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Craniofacial morphology in patients with sickle cell disease: a cephalometric analysis

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SUMMARY The aim of the study was to evaluate the craniofacial morphology in Caucasian patients with sickle cell disease (SCD) by comparing them with a healthy group paired for gender and age, by means of lateral cephalometric radiographs. Thirty-six Sicilian patients with SCD (17 females and 19 males), including 14 $\beta^s\beta^s$ (mean age 28 ± 5.9 years), 13 $\beta^s\beta^{0th}$ (mean age 27.5 ± 8 years), and nine $\beta^s\beta^{+th}$ (mean age 32.8 ± 9.9 years) were examined. The control group consisted of 36 subjects (mean age 28.9 ± 8 years) without recognized haematological abnormalities. The means and standard deviations were calculated for each cephalometric variable. A two-sample *t*-test was used to compare the means between the study and control groups. One-way analysis of variance and Dunnet's multiple comparison test were used in order to analyse the differences between the control group and the subgroups divided according to genotype. The level of significance used was $P < 0.05$.

The cephalometric findings indicated a posterior rotation of the mandible and a tendency towards a vertical pattern (clockwise), with lower ($P = 0.000$) and total ($P = 0.002$) face heights increased in comparison with the control sample. These findings were more pronounced in subjects with SCD ($\beta^s\beta^s$). In all patients, there was a significantly greater maxillary incisor proclination than in the control group. The upper first molar position to the PTV line was significantly increased but only in patients with compound heterozygosis $\beta^s\beta^{th}$.

The SCD patients did not exhibit the craniofacial abnormalities noted in black American patients with SCD; the craniofacial features observed, reflecting the degree of clinical expression of SCD in Sicilian patients, were of moderate severity.

Introduction

Sickle cell disease (SCD) is a hereditary blood disorder characterized by abnormally shaped red cells. The anaemia associated with SCD is caused by an abnormal haemoglobin mutation, haemoglobin (Hb) S, as a result of which glutamic acid is replaced by valine on the beta chain. This mutation causes chronic haemolytic anaemia and vaso-occlusive episodes with ischaemic injury of many tissues (Schilirò *et al.*, 1992a,b). There are several forms of SCD. The principal genotypes include homozygous sickle cell anaemia, sickle cell haemoglobin C disease, and sickle cell-β-thalassaemia.

Sicily is an endemic area for Hb S and the prevalence of the trait is approximately 2 per cent. The most common genotypes observed in Sicilian patients are Hb S-β^0-thalassaemia ($\beta^s\beta^0$) and Hb S-β^+-thalassaemia ($\beta^s\beta^+$), while homozygous sickle cell anaemia ($\beta^s\beta^s$) is less frequent, and SC is rare. The systemic complications of homozygous sickle cell anaemia are more severe than in compound heterozygosis Hb S/β-thalassaemia and in sickle cell haemoglobin C.

Although it is primarily a haematological disorder, SCD frequently exhibits multisystemic manifestations. Oral manifestations, while not common in SCD, include anaesthesia of the mandibular nerve (Friedlander *et al.*, 1980; Gregory and Olujohungbe, 1994), pulpitic pain and pulpal necrosis (Andrews *et al.*, 1983; Cox and Soni, 1984), which can be ascribed to the microvascular occlusions that tend to affect organs with terminal circulation (Kelleher *et al.*, 1996).

A review of the literature reveals histological changes in dental tissues (Okafor *et al.*, 1986), a greater incidence of caries in young African SCD patients, but no increase in periodontal disease (Crawford, 1988).

Although craniofacial features, such as maxillary protrusion and more forward growth of the mandible with significantly retruded maxillary and mandibular incisors, have been documented in black American children with SCD (Altemus and Epps, 1974; Shnorkian *et al.*, 1984), no craniofacial data have been reported for Caucasian individuals with SCD.

The purpose of this study was to cephalometrically compare the craniofacial and dento-skeletal morphology in skeletally mature Caucasian adults with sickle cell anaemia with that of healthy subjects.

