Leukemia Research 84 (2019) 106189

Contents lists available at ScienceDirect

Leukemia Research

journal homepage: www.elsevier.com/locate/leukres

Expression of platelet parameters and platelet membrane glycoproteins in childhood Burkitt lymphoma

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ARTICLE INFO

Keywords:
Platelet membrane glycoproteins
Platelet indices
Burkitt lymphoma
Flow cytometry

ABSTRACT

Platelet activation and functional changes in some haematological malignancies have been investigated with little or no known documentation on Burkitt lymphoma (BL). Abnormalities of platelets contribute to either haemorrhage or thrombotic episodes which are life-threatening in patients with BL. Thus, the study aimed at investigating the various platelet indices and platelet membrane glycoproteins in childhood Burkitt lymphoma. Platelet surface membrane glycoproteins (GPIIb/IIIa, P-selectin and GPIV using PAC 1, CD62p and CD36 monoclonal antibodies respectively) and platelet indices (Platelet Count [PLT], Plateletcrite [PCT], Mean Platelet Volume [MPV], Platelet Distribution Width [PDW] and Platelet Large Cell Ratio [P-LCR]) were determined in children with Burkitt lymphoma and healthy children (normal controls) based on flow cytometry and automated blood cell analysis techniques. PLT and PCT were higher in BL cases than in the normal controls with a significant difference in the PLT ($P = 0.02$). On the contrary, we observed a significant ($p < 0.05$) lower levels in the other platelet indices (MPV, PDW and P-LCR) in children with BL than the controls. With the exception of CD62 P, the other platelet membrane glycoproteins examined showed a decreased level of expression before and after the addition of an Adenosine -5- diphosphate (ADP) in cases of BL. In addition, PAC-1 was probably known to be associated with Burkitt Lymphoma (Odds Ratio [OR] 6.67, Relative Risk [RR] 3.13, 95% CI 1.06–9.21; $p = 0.02$). Finally, oral bleeding was observed to be the commonest bleeding episodes associated with childhood BL. Flow cytometry analysis and cell counting techniques of platelet assessment has described the expression of the platelet membrane glycoproteins and parameters in children with Burkitt lymphoma. Thus, children with Burkitt lymphoma tend to show normal to increased level of circulatory platelets but decreased platelet membrane glycoprotein expressions and platelet dysfunction.

1. Introduction

Platelets are blood components that play major role in haemostasis [1] leading to the formation of mechanical plugs. This prevents or minimizes the spontaneous leakage of blood through small vessels during vascular injury. In addition, it has the ability to cause cell adherence in some conditions such as infections, inflammation and some malignancies [2]. Under normal conditions, platelets exist as slightly convex discoid with its lipid membranes covered with glycoproteins with multiple functionalities [2]. The platelet membrane glycoprotein includes GPIb-IX-V, GPIa/IIa, GP VI, GP IV, GPIIb/IIIa and P-selectin which contribute in haemostatic response to vascular injury. In this study, we targeted at determining the level of expressions of three of these membrane glycoproteins (i.e., GP IV, GPIIb/IIIa and P-selectin) before and after addition of adenosine -5- diphosphate (ADP). GP IIb/IIIa is the most abundant glycoprotein expressed on platelet membranes. Platelet activation results from vascular endothelium damage which in turn leads to the expression and conformational change of the GP IIb/IIIa on the platelet membrane surface. This combined with fibrinogen to exert its physiological functions [3]. PAC-1 is a monoclonal antibody specific for the fibrinogen binding site exposed [2]. P-selectin, also known as lysosomal membrane protein or granular membrane

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https://doi.org/10.1016/j.leukres.2019.106189
Received 22 May 2019; Received in revised form 3 July 2019; Accepted 7 July 2019
Available online 12 July 2019

glycoprotein (GMP 140) belongs to the selectin family of cell adhesion molecules and rarely expressed during the quiescent stage. The activation of platelet under normal condition leads to the rapid fusion of CD62p with the plasma membrane and subsequent expression on the platelet surface. Therefore, CD62p is considered a major indicator of platelet activation [4]. GP IV with it specific monoclonal antibody CD36 is a platelet membrane glycoprotein that has been identified as a physiological receptor for collagen. Platelets interaction with collagen through the GP IV receptor results in activation and adhesion of platelet. These various membrane glycoproteins with their corresponding specific monoclonal antibodies were assessed in our study to investigate platelet functionality in children with Burkitt lymphoma.

