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Gender and age-related differences in Burkitt lymphoma – epidemiological and clinical data from The Netherlands

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Abstract

Although Burkitt's lymphoma (BL) is classified as one entity in the World Health Organisation (WHO) classification, we wondered whether BL should not be considered as a different disease in children compared with adults. Netherlands Cancer Registry (NCR) data were obtained from 1994 to 1998 ($n = 203$). Detailed clinical data from two treatment protocols were compared: one for adults up to the age of 65 years ($n = 27$) and one for children ($n = 80$). All slides of the two clinical studies were centrally reviewed which included immunophenotyping and when necessary breakpoint analysis of *MYC*/8q24. Only cases with an unambiguous diagnosis of BL (classical and atypical BL) were accepted. The age distribution of BL-patients showed a bimodal distribution with a peak at the paediatric age and a steady increase after approximately 60 years of age. Most of the patients were males (89% for children and 78% for adults) and only male patients showed this bimodality. Children more often had extranodal disease (81% vs. 59%), whereas adults more often had nodal disease (89% vs. 53%). Based on epidemiology and clinical presentation, the concept that BL is one disease should be re-challenged.

Keywords: Adult; Burkitt lymphoma; Child; Clinical presentation; Extranodal; Epidemiology; Gender

1. Introduction

Burkitt Lymphoma (BL) is a highly aggressive type of Non-Hodgkin's Lymphoma (NHL) [1]. Among all NHL in Western Europe, BL comprises 5% at most [1]. However, this percentage differs remarkably between children and adults. If patients with an immune deficiency are excluded, BL comprises approximately 40% of NHL cases in children compared with only 1–2% in adults [1,2]. Although the incidence of NHL is much higher in adults than in children, the incidence rates for BL in children are still twice as high as in adults [3].

Thus far, there is no explanation for this difference in incidence. Although BL is classified as a single (''real'') entity in the World Health Organisation (WHO) classification [1], we and others [4] wondered whether BL should not be considered a different disease in children compared with adults. The fact that two other lymphoid malignancies, precursor B cell acute lymphoblastic leukaemia (ALL) and anaplastic large cell lymphoma (ALCL), have a different genetic make-up and behave differently clinically in children and adults [1,5,6] might also support our hypothesis.

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In spite of the large number of clinical and epidemiological studies on BL in either children [7–10], adults [11–13] or both [14,15], few investigators have addressed possible differences between these two groups regarding epidemiology and clinical presentation [4]. Because of both the presence of a national cancer registry and the fact that many BL-patients are treated in clinical trials, thoroughly recorded epidemiological and clinical data are available on this disease in the Netherlands.

This gave us the opportunity to study the epidemiological and clinical characteristics of BL in children versus adults, with a focus on possible differences.

2. Patients and methods

2.1. Epidemiological data

Epidemiological data on BL in the Netherlands were retrieved from the Netherlands Cancer Registry (NCR). The NCR is a nationwide, population-based cancer registry containing data on the incidence, tumour localisation, stage and classification of all malignant neoplasms [16]. In this database, BL is defined according to the International Classification of Diseases for Oncology (ICD-O-3) [17] as morphology code 9867/3. Data from this registry were obtained from all registered BL patients in the period of 1994–1998. Patients were grouped in cohorts of 15 years. Incidence data were calculated using additional population data from Statistics Netherlands (CBS, Amsterdam, the Netherlands).

2.2. Clinical data

The NCR does not contain reliable data on the clinical characteristics necessary to test whether or not BL is one disease. For instance, data on the site of biopsy are available, but this does not necessarily correspond to the primary site of clinical presentation of the tumour. Therefore, clinical data of patients from two treatment protocols were used: the SNWLK-NHL-94 protocol for children aged 0–15 years (SNWLK is currently called SKION) and the HOVON-27-NHL-94 study for adults aged 16–65 years.