Subjects and methods

Subjects

Thirty-six Sicilian patients with SCD were examined (17 females and 19 males, ranging in age from 18.5 to 51.1 years),

including 14 $\beta^s\beta^s$ (mean age 28 ± 5.9, range 18.7–37.9 years), 13 $\beta^s\beta^{0th}$ (mean age 27.5 ± 8, range 18.5–42.3 years), and nine $\beta^s\beta^{+th}$ (mean age 32.8 ± 9.9, range 18.6–51.1 years) followed at the Department of Pediatric Hematology–Oncology, University of Catania, Italy.

None of the subjects displayed serious craniofacial dysmorphism, dysplastic-dystrophic or dysmetabolic syndromes, or any other systemic or local disease that could affect general body development or craniofacial morphology. No individuals were exposed to radiation therapy and totally or partially edentulous subjects in whom the upper and lower incisors were absent were excluded. None of the patients were regularly transfused; individuals who had undergone orthodontic treatment were also excluded. During infancy, none of the patients exhibited adeno-tonsillar hypertrophy, and none had undergone adeno-tonsillectomy

Diagnosis of SCD was performed by means of haematological, molecular, and genetic studies. The β^s haplotype was type Benin in all patients. The β-thal alleles identified in subjects with compound Hb S-β-thal heterozygotes were CD 39, IVS-I-1, IVS-II-1, IVS-I-110, IVS-I-745, and IVS-I-6.

The control group consisted of 36 healthy patients (mean age 28.9 ± 8, range 18.5–51.2 years) without recognized haematological abnormalities or craniofacial dysmorphism, in the same age range as the experimental group, and paired for gender with SCD subjects. They were selected from the out-patient clinic of the Faculty of Dentistry Catania University, requiring routine dental or orthodontic treatment.

Each patient had a history taken and orthodontic intra- and extra-oral clinical examinations.

Cephalometric analysis

Each lateral cephalogram was obtained using a standardized radiographic technique, with a fixed focus-film distance of 152 cm and a soft tissue filter. The cephalograms were taken in the same cephalostat with the head positioned parallel to the Frankfort plane, with teeth in habitual occlusion and the lips relaxed.

The reference points, planes, and angles used in the cephalometric analysis (Jarabak 1973; Riolo *et al.* 1974; Ricketts 1981) are shown in Figure 1. The films were traced manually by one author (VL) using acetate paper and enlargement of the radiographs (10 per cent) was corrected.

Reliability

Intra-observer errors in landmark identification were detected by digitizing the radiographs twice with a 2 month interval. When there were two images of a structure, the midpoint between these images was chosen.

In order to minimize measurement error, linear and angular measurements were performed twice, and the estimated error between the measurements was calculated using Dahlberg's (1940) formula, $E=\sum d^2/2n$, where d is the difference between the first two measurements and n is the number of double digitizations.

The variance between repeated measurements ranged from ±0.03 to ±0.36 mm for linear measurements, with the greatest error for S–Ba (posterior cranial base), and between