Burkitt lymphoma (BL) is a high grade Non-Hodgkins Lymphoma (NHL) characterized by a mass of diffuse small non – cleaved B lymphoid cells [5,6]· The African type (endemic) identified by facial or jaw tumor is the most common childhood cancer in sub-Saharan Africa [7]. Meanwhile we observed in our study that most of the children with Burkitt lymphoma presented with abdominal enlargement which is a classical feature of the sporadic type. Several clinical implications are accompanied with Burkitt lymphoma of which bleeding or thrombotic episodes could possibly be reported.

However, no studies have demonstrated the expression of the various platelets membrane glycoproteins and platelet indices in Burkitt lymphoma. Most studies into platelet–leukemia interactions have been carried out in the context of myeloid leukemia, although a few studies have investigated platelet function in lymphoblastic leukemia's [8,9,2]. The interactions could possibly affect the normal platelet activity contributing to bleeding episodes. Hence, the need to investigate the expression of the various platelet membrane glycoproteins and platelet parameters in children with Burkitt lymphoma to minimize the risk of coagulopathy.

In this study, we have investigated the platelet function in children with Burkitt lymphoma by analyzing the platelet parameters and platelet membrane glycoproteins. Whole blood flowcytometry was employed to detect the various platelet membrane glycoproteins and an automated haematology analyzer was used in the detection of the platelet parameters. In addition, we evaluated the bleeding score of these patients using the standardized bleeding score. The assessment of the peripheral platelet membrane glycoprotein expression and functionality was established in newly diagnosed cases and few BL patients on management. However, samples were collected prior to chemotherapy.

2. Materials and methods

2.1. Ethical consent

Ethical clearance was obtained from the Committee on Human Research Publication and Ethics, School of Medical Sciences, Kwame Nkrumah University of Science and Technology, Kumasi, Ghana and KATH (reference CHRPE/AP/054/18). Blood samples were collected from the participants only after an informed consent was given by their parents/guardians.

2.2. Patients and normal controls participants

Following ethical approval, an unmatched case control study involving a total of 31 children (whose parents agreed to participate in the study by signing the consent form) between the ages of 2–16 years were recruited. Out of the 31 children, 15 healthy children with no history of Burkitt lymphoma were selected as normal controls while the remaining sixteen were cases of Burkitt lymphoma. Histological and bone marrow examinations in accordance with the 2008 World Health Organization (WHO) classification were used as the basis for diagnosing Burkitt lymphoma. The sixteen Burkitt lymphoma cases had 6 children who were newly diagnosed and the remaining 10 were old cases. However, blood samples were collected prior to chemotherapy in all patients under management.

2.3. Bleeding score assessment

The bleeding status of the BL cases were assessed using a standardized bleeding scale that measures bleeding at six different anatomic sites (i.e. epistaxis, cutaneous bleeding, oral cavity bleeding, gastrointestinal bleeding, Haematuria and bleeding from minor wounds or surgery). Bleeding score was later summarized into bleeding and no bleeding, the type of bleeding and its corresponding score. The bleeding symptoms was scored from grade 0 (absence or no symptoms) to grade 3 (symptoms requiring medical intervention) and the overall bleeding score was achieved by adding the scores for all of the bleeding symptoms [10].

2.4. Sample collection technique

Venous blood (6.5 ml) was collected into two tubes containing K_3 EDTA and sodium citrate vacutainer tube (Beckton-Dickinson). 4.5 ml of the blood was first dispensed into the sodium citrate tube for flowcytometry and the remaining 2 ml placed in the K_3 EDTA sample tube for a complete blood count (platelet parameters/ indices). The experiment was performed at Komfo Anokye Teaching Hospital (Serology and Haematology unit) and at the Kumasi Centre for Collaborative Research into Tropical Medicine (KCCR).

