Autoimmune hepatitis in a North American Aboriginal/First Nations population

GY Minuk MD[1,2], S Liu BSc[1], K Kaita MD[1], S Wong MD[1], E Renner MD[1], J Rempel PhD[1,3], J Uhanova MD MSc[1]

GY Minuk, S Liu, K Kaita, et al. Autoimmune hepatitis in a North American Aboriginal/First Nations population. Can J Gastroenterol 2008;22(10):829-834.

North American Aboriginal populations are at increased risk for developing immune-mediated disorders, including autoimmune hepatitis. In the present study, the demographic, clinical, biochemical, serological, radiological and histological features of autoimmune hepatitis were compared in 33 First Nations (FN) and 150 predominantly Caucasian, non-FN patients referred to an urban tertiary care centre. FN patients were more often female (91% versus 71%; P=0.04), and more likely to have low serum albumin (69% versus 36%; P=0.0006) and elevated bilirubin (57% versus 35%; P=0.01) levels on presentation compared with non-FN patients. They also had lower hemoglobin, and complement levels, more cholestasis and higher serum immunoglobulin A levels than non-FN patients (P=0.05 respectively). Higher histological grades of inflammation and stages of fibrosis, and more clinical and radiological evidence of advanced liver disease were observed in FN patients, but the differences failed to reach statistical significance. The results of the present study suggest that in addition to being more common, autoimmune hepatitis may be more severe in FN populations, compared with predominantly Caucasian, non-FN populations.

Key Words: *Aboriginal; Autoimmune hepatitis; Cirrhosis; First Nations; Hepatitis; Liver disease*

L'hépatite auto-immune au sein d'une population autochtone et des Premières nations d'Amérique du Nord

Les populations autochtones nord-américaines sont plus vulnérables aux troubles d'origine immunitaire, y compris l'hépatite auto-immune (HAI). Dans la présente étude, les auteurs ont comparé les caractéristiques démographiques, cliniques, biochimiques, sérologiques, radiologiques et histologiques de l'HAI de 33 patients des Premières nations (PN) à celles de 150 patients à prédominance blanche qui ne faisaient pas partie des PN, tous aiguillés dans un centre urbain de soins tertiaires. Les patients des PN étaient surtout de sexe féminin (91 % par rapport à 71 %, P=0,04) et étaient plus susceptibles que les autres patients d'avoir des taux faibles d'albumine sérique (69 % par rapport à 36 %, P=0,0006) et élevés de bilirubine (57 % par rapport à 35 %, P=0,01) à la présentation. Leurs taux d'hémoglobine et de compléments étaient également plus faibles et leurs taux de cholestase et d'immunoglobuline A sérique, plus élevés que ceux des autres patients (P=0,05 dans tous les cas). On constatait des phases d'inflammation histologique et de fibrose plus avancées et un plus grand nombre de preuves cliniques et radiologiques de maladie hépatique chez les patients des PN, mais ces différences n'étaient pas statistiquement significatives. Selon les résultats de la présente étude, l'hépatite auto-immune n'est pas seulement plus courante, mais pourrait également être plus grave au sein des PN qu'au sein des populations à prédominance blanche ne faisant pas partie des PN.

Autoimmune hepatitis (AIH) is an immune-mediated inflammatory disease of the liver that can present as fulminant hepatic failure, acute or chronic hepatitis, or cirrhosis (1). The majority of AIH patients are women in their second or third decades of life. Fatigue and right upper quadrant discomfort are the most common subjective complaints. Laboratory investigations may reveal leukopenia, thrombocytopenia, elevated serum aminotransferases, the presence of autoantibodies (particularly antinuclear antibodies and antismooth muscle antibodies), hypergammaglobulinemia, hypocomplementemia and human leukocyte antigen (HLA) B8 DRB 1*03 or DRB1*04 haplotypes (1-4). Histologically, interface hepatitis, lymphoplasmacytic infiltrates and hepatocyte rosetting are characteristic findings (5). Untreated cases may progress to liver failure requiring liver transplantation (6). A rapid and often complete biochemical response to immunosuppressive agents can be both of diagnostic and therapeutic value (7).