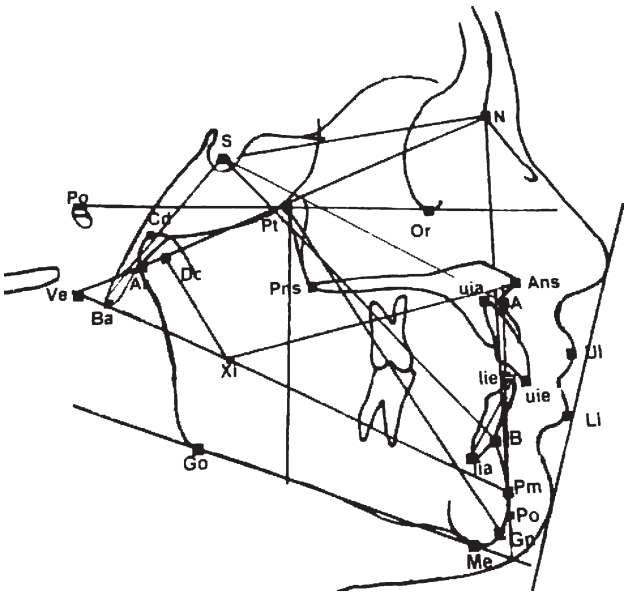

Figure 1 Reference points or lines used in the cephalometric analysis: A = point A: the deepest point on the curvature of the maxillary alveolar process; Ans = anterior nasal spine: the extreme anterior point on the maxilla; Ar = articulare: the point of intersection of the dorsal contour of the condylar head and the contour of the external cranial base; B = point B: the deepest point on the curvature of the mandibular alveolar process; Ba = basion: the most inferior posterior point on the sagittal plane on the anterior border of the foramen magnum; Cc = cranial centris point: the point of crossing of the facial axis and Ba–N plane; Cd = condylion: the extreme superior point on the condylar head; Dc = the intersection point between the condyle axis (Xi–Cd line) and the Ba–N plane; Gn = gnathion: the most downward and forward point on the mandibular symphysis, constructed by the intersection of the facial plane with the mandibular plane; Go = gonion: the midpoint of the mandibular angle between the mandibular ramus and corpus; lia = lower incisor apex: the root apex of the most anterior mandibular central incisor; lie = lower incisor edge: the tip of the crown of the most anterior mandibular central incisor; LL = vermillion border of the lower lip; Me = menton: the extreme inferior point of the mandibular symphysis; N = nasion: the extreme anterior point on the fronto-nasal suture; Or = orbitale: the deepest point on the infraorbital margin; Pm = protuberance menti: the point on the mandibular symphysis where the cortical plate ends and the supramental contour starts to recede into the alveolar process; NS = posterior nasal spine: the extreme posterior point on the maxilla; Pg = pogonion: the extreme anterior point of the mandibular symphysis; Pt = pterygoid point: the extreme superior point of the pterygopalatine fossa; S = sella: the midpoint of sella turcica; uia = upper incisor apex: the root apex of the most anterior maxillary central incisor; uie = upper incisor edge: the tip of the crown of the most anterior maxillary central incisor; UL = vermillion border of the upper lip; Ve = the intersection point between the corpus axis (Xi–Pm line) and Ba–N plane; Xi = centroid reference for the mandibular ramus. APg, subspinale–pogonion line (A–Po); ArGO, ramus line (Ar–Go); BN, basio-nasion line (Ba–N); Dc–Xi, condyle axis line (Dc–Xi); EL, Ricketts' E line; FH, Frankfort horizontal (Po–Or); ILi, long axis of the lower incisors (lie–lia); ILs, long axis of the upper incisors (uia–uie); ML, mandibular line (Go–Me); NS, nasion–sella line (N–S); NPg, nasion–pogonion line (N–Pg); PtGn, facial axis line (Pt–Gn); PTV, vertical pterygoid line (Pt perp); Xi–Pm, corpus axis line (Xi–Pm).

±0.18 and ±0.6 degrees for angular measurements, with the greatest error for N–S–Ba (cranial base angle). They were, however, not considered to be significant.

Statistical method

The means and standard deviations were calculated for each cephalometric variable. A two-sample *t*-test was used to compare the means between the study and control groups and one-way analysis of variance and Dunnet's multiple comparison test in order to analyse the differences between the control group and the subgroups divided according to genotype. The level of significance used was $P < 0.05$.

Results

The results for skeletal, dental, and soft tissue variables are reported in Tables 1 and 2.

Skeletal variables

Flexion of the cranial base described by angle N–S–Ba was normal in both the homozygous sickle cell anaemia

Table 1 Mean values and standard deviations (SD) for the cephalometric variables in patients with sickle cell disease, the subgroups and the controls.