2.5. Blood samples preparation for flow cytometry

To detect the membrane glycoproteins, the protocol described by Becton Dickson (BD) [11], for Platelet Activation, Staining and Analysis was used. Whole blood collected into sodium citrate tubes were processed within 20 min of blood collection. Two separate 12 × 75 mm test tubes were labeled for each patient; one tube contained blood with ADP and the other whole blood without ADP. 25 µL of 50 mg/mL adenosine diphosphate solution (ADP) was pipetted into the labeled 12 × 75-mm test tube labeled ADP. Whole blood of volume 0.225 mL was added to the ADP and gently swirled to mix. It was incubated at room temperature for 2 min. Another set of four test tubes were labeled as (PAC1-FITC + CD62p-PE, PAC1-FITC + CD62p-PE + ADP, CD36-PE and CD36-PE + ADP) for each case.

A volume (10 µL) of the various platelet-specific antibodies (PAC-1-FITC, CD62p-PE and CD36-PE) were pipetted into the appropriately labeled test tube. PAC-1 and CD62p were double stained while CD36 was in single separate tubes. Equal volumes of isotype control were added to the appropriately labeled test tubes. To demonstrate specific PAC-1 binding, 5 µL RGDS solution was added in the staining mixture of PAC-1 and CD62p in additional test tube. RGDS peptide competitively inhibits PAC-1 binding.

Using a fresh micropipette tip each time, 2.5 µL of unstimulated blood was added to the tubes labeled without ADP while 2.5 µL of activated fresh whole blood was added to the tubes labeled with ADP. The tubes were gently swirled to mix and incubated for 15 min at room temperature in the dark. 500 µL of cold (2° to 8 °C) 1% paraformaldehyde solution was added to each tube and vortexed. Stained and fixed cells were stored at 2° to 8 °C in the dark. The prepared samples were transported to KCCR and analyzed within 1–2 h after preparation using the FACSCalibur flow cytometer (Becton-Dickson).

2.6. Acquisition and analysis

Acquisition and analysis of the processed samples were performed on scatter gating using CellQuestPro software of the FasCalibur (Becton Dickinson). The flow cytometry settings or acquisition of platelets were optimized by changing the linear scale to logarithmic signal amplification in all five detectors. FacsComp was used in daily CaliBrite beads

calibration. A total of 10,000 events in a log side scatter versus forward scatter were collected for each sample.

The analysis of the platelet activation markers PAC-1, CD62p and CD36 were based on the gated population enclosing platelets as defined by forward scatter (FSC) and side scatter (SSC) characteristics. To avoid non-specific binding, the threshold was set using the cells stained with isotype control antibody or RGDS. The platelet fluorescence of the activation markers was measured as percentage platelet expression and mean florescence.

2.7. Detection of platelet-related parameters (PLT, MPV, PDW, PCT, and P-LCR)

Venous blood collected into anticoagulant EDTA-K_2 sample tubes were analyzed using the sysmex XT4000i haematology analyzer to detect the various platelet indices.

2.8. Detection of prothrombin (PT) and Activated Partial Thromboplastin Time (APTT)

PT and APTT were performed for all the study participants. Venous blood collected into Sodium citrate anticoagulant sample tubes were spun for 15 min. Fifty (50) µl of plasma was added to 100ul of the PT reagent and 100ul of the APTT reagent (and an equal volume of $Cacl_2$) for the measurement of PT and APTT using CoaRad 2A (Axiom, Germany) - semi auto analyzer.

2.9. Statistical analysis

The data obtained in this study was analysed using EPI v7.2.0.1 info (CDC) and Graphpad prism 5. All the categorical variables and continuous variables were summarized by descriptive analysis. Continuous data was expressed as median (25th and 75th percentile) for skewed data and the difference between the various groups was tested using the student *t* test (Mann Whitney). The effect of the categorical variables on the possible disease outcome was estimated using the Odds ratio (OR) with 95% confidence intervals (CI) for multivariate and univariate analysis. The various proportions were assessed using $X^{2\ -}$ test. A p-value < 0.05 was considered statistically significant.

3. Results

3.1. Comparison of Age and Gender among the Burkitt Lymphoma children and normal controls

Table 1 summarized the age and gender among the participants of the Normal control and Burkitt lymphoma groups in the study. The median age difference among the two groups was not statistically significant (p = 0.21) as indicated in Table 1. However, the median age of Burkitt lymphoma [7.5(5.0–11.5) years] was lower than the normal controls [11.0 (8.0–12.0) years]. In addition, we recorded slight increase in the number of females compared to the males in the normal control group while equal number of males and females were documented in the Burkitt lymphoma group.

