Clinical Genetics 1985: **28**: 367–374

A new syndrome: thrombocytopathia, muscle fatigue, asplenia, miosis, migraine, dyslexia and ichthyosis

HELGE STORMORKEN[1], OTTAR SJAASTAD[2], ASBJØRN LANGSLET[3], ILMAR SULG[2], KJELL EGGE[4] AND JØRGEN DIDERICHSEN[5]

[1]Research Institute for Internal Medicine, Rikshospitalet, Oslo, [2]Dept. of Neurology, University of Trondheim Hospital, Trondheim, [3]Dept. of Pediatrics, Ullevaal Hospital, Oslo, [4]Dept. of Eye Diseases, Rikshospitalet, Oslo, and [5]Oslo City Community Health Service, Norway

A new multifacetted syndrome inherited as an autosomal, dominant trait is described encompassing not only two hitherto undescribed hereditary defects – thrombocytopathia and asplenia – but also muscle contractile defect, migraine-like headache, miosis, dyslexia and ichthyosis. None of these defects has so far been assigned to a specific chromosome or linkage group. Further studies on the various aspects of the syndrome are in progress.

Received 14 November, 1984, revised, accepted for publication 30 July 1985

Key words: Asplenia; dyslexia; ichthyosis; migraine; miosis; muscle defect; thrombopathia.

In 1974 a four-year-old boy was admitted to Ullevål Hospital because of a scalp hematoma after an accident. The following year he was referred to the Coagulation Laboratory, Rikshospitalet, where his mother had been examined in 1957 for a hemorrhagic diathesis, the cause of which was thrombocytopathia with a mild thrombocytopenia. Examination of the son revealed a similar platelet dysfunction. From birth, both mother and son had a pronounced miosis.

The peripheral blood smear indicated that other abnormalities were present, and since 1978, both the proband and her son have been subjected to repeated studies. The present report is centered on the clinical and genetic studies of the family. Detailed accounts of the specialized investigations performed on the various pathologies encountered are under preparation for publication in appropriate journals.

All investigations were done after informed consent had been obtained.

Material and Methods

Available for study were all members of generations V and IV (Fig. 1), with the exception of IV, 3, who died at delivery. In generation III, all were available except the proband's mother (III, 2) who cooperated on only one occasion. In generations I and II all are deceased.

Physical Characteristics

The proband and her son have a conspicuous appearance. They are both of small stature, with the eyes deeply set and the forehead high and arched. The minute pupils emphasize their special look (Fig. 2a, b). The proband's mother's face is similar, but less characteristic, and the pupil diameter is

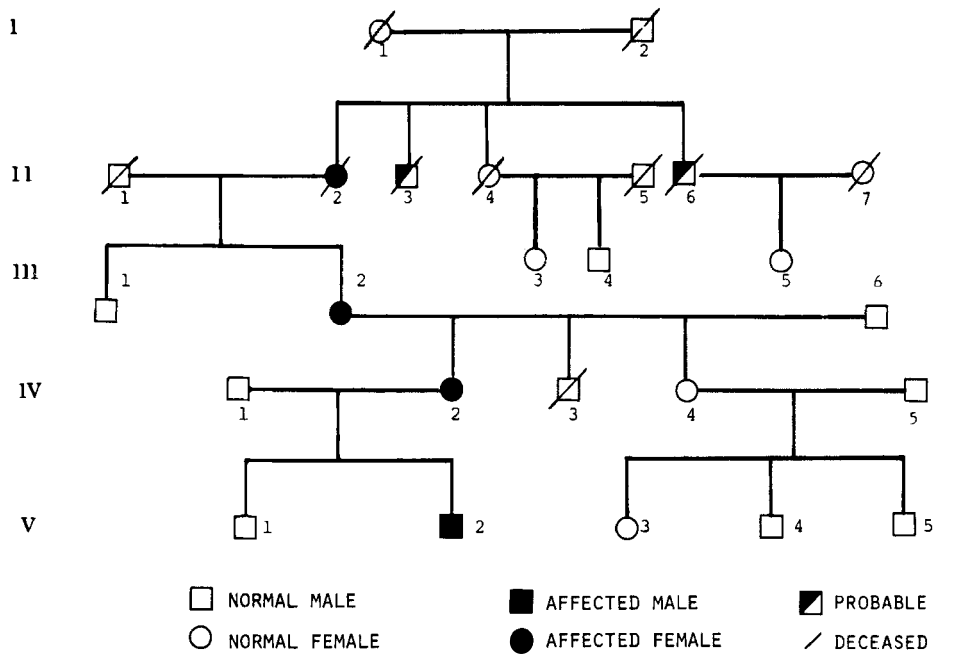

Fig. 1. Pedigree.