Variable	Control group (n = 36)		$\beta^s\beta^s/\beta^s\beta^{0th}/\beta^s\beta^{+th}$ (n = 36)		$\beta^s\beta^s$ (n = 14)		$\beta^s\beta^{0th}$ (n = 13)		$\beta^s\beta^{+th}$ (n = 9)	
	Mean	SD	Mean	SD	Mean	SD	Mean	SD	Mean	SD
Craniofacial measurements										
Posterior cranial base S–Ba (mm)	48	4.3	45.9	3.2	45.6	3.2	46.3	3.0	43.8	2.3
Anterior cranial base S–N (mm)	73.5	3.6	72.7	4.7	71.3	3.4	75	4.70	70.3	4.9
Cranial base angle N–S–Ba(°)	132.7	6.7	135	5.6	136.3	6.3	134.2	5.49	133.3	4.2
Skeletal facial measurements										
Mandibular length Cd–Gn (mm)	124.3	7.6	123.9	8	124	7.3	125	7.54	120.1	10.2
Mandibular body length Go–Gn (mm)	79.3	5.2	76.4	6.3	76	5.9	77	6.76	75.2	7.0
Mandibular ramus length Cd–Go (mm)	65.6	6.4	65.8	4.7	66.1	3.9	65.6	4.94	63.8	7.1
Maxillary length Ans–Pns (mm)	57.5	8.5	58.7	5	58.8	3.6	59.3	3.61	57.3	7.0
Anterior face height N–Me (mm)	128.2	9.6	128.7	9.2	131.6	8.2	129.3	9.65	123	10.0
Posterior face height S–Go (mm)	86	8.2	83.4	5.6	83.9	6.3	83.1	5.05	82.1	7.4
Facial convexity A–NPo (mm)	1.6	2.3	2.7	3.7	2.4	3.2	3.7	4.69	1.1	2.9
SNA angle (°)	80.4	4.2	80.5	3.3	79.8	2.7	80.9	3.64	81.1	3.5
SNB angle (°)	77.5	4.4	76.7	3.1	76.4	3.1	76	2.70	78.7	2.9
ANB angle (°)	3	1.9	3.8	3	3.4	2.6	4.8	3.18	2.3	2.8
Mandibular angle (°) Ar–Go–Me	122.2	6.7	127.9	6	129.4	6.3	126.7	6.67	126.7	4.0
Face axis angle (°) Ba–Cc–Gn	88.9	5.2	88.8	4.1	88.4	4	88.6	3.97	90.7	4.3
Face depth angle (°) FH–NPo	90.1	3	90	3.2	90.1	2.5	89.1	3.58	91.6	3.3
Total face height angle (°) N–Ve–Pm	57.3	6.7	61.7	4.8	63.2	5	61.4	5.13	59.7	3.8
Lower face height angle (°) Ans–Xi–Pm	44.2	5.2	50.1	4.9	52.3	5	49.3	4.63	48.4	4.5
Mandibular plane to FH (°) FH–GoME	20.9	6.5	25	5.7	27	5.2	24.9	6.30	22.1	3.7
Mandibular arc angle (°) XiPm–DcXi	36.5	5.4	31	5.6	30.9	6.4	29.9	5.79	33.5	3.0
Dental measurements										
Upper incisor inclination angle (°)	95.9	19.1	109.4	6.7	107.9	6.7	110.5	6.28	112.3	5.8
Lower incisor inclination angle (°)	93	8.9	93.2	9.2	89.8	6.9	96.6	11.26	93.6	8.6
Lower incisor to A–Po (mm)	1.2	2.8	1.2	2.5	0.9	2.7	1.8	2.28	2.3	2.2
Lower incisor to A–Po angle (°)	24.2	5.1	25.3	5.9	24.2	5.5	27.3	5.51	28.1	5.8
Interincisal angulation (°)	130.4	12.8	128.3	9.8	130.5	10.2	124.7	8.28	124.5	7.7
Molar position to PTV (mm) 6-PTV	20.9	4	22.8	4.7	23.4	1.9	22.5	3.25	25.7	7.3
Facial soft tissue measurements										
Ricketts' E line: upper lip (mm)	−6	2.7	−4.3	3.2	−5	2.6	−3.1	3.98	−4.5	2.3
Ricketts' E line: lower lip (mm)	−3.5	2.4	−1.8	3.5	−2.2	2.9	−1.1	4.54	−1.5	2.5

Table 2 Cephalometric variables, with statistically significant differences (Student's *t*-test), used in the study for the comparison between sickle cell disease (SCD) and control groups, and one-way analysis of variance (ANOVA) and Dunnet's multiple comparison of means between the $\beta^s\beta^s$, and $\beta^s\beta^{0th}$, and $\beta^s\beta^{+th}$ type of SCD and the control group.