A total of two participants in the BL group reported a bleeding history of minor type (grade 1–2). None of the participants had a history of grade 3–4 type of haemorrhage. Oral bleeding was the commonest bleeding type observed to be associated with children with Burkitt lymphoma. Meanwhile, there was no significant difference when we try establishing an association between the Burkitt lymphoma and bleeding episodes (OR 3.0, RR 2.0, 95%CI 1.39–2.86; p = 0.35).

Table 1
Comparison of age and gender among the three groups.

Group	Case	Gender Male Female	Median Age (Years)[a]
Lymphoma	16	8 8	7.5(5.0–11.5)
Controls	15	7 8	11.0(8.0–12.0)
Total	**31**	**15 16**	
			p-value > 0.05

[a] Data are presented as medians, with inter-quartile ranges in parentheses.

3.2. Detection of the Mean Florescence Intensity (MFI) of platelet membrane glycoproteins during resting and activation phase

The MFI of the platelet membrane glycoproteins was expressed as median and interquartile ranges. From the graphs, the addition of Adenosine-5- Diphosphate (ADP) indicated ex vivo functional status and 'NO AGONIST' represents the platelet membrane glycoprotein expression at resting phase. The addition of ADP (0.2 µmol/L) was to assess platelet response to agonist stimulating platelets through P2Y12 receptors (platelet specific surface receptor for ADP).

3.3. Expression of PAC-1 analysis

The MFI expression at the resting phase of PAC-1 was higher in the Controls (19.67 [8.58–34.54]) compared to the lymphoma group (12.75 [5.04–17.27]) without any significant difference (p = 0.06). After the addition of ADP, the MFI expression of PAC-1 was increased in both study groups but it remains higher in the controls (30.32[25.44–35.52]) than the lymphoma groups (22.64[17.35–30.34]) with a significant difference (p = 0.02) as shown in Fig. 1.

3.4. Expression of CD62p analysis

The MFI expression of CD62p during the resting phase in the Controls (102.6[79.29–140.00]) was slightly lower compared to the lymphoma group (106.3[59.29–175.80]) without any significant difference (p = 0.09). However, after the addition of ADP, the level of expression of CD62p decreased in Burkitt lymphoma cases (85.33[59.37–170.8]) but increased in the normal Controls (106.8 [78.95–150.50]). Meanwhile, the difference among the two groups was not statistically significant [p = 0.77] (shown in Fig. 2).

3.5. Expression of GPIV (CD36) analysis

The MFI expression of CD36 was lower in children with BL (194.80[117.60–291.10]) compared to the Controls (250.6[112.5–530.1]) in the absence of ADP with no statistical significant difference (p = 0.46). Meanwhile, following the addition of the ADP, the expression decreased in the lymphoma group (164.10 [89.21–272.0]) but increased in the Controls (364.90[172.00–460.80]). The difference in the expression of CD36 was statistical significant

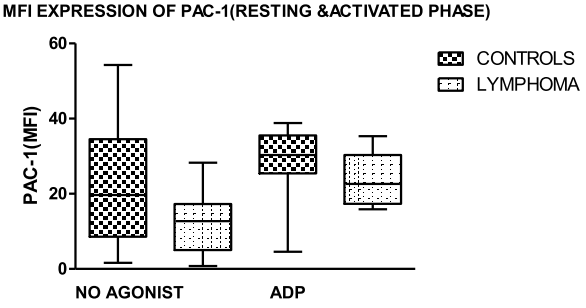

Fig. 1. MFI of PAC1 before (indicated as 'No agonist') and after (indicated as 'ADP') addition of an ADP in normal controls and lymphoma groups. Abbreviation PAC 1, Procaspase-activating compound 1; ADP, Adenosine -5-phosphate; MFI, Mean Florescence Intensity.

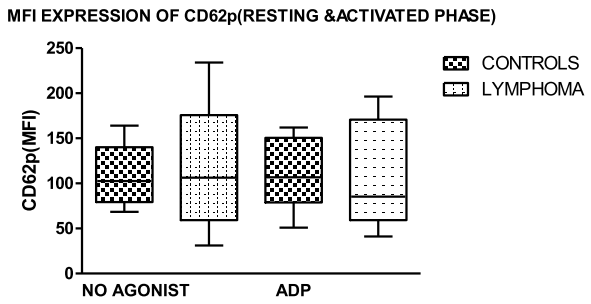

Fig. 2. MFI Expression of CD62p in the Controls and lymphoma groups before and after addition of ADP. Abbreviation CD62p, Cluster of Differentiation 62 for platelet; ADP, Adenosine -5- phosphate; MFI, Mean Florescence Intensity.