The HOVON (Dutch-Belgian Haemato-Oncology Co-operative Study Group) study was a multicentre phase II study performed between 1994 and 2002 in newly diagnosed patients aged 16–65 with high-risk (defined by stage and lactate dehydrogenase (LDH)), intermediate- or high-grade NHL, as defined according to the Working Formulation (this classification system was used for entry of patients since this clinical study started before publication of the Revised European American Lymphoma (REAL) and WHO classification). According to the HOVON protocol, BL patients were excluded if they had prior treatment or any other malignancy, human immunodeficiency virus (HIV) positivity, immune deficiency, or presented with severe major organ dysfunction or metabolic disease, a WHO performance status >2, central nervous system (CNS) involvement, a manifest leukaemic phase of BL (bone marrow (BM) involvement >30% or >5% malignant cells in the blood), or Ann Arbor stage I non-bulky (<10 cm) disease with normal serum LDH.

The SNWLK (Dutch Childhood Oncology Group (DCOG)) protocol was the standard treatment protocol for children aged 0–15 years with any B-NHL in the Netherlands, including all cases of paediatric BL.

All patients underwent standard staging procedures. Lymph node involvement in the abdomen was always confirmed by computerised tomographic (CT) scanning or (rarely in children) ultrasound. Multiple extranodal intra-abdominal localisations were coded as disseminated abdominal mass. For the comparison of the clinical data between children and adults, a selection of paediatric patients from the SNWLK was made according to the inclusion criteria of the adult HOVON protocol, as the latter was the most restrictive (Fig. 1). For these selected patients, the following clinical data were retrieved: patient characteristics, blood and bone marrow investigations, tumour pathology and the stage and localisation of the tumour. We determined the Murphy [18] and Ann Arbor [19] stage for both groups according to the localisation and extent of the tumour. The variables LDH level, Ann Arbor stage and Performance Status determined the age-adjusted International Prognostic Index (IPI) [20], although we realise that the classical IPI was neither designed for children nor validated for BL.

2.3. Central pathology review

All cases from both the adult (HOVON) and paediatric (SNWLK) protocols were submitted to central pathology review. The HOVON cases were reviewed by one expert haematopathologist and the SNWLK cases were reviewed by a panel of pathologists (including the haematopathologist). All cases that did not fulfil the criteria of classical BL or atypical BL according to the WHO classification [1] were rejected, with the aim of selecting all unambiguous BL patients. In all cases, immunohistochemistry was performed (see below) to exclude DLBCL with Burkitt's features and precursor B-cell lymphoblastic lymphoma/leukaemia. Classical BL was defined according to the WHO classification [1], based upon the characteristic monomorphic morphology in combination with a positive immunohistochemical staining on formalin-fixed and paraffin-embedded tissue sections for CD20 (or CD79a), CD10 and bcl-6, a high proliferation rate defined by a MIB-1/Ki-67 labelling index of >95% and the absence of bcl-2 expression in the tumour cells.