Variable	SCD versus control group (*t*-test)		$\beta^s\beta^s/\beta^s\beta^{0th}/\beta^s\beta^{+th}$ versus control group (ANOVA)	
	P value	Significance	*P* value	Significance
Posterior cranial base S–Ba	0.028	*	0.014	*
Anterior cranial base S–N			0.019	*
Mandibular body length Go–Gn	0.014	*		
Mandibular angle Ar–Go–Me	0.000	***	0.003	**
Total face height angle N–Ve–Pm	0.002	**	0.011	*
Lower face height angle Ans–Xi–Pm	0.000	***	0.000	***
Mandibular plane to FH FH–Go–Me	0.007	**	0.01	*
Mandibular arc angle XiPm–DcXi	0.000	***	0.000	***
Upper incisor inclination angle uie–uia/Ans–Pns	0.000	***	0.001	**
Molar position to PTV 6-PTV (mm)			0.015	*
Ricketts' E line upper lip	0.021	*	0.025	*
Ricketts' E line lower lip	0.020	*		
Multiple comparison of means (Dunnet's test)				
Posterior cranial base (S–Ba)	+			
Mandibular body length (Go–Gn)				
Mandibular angle (Ar–Go–Me)	+			
Total face height angle (N–Ve–Pm)	+			
Lower face height angle (Ans–Xi–Pm)	+	+		
Mandibular plane to FH (FH–Go–Me)	+			
Mandibular arc angle (XiPm–DcXi)	+	+		
Upper incisor inclination angle (uie–uia/Ans–Pns)	+	+	+	
Molar position to PTV (mm) 6-PTV			+	
Ricketts' E line upper lip		+		

*$P < 0.05$, **$P < 0.01$, ***$P < 0.001$.

and heterozygous haemoglobin S groups, while posterior (S–Ba) and anterior (S–N) cranial base lengths were significantly reduced ($P = 0.014$ and $P = 0.019$, respectively). Maxillary linear and angular measurements did not differ significantly from those of the control patients. The mandible exhibited no sagittal deviation (SNB angle, facial axis: Ba–Cc–Gn angle, facial angle: FH–NPo angle), while the jaw angle (Ar–Go–Me) was significantly increased ($P = 0.000$). The proportions of the mandible as manifested by the mandibular arch (Xi–Pm/Dc–Xi angle) deviated significantly, reflecting an altered mandibular shape, with an obtuse angle.

Maxillo-mandibular relationship. The basal sagittal jaw relationship (ANB angle) was unchanged compared with the controls, while both inferior (Ans–Xi–Pm) and total (N–Ve–Pm) face height angles were significantly increased ($P = 0.000$ and $P = 0.002$, respectively).

Dental relationship. In all patients, there was significantly greater maxillary incisor proclination than in the control group.

Soft tissue variables. Protrusion of the upper and lower lip, in relation to Ricketts' E line, was significantly greater in those patients who exhibited a biprotrusive profile.

None of the subjects displayed significantly increased levels of periodontal disease.

Discussion

In the present study, the SCD patients showed a characteristic craniofacial structure, with some linear and angular dimensions differing from those of the control group.

All SCD patients presented a significantly more pronounced vertical (clockwise) pattern as inferior (Ans–Xi–Pm) and total (N–Ve–Pm) face height angles ($P = 0.000$ and $P = 0.002$, respectively) and posterior rotation of the mandible was increased in comparison with the controls.

Cephalometric values indicating mandibular posterior rotation and increased total and inferior face heights varied according to the genotype of the disease. This deviation followed the same specific pattern for all genotypes ($\beta^s\beta^s$, $\beta^s\beta^{th}$), but the most severe craniofacial changes in the dolicofacial pattern were associated with the sickle cell anaemia patients.

The maxillary incisors were significantly labially inclined in all patients, while the upper first molar position to PTV line was significantly increased only in those with compound heterozygosis $\beta^s\beta^{th}$.

Previous studies of subjects with SCD refer exclusively to black American paediatric patients, who exhibited maxillary protrusion and more forward growth of the mandible with significant retrusion of the maxillary and mandibular incisors (Altemus and Epps, 1974; Shnorkian *et al.*, 1984).