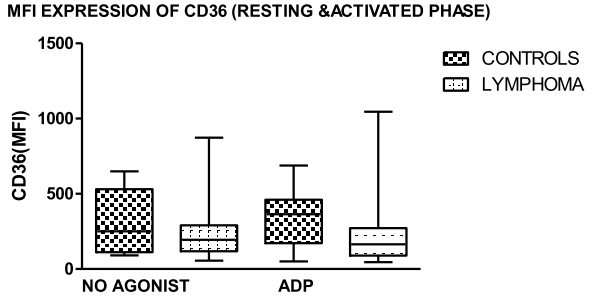

Fig. 3. MFI Expression of CD36 in the absence and presence of an agonist (ADP) in the normal and Burkitt lymphoma groups. Abbreviation CD36, Cluster of Differentiation 36; ADP, Adenosine -5- phosphate; MFI, Mean Florescence Intensity.

($p = 0.04$) as shown in Fig. 3.

3.6. Establishing a link between Burkitt lymphoma and platelet activation markers

Table 2 showed an association between Burkitt lymphoma and the platelet membrane glycoproteins. It was observed that PAC 1 was associated with BL with a statistically significant difference ($p < 0.05$) while the expression of CD36 and CD62p shown no significant association.

3.7. Detection of platelet indices

Platelet (PLT) count and PCT were found to be higher in patients with Burkitt lymphoma than in the controls as shown in Table 3. On the contrary, PDW, P-LCR and MPV were observed to be lower in children with Burkitt lymphoma in comparison to the controls. The differences in the expression of the various platelet indices (PLT, PDW, P-LCR, and MPV) were statistically significant with the exception of the PCT.

3.8. Clotting profile (PT & APTT)

Prothrombin time (PT) and activated partial thromboplastin time (APTT) were measured in the participants to confirm and rule out suspected coagulopathy or antiplatelet agents such as aspirin, warfarin or heparin. None of the cases in the normal controls recorded abnormal PT and the APTT. On the contrary, we reported a slight increase of 2 s above the normal reference range of the PT (9.5–13.5 s) and APTT (30–40 s) in a single case of Burkitt lymphoma. However, none of the participants with bleeding episodes had prolong PT or APTT.

Table 2
Association between Burkitt lymphoma and platelet membrane glycoproteins markers.

Platelet Markers	Odds ratio (OR)	Relative Risk (RR)	Confidence Interval (CI)	p-Value
PAC 1	6.67	3.13	1.06–9.21	0.02
CD 62p	0.90	0.93	0.39–2.27	0.87
CD36	0.90	0.93	0.39–2.27	0.87

Table 3
Comparison of platelet indices in children with Burkitt Lymphoma and Normal controls.

Platelet indices	Controls	Lymphoma	P-value
PLT(10^3/μL)	197(169–237)	271(214–406)	0.020
PCT (%)	0.23(0.18–0.26)	0.19(0.26–0.41)	0.230
MPV (L)	11.1(9.90–12.90)	9.45(7.48–9.80)	0.001
PDW (fL)	13.30(11.0–16.40)	10.30(7.95–11.65)	0.003
P-LCR (%)	29.50(22.80–36.90)	21.50(9.30–24.30)	0.010

4. Discussion

Upon examining platelet surface membrane glycoproteins using the various monoclonal antibodies (i.e., PAC1, CD62p and CD36) in this study, we observed a decreased level of the platelet membrane glycoprotein expression in Burkitt lymphoma cases. This was reported both in the resting phase and after addition of the ADP with the exception of the CD62 P which showed a slight increase in the resting phase (Figs. 1–3). Huang et.al [2] similar studies in childhood acute lymphoblastic leukaemia (ALL) reported an increased level of expression of PAC1 in the absence of an agonist which was not in agreement with our findings. This study was the first to assess platelet functionality in Burkitt lymphoma patients and it was somehow debatable comparing our findings with a different disease group. However, their outcome with respect to the CD62 P was in support with our study. Again, Psaila et al. [12], also observed a decreased PAC 1 level in patients with Acute myeloid leukaemia (AML) or Myelodysplastic syndrome (MDS) which was in accordance with our outcome. However, the CD62 P expression level was decreased in these same study participants during the quiescent phase which was contrary with our findings. Moreover, the insignificant difference ($p > 0.05$) in the expression of CD62p among the BL and the normal control groups in this study was in accordance with Leinoe et al., [13], findings in patients with AML.