Recent data suggest that autoimmune disorders and AIH in particular, are more common in the Aboriginal and First Nations (FN) populations of North America (8-12). Indeed, in British Columbia, immune-mediated liver disorders exceed chronic hepatitis C as the most common underlying liver disease in FN patients referred for transplantation (13). An alternative but not mutually exclusive explanation for the latter finding would be that AIH is more severe in FN patients as described in other ethnic populations (14-17). Thus, the purpose of the present study was to compare the clinical, biochemical, serological, radiological and histological features of AIH in FN with non-FN patients. Because vitamin D deficiency has recently been implicated in the pathogenesis of autoimmune

[1]*Department of Medicine;* [2]*Department of Pharmacology and Therapeutics;* [3]*Department of Immunology, University of Manitoba, Winnipeg, Manitoba*

Correspondence: Dr GY Minuk, 803F – 715 McDermont Avenue, Winnipeg, Manitoba R3E 3P4. Telephone 204-789-3204, fax 204-789-3987, e-mail gminuk@cc.umanitoba.ca

Received for publication March 26, 2008. Accepted July 11, 2008

TABLE 1
Characteristics of the study population (n=183)

Characteristic	
Age, years, (mean ± SD)	47±16
Female sex, n (%)	141 (77)
Ethnicity, n (%)	
First Nation	33 (18)
Non-First Nation	150 (82)
Symptoms, n (%)	127 (69)
Liver biopsied, n (%)	82 (45)
Treated, n (%)	110 (60)
Median follow-up, months	30.2

diseases common to FN populations, the study also documented the amount of sun exposure, vitamin D-enriched food intake and serum 25-hydroxy vitamin D levels in FN and non-FN patients with AIH (18).

METHODS

Subjects were identified for the present study by accessing a computerized database developed by the Section of Hepatology at Winnipeg's Health Sciences Centre (Winnepeg, Manitoba), an urban tertiary care referral centre for a population of approximately 1.2 million individuals of whom 5% to 10% are FN, predominantly Cree-Ojibwa (19). The database was initiated in 1987 and contains demographic, clinical, laboratory, radiological and/or histological findings on more than 95% of all referrals. For the purpose of the present study, patients without other causes of liver disease who satisfied the revised scoring system for a probable or definite diagnosis of AIH as outlined by the International Autoimmune Hepatitis group were designated the study population. All laboratory testing was performed by the Health Sciences Centre's hematology, biochemistry, immunology and olecular diagnostics laboratories using standard laboratory techniques.

Statistical analysis

Categorical variables were evaluated using χ^2 analyses. The χ^2 test of association (F-test when warranted) was used to examine differences in demographic factors and clinical variables. The Armitage Proportion Trend Test was used to examine proportions for trends. Continuous variables were assessed using Student's *t* test for parametric data and Mann-Whitney tests for nonparametric data, or ANOVA. The 95% CI for means, medians and for significant differences were calculated. Fold increase was calculated for liver enzyme and function tests using the upper limit of normal for the corresponding test as the reference value. $P<0.05$ was considered significant. All statistical analyses were performed using the Number Cruncher Statistical Systems 2001 software package (Ness, USA).

RESULTS

Demographics

From a database of approximately 10,200 records, a total of 183 (1.8%) individuals fulfilled International Autoimmune Hepatitis Group diagnostic criteria for AIH, and tested negative for other causes of liver disease. The mean (± SD) age of the study population was 47±16 years with the majority (77%) being female (Table 1). Thirty-three (18%) were FN and 150 (82%) were non-FN. The majority of non-FN patients were Caucasian with fewer than 10% being Asian, African or of other ethnicity. As shown in Table 2, the mean ages of FN and non-FN patients were similar. However, 30 of 33 FN patients (91%) were female compared with 111 of 150 (74%) non-FN patients (P=0.04). Patient follow-up data was available for a median of 30.2 months for the entire study population (Table 1) with a median of 32.4 months (range 0.1 to 122.4 months) in FN and 28.8 months (range 0.1 to 186 months) for non-FN patients (P=0.78).