larger. The maternal grandmother, on the other hand, was a true replica of the proband and the proband's son in appearance, down to the minute pupils. This information is based on two sources: clear portraits and confirmation by members of generation III and the proband. Because of her mother's alcoholism, the proband was

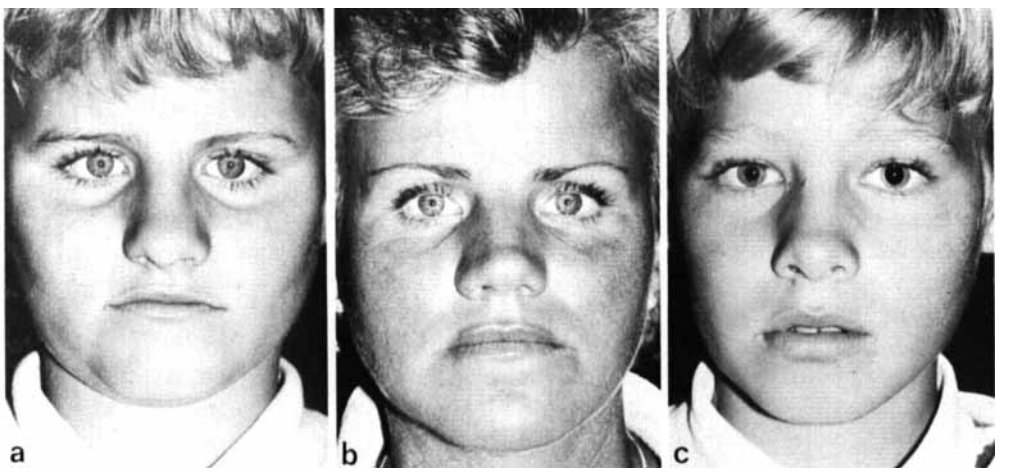

Fig. 2. The propsita (b) with affected son (a) and healthy son (c). One drop of mydriatic (10% metaoxedrine) was instilled in left eye of each 1 h before the picture was taken. Note both the basal pupil diameter and the reaction to the mydriatic in the healthy son as opposed to mother and brother. Note also the extreme similarity between mother and affected son.

fostered by her grandmother until she married, and can thus give first hand information both on the pupils, the bruising, the headache, the dyslexia and the ichthyosis.

Bleeding Tendency

The most conspicuous clinical sign besides the small pupils in the proband and her son is their tendency to bruise easily right from early childhood. In the proband, the first serious bleeding episode, at four years of age, was caused by a fall from a ladder resulting in a head injury. A scalp hematoma developed, and she was kept under observation in hospital for two weeks. At ten years of age, while riding a bicycle, she had an accident causing a large hematoma involving the perineum, labia majores and the lower part of the abdomen. This required two weeks of hospital care. The following year she was examined at the Coagulation Laboratory, Rikshospitalet, where abnormal thrombocyte function with a mild thrombocytopenia was found. She has since experienced several minor hematomas of traumatic origin on various parts of the body. Non-traumatic bleeding signs other than the tendency to bruise easily are frequent nose bleedings, for which she has undergone cauterization several times. Menstrual problems have been minor.

In 1970 she gave birth to her first son and later that year had an appendectomy. In 1972 her second son was delivered by Caesarean section. Although excessive bleeding was noted, transfusions were not performed.

Paradoxically, her first son also developed a scalp hematoma after a minor accident in his fourth year of life and, as with his mother, a tendency to bruise easily, nose bleedings and minor traumatic hematomas are typical features.