The cephalometric findings, observed in the Sicilian patients, indicated only a tendency towards a vertical pattern with respect to the most extreme craniofacial changes, particularly in the maxillary structure described in black populations. This can be explained by the less severe clinical manifestations of SCD in Sicilian patients compared with black patients (Schilirò *et al.*, 1992a,b). In Sicily, SCD is intermediate in severity between the more severe African form and the milder form seen in Saudi Arabia and India. Sickle haemoglobinopathies are diseases in which clinical features are modulated by various genetic and environmental factors. The type of occupation, diet, upbringing, and socio-economic conditions greatly influence the expression of the disease, and in the patients studied, these acquired conditions were satisfactory and quite uniform. The genetic factors known to improve disease expression include the coexistence of α thalassaemia, the β-thalassaemic allele, and the presence of HPFH or δβ-thalassaemia. The β^s gene haplotype in the studied patients was Benin type, as commonly observed in West and North Africa and in South-West Saudi Arabia. However, the Hb F levels in Sicilian patients with SCD were higher than those usually associated with the Benin haplotype. The beneficial effects of high levels of foetal haemoglobin in SCD have been recognized for many years. Clinical studies have demonstrated an inverse correlation between foetal haemoglobin level and the severity of SCD (Charache, 1990; Steinberg *et al.*, 1995). In a previous study of Sicilian patients with SCD, Roth *et al.* (1980) also reported higher levels of Hb F (mean 10.5 ± 3.2) than in American $\beta^s\beta^s$ blacks patients (mean 2.8 ± 1.6).

Conclusion

The craniofacial features observed were of moderate severity, reflecting the fact that the clinical expression of SCD in Sicilian patients is also moderate. This is in agreement with the findings of Schilirò *et al.* (1992a).

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References

Altemus L A, Epps C W 1974 Cephalofacial characteristics of North American individuals with sickle cell disease. Quarterly of the National Dental Association 32: 80–88

Andrews C H, England M C, Kemp W B 1983 Sickle cell anemia: an etiological factor in pulpal necrosis. Journal of Endodontics 9: 242–252

Charache S 1990 Fetal hemoglobin, sickling, and sickle cell disease. Advances in Pediatrics 37: 1–31

Cox G M, Soni N N 1984 Pathological effects of sickle cell anemia on the pulp. ASDC Journal of Dentistry for Children 2: 128–132

Crawford J M 1988 Periodontal disease in sickle cell disease subjects. Journal of Periodontology 59: 164–169

Dahlberg G 1940 Statistical methods for medical and biological students. Interscience Publications, New York

Friedlander A H, Genser L, Swerdloff M 1980 Mental nerve neuropathy: a complication of sickle-cell crisis. Oral Surgery, Oral Medicine, and Oral Pathology 49: 15–17

Gregory G, Olujohungbe A 1994 Mandibular nerve neuropathy in sickle cell disease. Local factors. Oral Surgery, Oral Medicine, and Oral Pathology 77: 66–69

Jarabak J R 1973 Technique and treatment with the light wire appliance, 2nd edn. C V Mosby, St Louis

Kelleher M, Bishop K, Briggs P 1996 Oral complications associated with sickle cell anemia: a review and case report. Oral Surgery, Oral Medicine, Oral Pathology, Oral Radiology and Endodontics 82: 225–228

Okafor L A, Nonnoo D C, Ojehanon P I, Aikhionbare O 1986 Oral and dental complications of sickle cell disease in Nigerians. Angiology 9: 672–675

Ricketts R M 1981 Perspectives in the clinical application of cephalometrics. The first fifty years. Angle Orthodontist 51: 115–150

Riolo M L, Moyers R E, McNamara Jr J A, Hunter W S 1974 An atlas of craniofacial growth: cephalometric standards from the University School of Growth Study. Monograph No. 2, Craniofacial Growth Series. Center for Human Growth and Development, University of Michigan, Ann Arbor

Roth Jr E F *et al.* 1980 Sickle cell anaemia in Sicily. Journal of Medical Genetics 17: 34–38

Schilirò G *et al.* 1992a Clinical, hematological, and molecular features in Sicilians with sickle cell disease. Hemoglobin 16: 469–480

Schilirò G, Samperi P, Testa R, Gupta R B, Gu L-H, Huisman T H J 1992b Clinical, hematological, and molecular features in Sicilians patients with Hb S-β-thalassaemia. American Journal of Hematology 41: 264–269

Shnorkian H I, Chapman D C, Nazif N M, Zullo T G 1984 Cephalometric study of American black children with sickle-cell disease. ASDC Journal of Dentistry for Children 6: 431–433

Steinberg M H *et al.* 1995 Gender and haplotype effects upon hematological manifestations of adult sickle cell anaemia. American Journal of Hematololgy 48: 175–181