Symptoms

Symptoms were reported at presentation in 127 individuals (69.4%). A similar percentage of FN and non-FN patients were symptomatic (Table 2). The nature of symptoms were also similar in the two groups with fatigue being most common (52% of FN versus 43% of non-FN patients), followed by right upper quadrant pain (12% of FN versus 25% of non-FN) and jaundice (24% of FN versus 19% of non-FN patients). Symptoms reported in less than 20% of the entire study population included arthralgia (19%), nausea (19%), weight loss (18%), dark urine (18%), pruritis (15%), pale stool (12%), anorexia (11%) and flu-like illness (10%). Symptoms in fewer than 10% of patients included peripheral edema, oligomenorrhea, diarrhea, vomiting, myalgia, spontaneous bruising, constipation, confusion and gastrointestinal bleeding. Overall, 49% of FN and 39% of non-FN patients had one to three symptoms, 18% and 20% had four to six symptoms and 3% and 13% had seven to 10 symptoms, respectively. These differences between FN and non-FN patients were not statistically significant. The presence or absence of symptoms did not significantly alter decisions regarding proceeding to liver biopsy or treatment. Thus, of those who underwent liver biopsy, 72% were symptomatic compared with 67% of those who remained unbiopsied (P=0.52). In terms of treatment, 62% of symptomatic patients received immunosuppressive therapy compared with 54% of asymptomatic patients (P=0.46).

Laboratory findings

As shown in Table 2, at the time of diagnosis, hemoglobin levels were significantly lower in FN compared with non-FN patients (125±22 g/L versus 139±15 g/L, respectively; P=0.03) but white blood cell and platelet counts were similar in the two groups. Leukopenia was present in 21% of FN and 17% of non-FN patients (P=0.67) and thrombocytopenia was present in 43% of FN and 26% of non-FN patients (P=0.22).

The results of liver biochemistry testing at the time of diagnosis, peak values during the course of their disease and last recorded results are provided in Table 3. Although mean serum albumin, bilirubin levels and international normalized ratios were similar in the two groups at the time of diagnosis, a greater percentage of FN patients had hypoalbuminemia (69% of FN versus 36% of non-FN, P=0.0006) and hyperbilirubinemia (57% of FN versus 35% of non-FN patients; P=0.01) than non-FN patients. The mean and percentage of patients with elevated serum aminotransferases (aspartate and alanine), alkaline phosphatase and gamma-glutamyltransferase levels were similar in the two groups. With the exception of higher serum alkaline phosphatase and gamma glutamyltransferase values and lower serum albumin levels in FN patients at the

TABLE 2
Data at presentation for First Nations (FN) and non-FN patients with autoimmune hepatitis

Variable	FN (n=33)	Non-FN (n=150)	P
Age, years	46.1±12.5	47.2±16.7	0.71
Female sex, n (%)	30 (91)	111 (74)	0.04
Follow-up, months, median (range)	32.4 (0.1–122.4)	28.8 (0.1–186.0)	0.78
Symptoms, n (%)	23 (70)	104 (70)	0.97
Fatigue	17 (52)	64 (43)	0.40
Right upper quadrant pain	4 (12)	36 (25)	0.11
Jaundice	8 (24)	28 (19)	0.48
Hemoglobin (NV 120 g/L to 160 g/L)	125±22	139±15	0.03
White cells (NV 4.5×10^9/L to 11.0×10^9/L)	6.6±3.0	6.5±2.6	0.80
Platelets (NV 140×10^9/L to 440×10^9/L)	198±92	212±9.5	0.63
Alanine aminotransferase (NV <35 U/L)	134±171	310±541	0.39
Aspartate aminotransferase (NV 10 U/L to 32 U/L)	131±157	288±497	0.65
Alkaline phosphatase (NV 30 U/L to 120 U/L)	174±72	164±143	0.06
gamma-glutamyltransferase (NV 5 U/L to 29 U/L)	233±238	159±181	0.12
Albumin (NV 33 g/L to 45 g/L)	36.2±13.6	35.4±6.7	0.36
Bilirubin (NV 2 µmol/L to 10 µmol/L)	49.8±108.3	54.9±116.3	0.74
International normalized ratio (NV 0.9 to 1.1)	1.16±0.36	1.21±0.45	0.52
Antinuclear antibodies			
Positive, n (%)	28/29 (99)	107/121 (88)	0.34
Titre (1/x)	860±1423	1133±2238	0.19
Antismooth muscle antibody			
Positive, n (%)	9/20 (45)	39/80 (49)	0.60
Titre (1/x), mean ± SD	251±245	505±630	0.31
Immunoglobulin (Ig)			
IgA (NV 0.7 g/L to 3.8 g/L)	5.0±2.0	3.5±2.4	0.0001
IgG (NV 6.9 g/L to 16.2 g/L)	22.7±10.2	23.2±21.9	0.48
IgM (NV 0.6 g/L to 2.6 g/L)	2.3±1.4	2.8±2.0	0.34
C3 (NV 0.88 g/L to 2.01 g/L)	0.9±0.3	1.18±0.4	0.04
C4 (NV 0.16 g/L to 0.47 g/L)	0.19±0.09	0.20±0.07	0.05
Human leukocyte antigen, n (%)			
B8-positive	11/26 (42)	2/4 (50)	0.77
DR3-positive	11/26 (42)	1/3 (33)	0.77
DR4-positive	10/25 (40)	2/3 (67)	0.38
Abdominal imaging at diagnosis, n (%)			
Hepatomegaly	6/24 (24)	17/102 (17)	0.51
Irregular liver edge	11/24 (46)	36/102 (35)	0.34
Varices	2/24 (8)	7/102 (7)	0.85
Splenomegaly	9/24 (38)	41/102 (40)	0.81
Ascites	1/24 (4)	15/102 (15)	0.29
Histology			
Grades 0 to 2	7/17 (41)	40/65 (62)	
Grades 3 to 4	10/17 (59)	25/65 (39)	0.17
Stages 0 to 2	7/17 (41)	41/54 (63)	
Stages 3 to 4	10/17 (59)	24/65 (37)	0.18