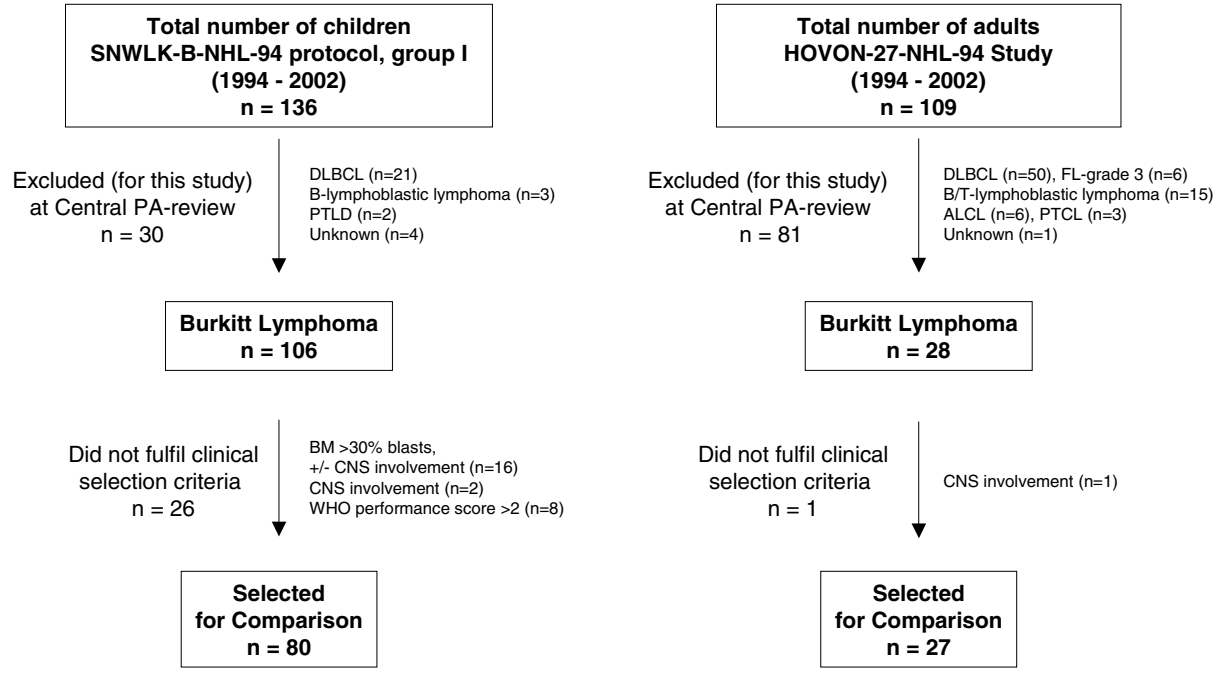

Fig. 1. Flow chart clarifying the patient selection for clinical comparison of children versus adults. Right part: adult Burkett lymphoma (BL) patients entered in the HOVON-27-NHL-94 study. Left part: childhood BL entered in the SNWLK-B-NHL-94 study. Of note, the HOVON-27-NHL-94 study was designed for a large variety of aggressive lymphoma cases including DLBCL, which explains why so many cases were not included in the present study on BL. CNS, central nervous system; WHO, World Health Organisation; BM, bone marrow; DLBCL, diffuse large B-cell lymphoma; FL, follicular lymphoma; PA, pathology; ALCL, anaplastic large cell lymphoma; PTLD, post-transplant lymphoproliferative disease; PTCL, peripheral T-cell lymphoma.

In all cases with an atypical morphology compatible with a diagnosis of atypical BL [1], the additional demonstration of a *MYC*/8q24 breakpoint was requested, as determined by conventional cytogenetic or fluorescent *in situ* hybridisation analysis (FISH) [21,22]. Diffuse Large B-Cell Lymphoma (DLBCL) with morphological features of BL (e.g. starry-sky and monomorphic appearance, high MIB-1/Ki-67 labelling index) were excluded as much as possible using morphology, the abovementioned immunohistochemical markers as well as FISH analysis for *MYC*/8q24 breakpoints and *BCL-2*/18q21 breakpoints [21,23].

2.4. Statistics

Descriptive statistics were used for all data. Differences between non-parametric data were analysed with the Fisher's Exact Test or the Pearson χ-square Test. Continuous data were analysed with either the Student *t*-Test for normally distributed data or the Mann–Whitney *U* Test for skewed distributed data.

Incidence rates (IR) were calculated per million person-years. Ninety-five percent Confidence Intervals (95% CI) around the incidence rates were calculated under the Poisson distribution assumption. In addition, multivariable Poisson regression analysis was performed to evaluate the effect of age, as well as gender, on the incidence of BL.

3. Results

3.1. Epidemiological data from the NCR

In the period of 1994–1998, 203 BL patients (137 males and 66 females) were registered in the NCR (Table 1). As Fig. 2 shows, BL occurred at all ages, but was more frequently observed in children compared with adults, with incidence rates of 4.4 (95% CI: 3.4–5.6 and 2.2 (95% CI: 1.8–2.6), respectively. It also shows that the incidence (IR) of BL was higher in males than in females (IR of 3.5 (95% CI: 3.0–4.2) for males compared with 1.7 (95% CI: 1.3–2.1) for females).

Multivariable analysis, with age and gender as independent variables, showed both age and gender as strong predictors of the occurrence of BL. In addition, a significant interaction of age and gender ($P = 0.02$) was observed, indicating a different relationship between age and the occurrence of BL in males and females. In the male patients, a bimodal age distribution with a peak for the paediatric age group of 0–15 years and a steady increase after approximately 60 years of age was observed. Boys had a significantly higher risk of BL compared with male adults below and over the age of 60 years, with relative risks of 3.2 (95% CI: 2.2–4.6, $P < 0.01$), and 1.6 (95% CI: 1.0 –2.5, $P = 0.048$), respectively. Adult males over 60 years had a doubled risk of BL (95% CI: 1.3–3.2, $P < 0.01$) compared with adult

Table 1
Epidemiology of Burkitt's Lymphoma in the Netherlands (NCR data registry 1994–1998)

	0–15 Years, $n = 66$	16–60 Years, $n = 89$	>60 Years, $n = 48$	Total, $n = 203$
Age (years)				
Median (range)	7.5 (2–15)	36 (16–60)	71.5 (61–89)	34 (2–89)
Gender				
Male	54 (82%)	57 (64%)	26 (54%)	137 (67%)

NCR, Netherlands Cancer Registry.