The proband's mother suffers from the same type of hemorrhagic diathesis, the bruises often taking on the appearance of cosmetically ugly reddish brown suggilations. According to the proband and generation III members, her maternal grandmother had the same tendency towards bruising easily. The same is said of II, 3 and 6, by generation III members, but this information must be considered with caution. According to medical history and inspection, there has never been a tendency

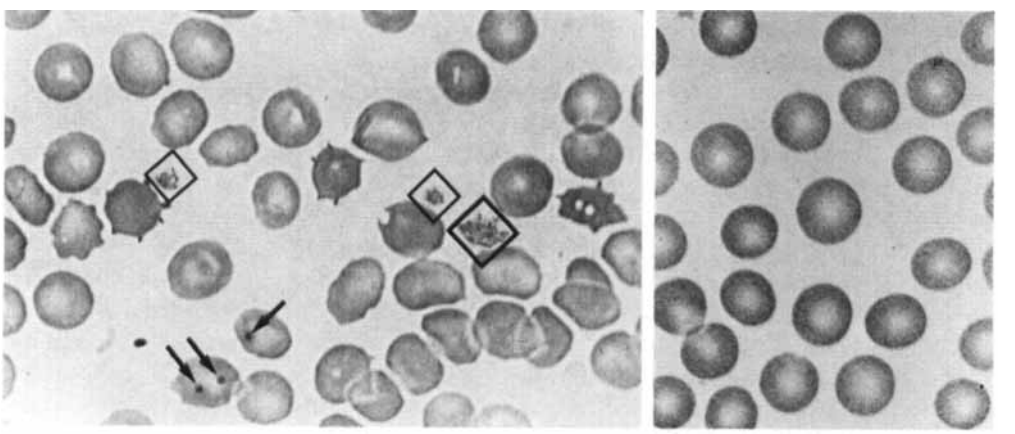

Fig. 3. Appearance of red cells and platelets in a peripheral blood smear. Note the various abnormal forms of red cells and the Howell-Jolly bodies (arrows). Two normal-sized and one giant platelet are also seen. Normal red cells on the right.

to bleeding in any other living member of the family.

The clinical laboratory investigations showed a consistently prolonged bleeding time in the proband and her first son. Coagulation and fibrinolytic parameters were normal and von Willebrand's disease was excluded. Platelet size and morphology were abnormal (Fig. 3) but less so in the proband's mother. Both platelet aggregation and secretion were decreased and the 5-hydroxytryptamine uptake and storage mechanisms were disturbed.

The Muscular Defect

As early as in primary school neither the proband nor her affected son could keep up with their classmates during physical exercise. This was mainly due to spasms, particuarly in the calf muscles, which became tender and hard on palpation, and could last for hours. In the proband the tendency to spasms has diminished with age, and presently she experiences a general sore feeling in the musculature after exercise. The spasms are not accompanied by red urine or low back pain. There is no clinical myotonia in the upper extremities, but a bilateral weakness of the sternocleidomastoid muscles is evident. In the proband, the weakness is also present in the radialis group and shoulder girdle muscles. When subjected to an ergometer electrocardiographic study (kindly performed by Dr. J. Erikssen, Section of Cardiology, Rikshospitalet), she had to stop after only 6 min on 300 Kp because of general fatigue in the calf and thigh muscles. Neither her pulse rate nor blood pressure increased pathologically, and the decline followed a fairly normal pattern.

The latency times for the mechanically and electrically triggered Achilles reflexes are normal in both the proband and her son. However, the duration of muscle response is abnormally increased, the slowing being present both in the initial and in the declining phase. The M-responses have a slight myoclonic appearance. On the other hand, motor and sensory conduction velocities are within normal limits both proximally and distally.

The information on the muscle weakness in the proband's mother is ambiguous, and neither positive nor negative information is available for II,2. Muscle weakness is not present in any other current member of the family.

Anemia – Erythrocytes – Asplenia

Moderate anemia (Hb between 10.5–11.5 g/L) is recorded every time hemoglobin has been measured in both the proband and her affected son. Its nature has not yet been clarified, but it is iron-refractory; serum iron, TIBC, vitamin B_{12}, folic acid and haptoglobin are normal. Red cell osmotic fragility is borderline low. Bone marrow biopsy revealed an increased erythropoiesis.