Data presented as mean ± SD unless otherwise specified. C Complement; NV Normal values

time of their last visit, the mean values of the remaining liver biochemistry tests were similar when maximum (or in the case of albumin, minimum) values and last recorded results were considered.

The results of immunological testing are also provided in Table 2. The percentage of positive antinuclear antibody tests and their titres were similar in FN and non-FN patients. The same was true for antismooth muscle antibody testing. Serum immunoglobulin A levels were significantly higher (P=0.0001) in FN patients but IgG and IgM levels were similar in the two groups. Both complement (C) 3 and 4 levels were lower in FN patients compared with non-FN patients (P<0.05, for both). Finally, when performed, HLA typing was positive for HLA B8, DRB1*03 and DRB1*04 haplotypes in 42%, 42% and 40% of FN patients respectively. This testing was only performed in three or four non-FN patients.

TABLE 3

Liver biochemistry testing at various times in First Nations (FN) (n=33) and non-FN (n=150) patients with autoimmune hepatitis

Parameter	At diagnosis		Peak value		Last follow-up	
	FN	non-FN	FN	non-FN	FN	non-FN
Albumin (g/L)	36.2±13.6	35.4±6.7	25±5.9	33±4.8	34.4±6.9	36.8±6.9*
Bilirubin (μmol/L)	49.8±108	54.9±116	141±170	125±155	34.9±109	19.9±33.8
International normalized ratio	1.16±0.36	1.21±0.45	1.6±0.4	1.7±0.7	1.17±0.36	1.1±0.2
Alanine aminotransferase (U/L)	134±171	301±541	379±473	604±751	49.9±52.9	62.9±87.9
Aspartate aminotransferase (U/L)	131±157	288±497	412±771	520±641	44.8±27.9	55.3±73.7
Alkaline phosphatase (U/L)	174±72	164±144	230±77	251±183	145±69	114±80**
Gamma-glutamyltransferase (U/L)	233±238	159±181	346±257	296±290	164±158	103±129*

*All data presented as mean ± SD. *P<0.05 versus FN; **P<0.005 versus FN. See Table 2 for normal range laboratory values*

TABLE 4
Child-Turcotte-Pugh (CTP) scores for First Nations (FN) and non-FN patients with autoimmune hepatitis

	FN		non-FN			Total	
	n	%	n	%	P	n	%
Baseline CTP score							
Below 5 points	0	0.0	11	7.6	0.22	11	6.2
Class A	24	72.7	91	63.2	0.32	115	65.0
Class B	8	24.2	33	22.9	0.94	41	23.2
Class C	1	3.0	9	6.3	0.76	10	5.6
Final CTP Score							
Below 5 points	0	0.0	5	3.5	0.62	5	2.8
Class A	24	72.7	108	75.0	0.83	132	73.6
Class B	5	15.2	28	19.4	0.75	33	18.6
Class C	4	12.1	3	2.1	0.03	7	4.0

Abdominal imaging

According to various abdominal imaging modalities (ultrasound, computed tomographic scanning or magnetic resonance imaging) obtained at the time of diagnosis, the percentage of subjects presenting with an enlarged liver, irregular liver border, esophageal or gastric varices, splenomegaly or ascites were similar in FN and non-FN patients (Table 2).