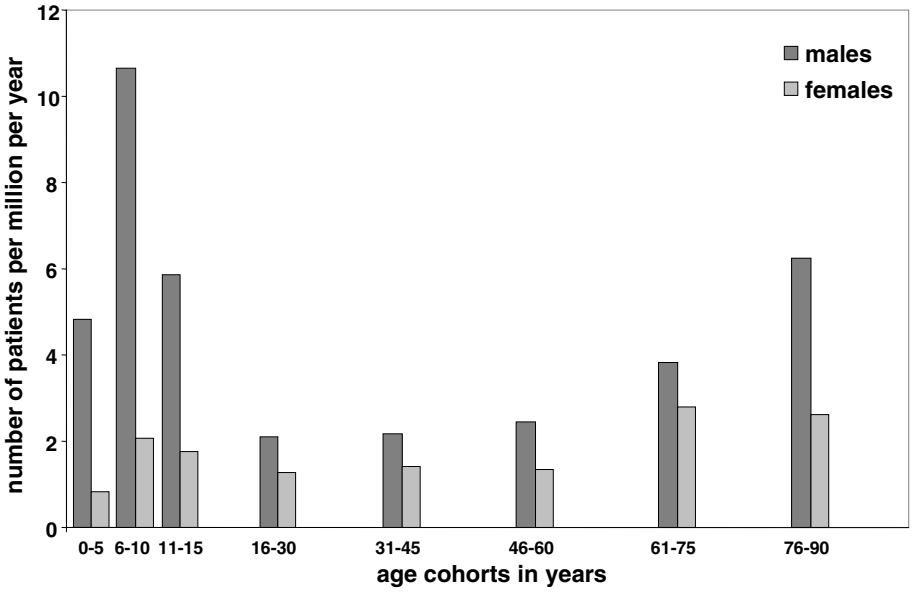

Fig. 2. Incidence of BL patients in the Netherlands. Incidence data were calculated using population data from Statistics Netherlands and epidemiological data from the Netherlands Cancer Registry (NCR). Bars represent the mean number of new patients per million inhabitants of that age cohort per year over the period of 1994–1998 in The Netherlands. Note that the age cohorts are different for children (cohorts of 5 years each) than for adults (cohorts of 15 years each).

males below the age of 60 years. In female patients, such a bimodal distribution was not observed. Girls had a comparable risk of BL compared with female adults below the age of 60 years, with a relative risk of 0.9 (95% CI: 0.4–1.7, $P = 0.68$) for the adults, compared with children. In female adults above the age of 60 years, the risk had increased significantly, compared with adults below 60 years, with a relative risk of 2.0 (95% CI: 1.2–3.5, $P = 0.01$).

3.2. Clinical data

After central pathology review, 28 adult patients from the HOVON-27 study and 106 paediatric patients from the SNWLK protocol fulfilled the final diagnosis of classical or atypical BL. All DLBCL with BL features were excluded, as were all other aggressive lymphoma cases (see Fig. 1).

Using the HOVON eligibility criteria for selection, 27 adults and 80 children remained for comparison of clinical characteristics (Fig. 1). Twenty-six children were left out from the comparative analysis, mainly because of initial CNS involvement or extensive BM disease. These 26 patients had a median age of 7 years (range 0–14 years), 70% was male, 14% had a normal LDH, 90% had more than 2 extranodal sites, and almost all (96%) had by definition Murphy stage III/IV disease. However, statistically, if we group together all patients and compare them with the selected patients, no significant differences were observed as far as age, gender and LDH levels were concerned. Clinical characteristics of the selected patients are shown in Table 2. In concordance with the NCR data, a male preponderance was seen both in children (89%) and adults (78%). The large majority of patients had a good performance status at presentation (72% of the children and 85% of the adults had a performance score of 0–1). BM involvement (with less than 30% blasts; see inclusion criteria in Fig. 1) occurred only incidentally (3% in children, 11% in adults). LDH levels were higher in children compared with adults ($P = 0.05$).

