS onset. Four other MCC cases, previously reported in HIV-infected individuals, also occurred before clinical AIDS (table). Thus, risk seems to be increased even with moderate immunosuppression. MCC could also occur excessively in the late stage of AIDS and be overlooked in the presence of other illnesses competing for medical attention.

Alternatively, other common exposures could increase MCC risk in AIDS. We did not have data on ultraviolet light exposure, which is posited as a risk factor for MCC.[1] Of eight MCC cases with HIV risk factor information, five (63%) occurred in homosexual or bisexual men (table), but this reflects the distribution of HIV risk factors among infected individuals, since in our cohort, (52%) of patients were men who had sex with men. We found additional MCC cases in an intravenous drug user and a heterosexual male (RR 19·0 [95% CI 2·3–68·5]), which argues against a risk factor for MCC limited to homosexual and bisexual men.

We could not review microscopic slides for our cases. Nonetheless, given the rarity of MCC, it seems improbable that clinicians would have diagnosed MCC without pathological confirmation. Indeed, two of our cases were identified through the National Cancer Institute's Surveillance, Epidemiology, and End Results (SEER) programme, which documents microscopic confirmation for more than 99% of MCC cases.[4] Theoretically, the number of MCC cases in our study might have been inflated if individuals under care for HIV/AIDS received frequent skin examinations for Kaposi's sarcoma, the most common skin tumour in AIDS. However, MCC is easily distinguished microscopically from Kaposi's sarcoma, and previous case reports (table) described pathological findings consistent with MCC. Furthermore, MCC behaves aggressively and frequently metastasises,[5] so screening would not have materially accelerated MCC diagnoses.

Notably, MCC cases arose in HIV-infected individuals who were much younger than typical for MCC, largely because most of our cohort patients were young adults (only 3% were age 60 years or older). With a low rate of new HIV infections in more-developed countries and the ageing of now-infected individuals, the age distribution of people with HIV will shift. Especially with current highly active antiretroviral therapies that delay AIDS onset but do not fully restore immunity, the incidence of MCC in HIV-infected individuals may rise with the increasing age of this population.

Contributors

All authors contributed to the design, analysis, and writing of the study. E A Engels led the analysis and writing of the paper.

Conflict of interest statement

None declared.

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