The decreased platelet reactivity in response to agonist in the Burkitt lymphoma group might have suggested that, platelets have undergone some degree of in vivo activation in these patients and therefore have a lower capacity for further ex vivo agonist stimulation. In addition, the malignant cells (lymphoma cells) might probably increase platelet adherence thereby interacting with the normal platelet functionality. Although children with BL presented with normal to high platelet count, they did not have the capacity to respond appropriately when stimulated ex vivo which might probably be suggestive of impairment or dysregulation of the various platelet activators. In trying to establish a link between BL and the platelet membrane glycoproteins, it was observed that BL was probably associated (OR 6.67, RR 3.13, 95% CI 1.06–9.21; $p = 0.02$) with PAC 1. This findings did not agree with Legason et al., [14], whose outcome suggested that CD36 is associated with endemic Burkitt lymphoma (eBL) risk. The reasons for the difference in the corresponding findings remain uncertain. The flow cytometry analysis of a case of a normal control (Fig. 4) and Burkitt lymphoma (Fig. 5) have been illustrated.

In respect to the various platelet parameters (PLT, PDW, MPV, P-LCR and PCT) investigated in our study, all except PCT recorded a significant difference ($p < 0.05$) among the BL and the normal controls. Platelet count (PLT) was a dynamic indicator of peripheral blood platelet production and destruction. Platelet production was used as a reference to assess platelet function and identify the cause of thrombocytopenia or thrombocytosis. During the study, thrombocytosis was observed in most children with Burkitt lymphoma, which is a major risk