Table 2
Clinical data and tumour localisation in selected SNWLK and HOVON patients (1994–2002)

	Children (n = 80)	Adults (n = 27)
Age (years)		
Median (range)	7 (0–15)	35 (16–64)
Gender		
Male	71 (89%)	21 (78%)
LDH (U/l)		
Normal	16 (24%)	9 (33%)
Elevated		
>1× upper limit of normal	22 (32%)	12 (44%)
>2× upper limit of normal	12 (18%)	4 (15%)
>4× upper limit of normal	18 (26%)	2 (7%)
No data	12	
Involvement		
Nodal sites only	16 (20%)[a]	11 (41%)[a]
Nodal and extranodal sites	26 (33%)	13 (48%)
Extranodal sites only	38 (48%)[b]	3 (11%)[b]
Extranodal sites involved		
1	28 (35%)	8 (30%)
⩾2	36 (45%)	8 (30%)
Specification extranodal sites		
Paranasal sinus/jaw	7 (9%)	1 (4%)
Lung	4 (5%)	2 (7%)
Pleura/pleural fluid[c]	16 (20%)	1 (4%)
GI-tract		
Ascites[d]	19 (24%)[a]	1 (4%)[a]
Omentum	12 (15%)	3 (11%)
Intestinal tract	34 (43%)	7 (26%)
Ileocaecal	27 (34%)	4 (15%)
Liver	8 (10%)	1 (4%)
UG-tract	12 (15%)	3 (11%)
Bone marrow	2 (3%)	3 (11%)
Other	5 (6%)	4 (15%)
Disseminated abdominal mass[e]	16 (20%)	5 (19%)
Bulky disease (cm)		
0–5	15 (28%)	7 (28%)
5–10	23 (43%)	3 (12%)
>10	15 (28%)[a]	15 (60%)[a]
No data	27	2
Ann-Arbor stage		
I–II	33 (41%)	15 (56%)
III–IV	47 (59%)	12 (44%)
Murphy stage		
I–II	24 (30%)	10 (37%)
III–IV	56 (70%)	17 (63%)
Age-adjusted IPI		
0–1	28 (41%)	17 (63%)
2–3	40 (59%)	10 (37%)
No data[f]	12	

LDH, lactate dehydrogrnase; GI, gastrointestinal; GU, genitourinary; IPI, International Prognostic Index.

[a] $P < 0.05$.

[b] $P < 0.001$.

[c] 7 of 16 cases (44%) were cytologically proven.

[d] 8 of 19 cases (42%) were cytologically proven.

[e] Localisations coded as 'disseminated abdominal mass' in the SNWLK dataset could not precisely be staged according to the Ann Arbor classification and were coded as Ann Arbor stage III–IV see Section 2.

[f] Due to missing LDH values.

When comparing all tumour localisations, extent and stages (Table 2), several differences between children and adults were apparent. The most striking difference was that children more often had extranodal disease compared with adults: exclusively extranodal disease was found in 48% of the children and 11% of the adult patients ($P = 0.001$). Preferential extranodal sites in children were the ileocaecal region, ascites and pleura/pleural fluid. In reverse, adult patients presented more frequently with exclusively nodal disease ($P = 0.04$), and more often in lymph nodes of the head and neck region (41% *vs.* 19%, $P = 0.04$), as well as the retroperitoneum (44% *vs.* 16%, $P = 0.01$). Furthermore, more adults than children had a large tumour of >10 cm (60% versus 28%, $P = 0.01$). According to the Murphy classification, the percentages of patients with advanced stage disease were comparable. In the Ann Arbor classification, more paediatric than adult patients tended to have advanced disease (stage III–IV), reflecting the higher incidence of extranodal disease in children, but this difference was non-significant. Additionally, the age-adjusted IPI seemed to be higher in children compared with adults, but this difference was also non-significant ($P = 0.07$).