Histology

A total of 17 (51%) FN and 65 (43%) non-FN patients underwent liver biopsies before treatment. The results are presented in Table 2. Although the majority (59%) of FN patients had either grade 3 or 4 (maximum score 4) inflammatory activity, compared with 39% of non-FN patients, this difference was not statistically significant (P=0.17). Similar results were obtained with respect to the stage of fibrosis in which 59% of FN and 37% of non-FN patients had stage 3 or 4 (maximum score 4) fibrosis (P=0.18).

Treatment

Immunosuppressive therapy was initiated in 61% of FN and 63% of non-FN patients. FN patients were more likely to be maintained on prednisone alone than non-FN patients (55% versus 30%, respectively; P=0.03). The median prednisone dose in FN patients was 10 mg/day and 7.5 mg/day in non-FN patients (P=0.45). Azathioprine served as single-agent maintenance therapy in 25% and 34% of FN and non-FN patients, respectively (P=0.14). A median dose of 100 mg/day was used for both groups. The combination of prednisone and azathioprine was used in 20% and 29% of FN and non-FN patients, respectively (P=0.42). When combination therapy was used, the median prednisone and azathioprine doses were 5 mg/day and 50 mg/day for FN patients and 7.5 mg/day and 75 mg/day for non-FN patients. These differences were not statistically significant.

Outcomes

At the time of their last visit, signs of advanced liver disease including radiological evidence of cirrhosis (33% of FN versus 24% of non-FN), clinical signs of encephalopathy (12% of FN versus 5% of non-FN) and radiological or clinical signs of ascites (24% of FN versus 11% of non-FN patients) were more common in FN patients but the differences failed to reach statistical significance (P=0.26, P=0.25 and P=0.09 respectively). Child-Turcotte-Pugh classification of patients at baseline and last follow-up are provided in Table 4. A higher percentage of FN patients were classified as Child-Turcotte-Pugh Class C compared with non-FN patients (12.1% versus 2.1%, repectively; P=0.03) at last follow-up; however, the number of subjects was limited.

Vitamin D studies

The results of vitamin D-related surveys and metabolite analyses are provided in Table 5. The percentage of patients with limited sunlight exposure (0 h/day to 1 h/day) and minimal consumption of vitamin D-enriched foods (less than two cups/day of milk, never or rarely consuming margarine, and zero to one servings of fish/week) were similar in FN and non-FN patients as were serum 25-hydoxy vitamin D levels.

DISCUSSION

Although not specifically designed to document the prevalence of AIH in this Aboriginal population, the results of the present study support previous reports (8-12) describing higher rates of autoimmune disorders in North American Aboriginal populations. In the present study, FN patients constituted 17% of all diagnosed AIH cases, whereas only 5% to 10% of the referral population were FN (19). The results also extend our understanding of AIH in Aboriginals by

describing the presentation and severity of disease in FN and non-FN patients. Based on a higher percentage of FN patients having abnormal liver function tests (hypoalbuminemia and hyperbilirubinemia) on presentation, a trend toward higher grades of inflammation and stages of fibrosis on liver biopsy, and clinical and radiological findings consistent with more advanced disease at last follow-up despite similar treatment, it would appear that AIH is more severe in FN than non-FN patients. However, because the majority of these results represent trends rather than statistically significant findings, a prospective study involving larger numbers of patients, followed for longer periods of time, is required to confirm this impression.

An alternative interpretation for the above findings would be that FN patients are presenting later in the course of their disease than non-FN patients. Such an interpretation is supported by the results of previous studies documenting more limited access to health care services in FN populations (20). However, the similar ages, prevalence of symptoms and radiological features of advanced disease at the time of diagnosis in FN patients and non-FN patients argue against this interpretation.

Whether more severe or presenting later in the course of the disease, once the diagnosis of AIH is established, biochemical evidence of response to immunosuppressive therapies was similar in both populations. At last visit, alanine aminotransferase values were within the normal range in 40% of FN and 34% of non-FN treated patients (P=0.62). However, because clinical and/or radiological signs of advanced liver disease were more common in FN patients at their last follow-up visit, histology rather than liver biochemistry may be a more useful parameter to guide immunosuppressive therapy in this population.