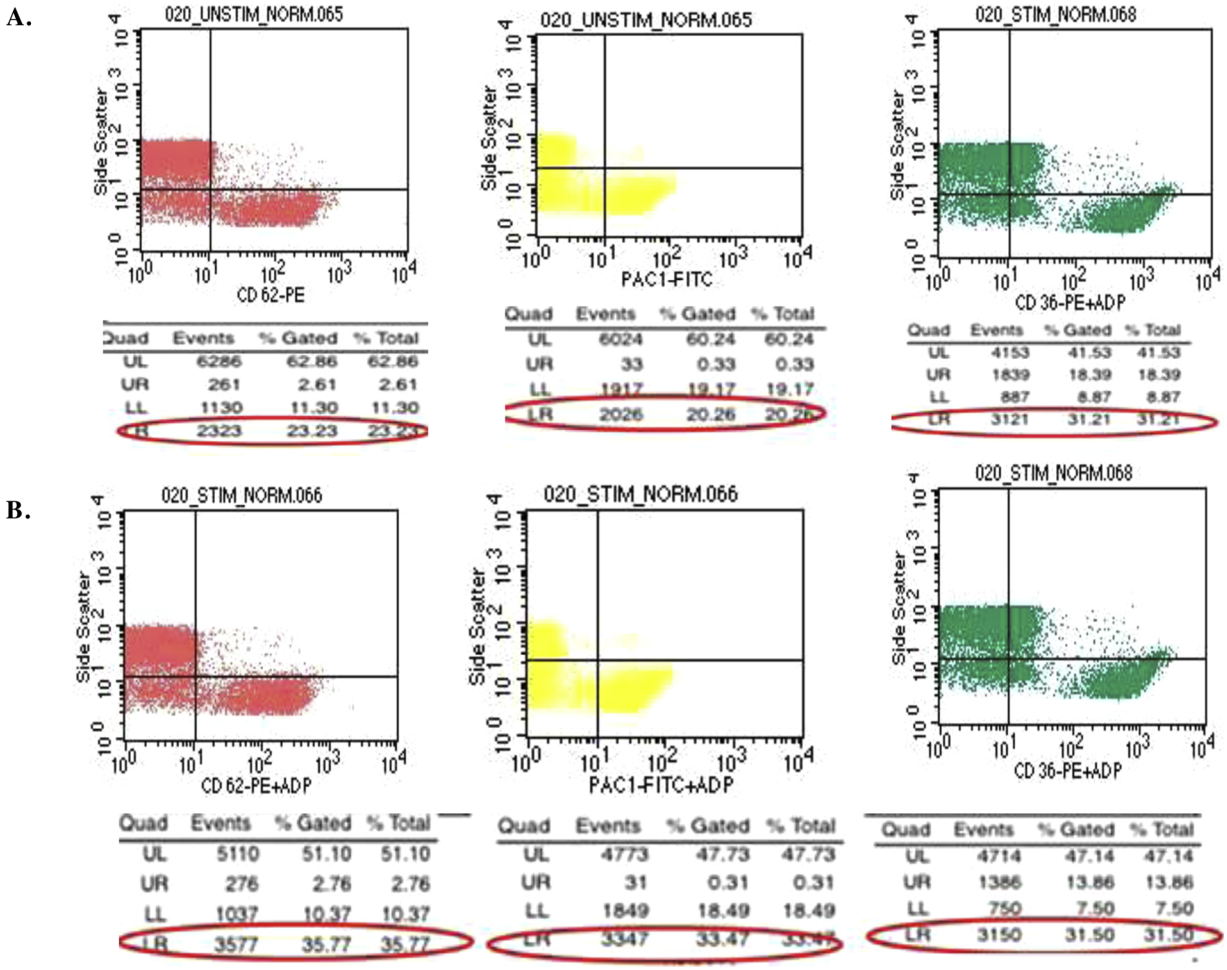

Fig. 4. The expression of the CD62p, PAC-1 and CD36 gated population in a normal case. A. No agonist. B. Addition of ADP. ⬭ indicates the percentage population gated. Abbreviation ADP, Adenosine -5- phosphate.

factor for thrombotic episodes. This contributed to the increased PLT in BL than in the normal controls. Meanwhile, this was not reflected in the platelet membrane glycoproteins expression and functionality. Similarly, the high level of PCT was a reflection of high platelet count in the Burkitt lymphoma group since PCT is always consistent with the changes in PLT (Table 3). However, the difference between Burkitt lymphoma and normal controls was not statistically significant. PCT is the volume occupied by platelets in the blood as a percentage.

Platelet large-cell ratio (P-LCR) was the best tool to assess megakaryocyte activity. Megakaryocyte arises from megakaryoblast by a process of differentiation from the haemopoietic stem cell in the bone marrow and responsible for platelet production [15]. P-LCR was an indicator of circulating larger platelets (> 12 fL) and a good monitoring tool for platelet activity. Large platelets was somehow a representative marker of immature platelets in this study, thus the lower P-LCR (shown in Table 3) observed in Burkitt lymphoma patients in comparison to the normal controls suggested decreased platelet activity.

Again, we recorded a low MPV and PDW (indicated in Table 3) in children with BL compared to the controls. MPV shows platelet enzymatic activity and functional status [16]. It was therefore, an indication of increased platelet diameter, which was used as a marker for production rate and platelet activation [17]. The PDW also directly measured the variability in platelet size, changes with platelet activation and reflects the heterogeneity in platelet morphology. MPV and PDW under physiological conditions have a direct relationship and both usually changes in the same direction [18]. The decreased MPV and PDW in addition to low P-LCR in children with BL might have suggested the decreased platelet activity during the stimulation phase. This finding was similar to a study by Psaila et al. [12], who reported a lower MPV in patients with MDS/AML than in ITP patients.

In summary, Children with Burkitt lymphoma tend to show increased to normal level of the platelet parameters but decreased platelet membrane glycoproteins and abnormal functionality. Thus, Flow cytometric analysis of platelet function and cell counting analyzers have contirbuted in the establishment of the expression of the platelet indices and membrane glycoproteins in children with Burkitt lymphoma.To the best of our knowledge, this is the first study that examines and defines the differences in expression of platelet surface membrane glycoproteins and platelet parameters in children with Burkitt lymphoma. Moreover, our major limitation in the study was the small sample size which was probably due to the decreased incidence rate as a result of the malaria control program. We also had a challenge in getting in contact with the old cases since few follow-up on management at the period of the study.