4. Discussion

Few lymphoid neoplasias present both in children and adults. The most commonly shared disorders are BL, ALCL and ALL. This common presentation in children and adults might suggest that these malignancies are homogeneous disorders. However, whereas this is apparently supported by the uniform histology, more refined analyses including (molecular) genetic data support the concept of tumour heterogeneity between children and adults. In ALCL, the paediatric cases commonly contain a chromosomal translocation with involvement of the *ALK* gene. In contrast, this translocation is relatively uncommon in adult cases [1,5,6]. The presence of this translocation or one of its variants is associated with a more favourable prognosis. Similar genetic and clinical differences are present between ALL in children and adults [1]. In analogy to these observations in ALCL and ALL and driven by a difference in incidence between children and adults, we wondered whether BL should or should not be regarded as one disease entity in children and adults. Based on the histology and additional immunophenotype and cytogenetics, BL seems to be one disease. Almost all cases harbour a chromosomal breakpoint at 8q24 involving the *MYC* oncogene. However, other molecular data are limited [24,25], and more detailed investigations including gene expression studies may be very informative with respect to the question of whether BL is really one disease.

In the present investigation, we approached this problem by studying both the epidemiology and the clinical presentation of BL. To study the epidemiology, we used data from the NCR covering all BL patients diagnosed in the Netherlands. For the clinical presentation, we used data from two treatment protocols for BL in the Netherlands.

In agreement with other publications [1–3], the NCR data showed that BL is more common in children than in adults. In agreement with others [26,27], we also observed a bimodal age distribution, with a peak incidence at 6–10 years and a steady increase of incidence after approximately 60 years of age. This supports the hypothetical existence of two disease entities for the different age groups. Of note, this bimodality was exclusively present in the male patients. For female patients, the incidence was remarkable stable at 1–3 new cases per million inhabitants for all age categories. This difference between both sexes might suggest essential differences in the disease itself or its genetic background. However, a biological basis for this assumption remains speculative. In this regard, the male preponderance in both children and adults, observed by us and others [3,8–12] is intriguing.

Regarding the clinical presentation of BL in our patient cohorts, we found several differences between children and adults concerning tumour localisation, extent and stage. Of note, both cohorts were matched regarding the various inclusion and exclusion criteria, which resulted in the exclusion of patients (paediatric and adult) with very advanced disease (i.e. CNS and/or BM involvement). Remarkably, frequency and extent of extranodal involvement was more pronounced in children, whereas nodal involvement was more prominent in adults. The biological basis of nodal versus extranodal involvement is still largely unknown. These differences might reflect complex differences in the expression of chemokines and chemokine receptors, as well as adhesion molecules and proteases involved in cellular motility [28]. In addition, differences in the microenvironment of the tumour cells at different ages of the patient might play an important role. For example, the involvement of the breast, occasionally seen in pubertal girls or lactating women, suggest that similar tumour cells show a different behaviour and localisation dependent on the presence of the appropriate microenvironment [29].

Bulky disease, as defined by masses larger than 10 cm, was more frequent in adults than in children. This might be related to the fact that relatively smaller masses will be diagnosed earlier in children, but this may also be related to the site of the tumour. For instance, a relatively small mass in the ileocaecal region might result in early clinical symptoms due to intestinal invagination, a well-known complication in BL of childhood. LDH levels were higher in children than in adults. This might suggest that BL in children is a more rapidly growing tumour [30].

Concerning the possibility to generalise our results, we would like to stress that our epidemiological data represent all BL-patients in the Netherlands registered over a five-year period. In contrast, the clinical data represent a certain selection of BL-patients, i.e., below the age of 65 years without a manifest leukaemic phase, CNS involvement or poor performance status. Whereas the NCR data can be considered representative for the incidence in Western Europe, the clinical data need to be interpreted with caution. Given the rarity of the disease, a larger series with detailed clinical information will be very difficult to collect.

In conclusion, BL shows a remarkable pattern of incidence with respect to age and gender, and it may be assumed that the clinical presentation in children is different from adults. Thus far, histological, immunophenotypical and genetic data support the idea that BL should be considered as a single disease entity. However, our observations argue for further studies. New tools, such as gene expression arrays, might give more insight in to the different behaviour of this aggressive lymphoma in children compared with adults.

Conflict of interest statement

None declared.

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