The mechanism in which AIH may be more common and severe in Aboriginal populations remains to be determined. Genetic predisposition involving increased HLA class II expression (DRB1 *0404 and 1402) has been suggested as the explanation for higher rates of juvenile rheumatoid arthritis in FN populations, but no such analyses have been performed for FN patients with AIH (21). Our laboratory has described a genetic and functional downregulation of the inhibitory cytokine interleukin-10 in FN compared with non-FN individuals, but these studies were performed in healthy or hepatitis C-infected subjects (22). Nonenzymatic glycation of target proteins, resulting in aberrant immunological responses has also been described more commonly in North American Aboriginal populations but these studies were confined to patients with rheumatoid arthritis rather than AIH (23). Finally, environmental factors have been implicated but the precise nature of these factors have yet to be elucidated (24). Based on the immune regulatory properties of vitamin D, emerging data suggesting that vitamin D deficiency may contribute to the pathogenesis of certain immune-mediated disorders, recently reported findings describing an increased severity of AIH in African-Americans (who tend to have low serum vitamin D levels) and higher rates of vitamin D deficiency in Aboriginal populations (14,18,25), we documented the amount of sun exposure, dietary intake of vitamin D-enriched foods and 25-hydroxy vitamin D blood levels in FN and non-FN AIH patients; the results however, were similar in the two groups.

Why serum alkaline phosphatase, gamma-glutamyltransferase, IgA, C3 and C4 levels differed in FN compared with non-FN patients at the time of diagnosis and/or last follow-up visit remains unclear. Previous studies (26) have documented a more cholestatic response to hepatocellular injury in FN patients; however, these differences were not present at diagnosis nor when maximal values were recorded. Serum IgA levels are increased in individuals who drink alcohol to excess and alcoholism is more prevalent in Aboriginal populations (27,28), but the study protocol excluded patients with additional causes of liver disease, a measure supported by the lack of alcohol-related findings on liver biopsy. While low serum C4 levels appear to be genetically determined in AIH (29), the explanation for lower serum C3 levels in FN patients remains unclear.

TABLE 5
Sunlight exposure, vitamin D intake and blood levels in First Nations (FN) and non-FN patients with autoimmune hepatitis

	FN (n=7)	non-FN (n=33)	P
Sun exposure (0 h/day to 1 h/day), %			
Winter	100	88	0.78
Spring	57	46	0.88
Summer	43	55	0.88
Fall	57	49	0.99
Milk (<2 cups/day), %	57	48	0.99
Margarine (never–rarely), %	33	55	0.99
Fish (0–1 servings/week), %	100	79	0.43
25-hydroxy vitamin D, nmol/L, mean ± SD	49.3±26.6	56.8±20.3	0.59

There are a number of limitations to the present study that warrant discussion. First, we do not know whether the results in this FN population can be extrapolated to other North American Aboriginal populations. Second, no attempt was made to grade the severity of symptoms to determine whether both the prevalence and severity of symptoms were similar in the two populations. Third, for reasons that are unclear, not all patients underwent complete laboratory testing and, in particular, only a small percentage of non-FN patients had HLA testing performed. Fourth, not all patient livers were biopsied. Thus, histological analyses were limited to only 40% to 50% of the patient population. Finally, the indications for treatment, selection of therapeutic agents and guidelines for maintenance and cessation of immunosuppressive therapy vary from centre to centre and from physician to physician. Hence, some of the differences in outcome described in the treatment of FN versus non-FN patients could reflect interphysician variability in management.

CONCLUSION

The results of the present study suggest that AIH is both more common and severe in this Aboriginal population. Further studies are required to confirm these findings and identify the mechanism(s) involved. In the interim, FN patients with elevated liver enzyme levels should be screened for AIH and managed much in the same way as non-FN patients with the possible exception of obtaining more frequent liver biopsies to help guide immunosuppressive treatment.

ACKNOWLEDGMENTS: The authors thank Ms Annette Nanowski for her prompt and accurate typing of the manuscript. Ms S Liu is the recipient of the Canadian Liver Foundation Summer Studentship Award.

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