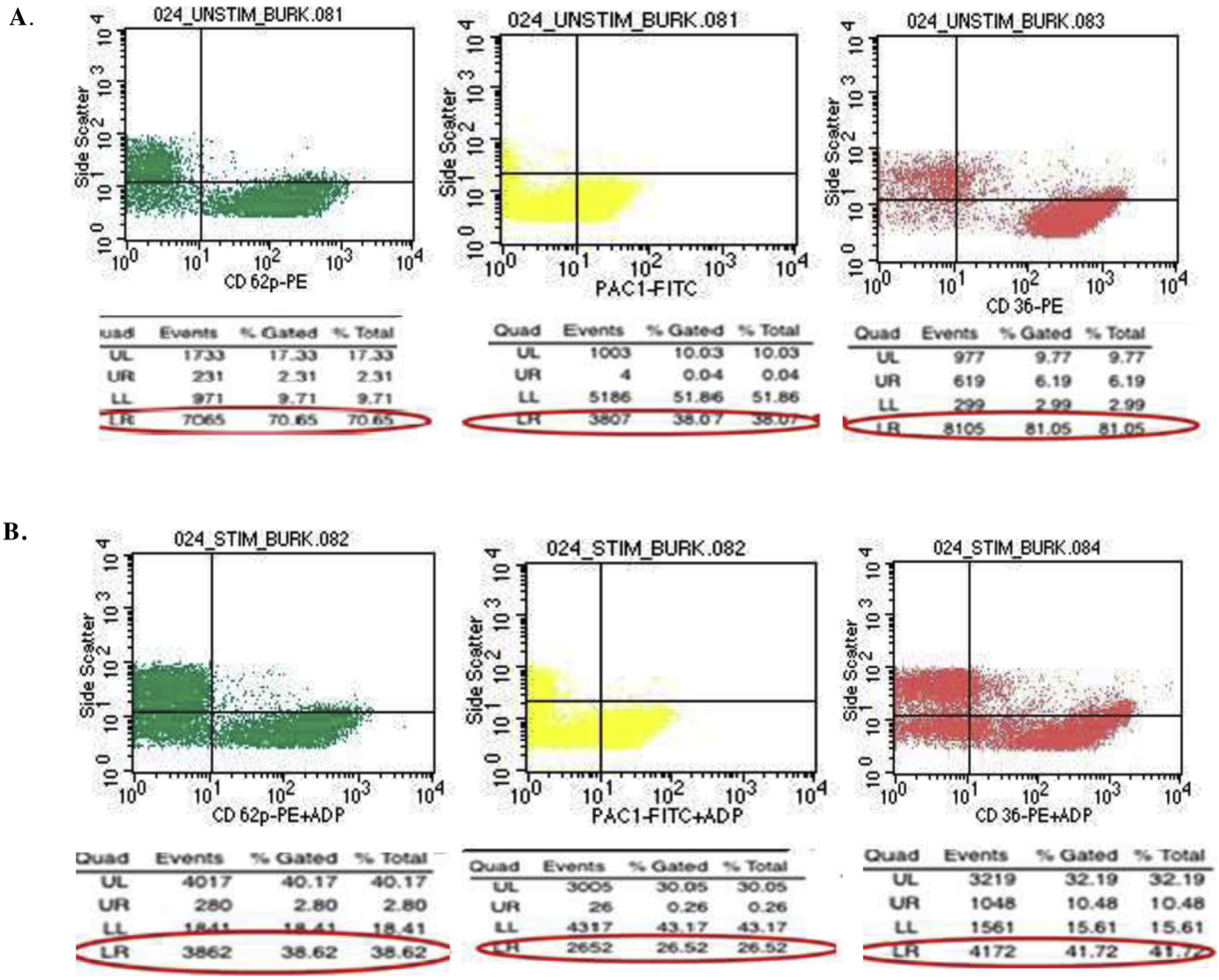

Fig. 5. The expression of the CD62p, PAC-1 and CD36 gated in a Burkitt lymphoma case. A. No agonist. B. Addition of ADP. ⬭ indicates the percentage population gated. Abbreviation ADP, Adenosine -5- phosphate.

Acknowledgements

We would like to acknowledge the various facilities; Kumasi center for collaborative Research in tropical medicine (KCCR)| and Komfo Anokye Teaching Hospital (KATH) that made this research possible. This research couldn't have been successfully achieved without the approval of these renowned institutions.

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