Abnormalities in erythrocyte morphology were discovered in the peripheral blood film: anisocytosis, poikilocytosis, crenation, fragmented red cells, few stomatocytes, moderate hypochromia and Howell-Jolly bodies, more numerous in the proband than in the son (Fig. 3). Thus, the picture was similar to that seen following splenectomy. Although this had not been done, abdominal computer tomography with contrast (kindly performed by the Department of Radiology, Rikshospitalet) indicated absence of the spleen in both the proband and her affected son.

The only blood sample we have been able to obtain from the proband's mother showed normal red cells, indicating the presence of spleen tissue. A CT scan verified the presence of the spleen, possibly somewhat smaller than normal. For obvious reasons, no information of this kind is available for the deceased generations, but red

cell alterations are absent in V,1, 3, 4, IV,4 and III,6.

The Ocular Defect

Extreme miosis in the absence of ptosis has been present from birth in both the proband and her son (Fig. 2a, b). The pupil is about 1–1.5 mm in diameter, and as measured by a Whittaker Corp. binocular, infrared pupillometer, the maximum diameter that can be obtained with mydriatics is about 2 mm. Both size and maximal dilation are nearly identical in proband and son. After 1 h adaptation to darkness, light exposition for 1 sec reduced the diameter by nearly half.

Darkness vision is clearly decreased in both the proband and the son. Visual acuity is fairly normal in both with correction. Nystagmus is absent, and forehead basal sweating was normal.

As regards visual fields, concentric contractions of the smaller isopters were noted in the son. The ERG showed prolongation of the latency time for A- and B-waves. As already stated, the pupils are larger in the proband's mother, whereas the maternal grandmother had pronounced miosis. According to descendents miosis was present also in II,3 and II,6, whereas the phenomenon is absent in the other existing members.

The Headache

The proband started to suffer from headache in adolescence. It is bilateral, localized in the temporal areas, and is fairly severe. During attacks there is photophobia and phonophobia, the vision is somewhat blurred, but there is no photopsia. Nausea accompanies the attacks, and for a period also vomiting, but this has lessened in recent years. Nose bleedings previously often accompanying the attacks now occur less frequently. For pain relief she is dependent on comparatively strong analgesics, bed rest and darkness.

The affected son also suffers from headache. His is not as characteristic as the proband's, but he is only now reaching the age at which her headaches started. The proband's mother suffers from headache, but the degree and characteristics are difficult to judge because of her alcoholism, which started at the early age of 18. The proband's maternal grandmother, however, had headache with all the characteristics of that of the proband, as testified to by all the members asked. According to the same sources, II,3 and 6 also suffered from headache, but seemingly of a milder degree. No other member of the family has a similar headache.

Dyslexia and Related Neurological and Neuropsychological Problems

After the second year in school, dyslexia was established as the cause for the affected son's severe learning disability. Subsequent investigation revealed the same disability in the proband and her mother, but to a milder degree. Retrospective analysis further showed that the proband's grandmother also had suffered from dyslexia. The boy has been thoroughly investigated, but since a detailed account will appear elsewhere (Diderichsen & Stormorken) only the most relevant findings are given below.

His ability to concentrate in school is seriously impaired as in "attention deficit disorder" (ADD), without being hyperactive, however. He spells words according to pronounciation, paying no regard to orthography, and mixes up and omits letters. Neuropsychological investigations with WISC and the Hallstead test battery revealed abnormal responses. Cerebral computer tomography and EEG were normal.

None of the other present members of the kindred have dyslexia.

Ichthyosis

From childhood, the proband has suffered

from scaling located mainly in the upper and lower extremities. The scales are fine and white, and emollient creams help to alleviate the problem. The ichthyosis is generalized and considerably more severe in the boy. The scaling is even more severe in the proband's mother but was only present in the maternal grandmother to an intermediate degree. None of the other living members of the family suffer from scaling.

Other Organs

A long series of parameters covering the function of most organs was investigated in the proband during hospital stays in 1978 and 1981. None turned out to be abnormal. There is therefore no indication that other organs are involved to any significant degree. It should also be stressed that no evidence of anatomical abnormalities of internal organs other than the asplenia was found.

Other Laboratory Tests

Urine amino acid analysis (kindly performed by the Department of Clinical Chemistry, Rikshospitalet, using a Kontron Liquimat III amino acid analyser) displayed no abnormality either in the proband or in her son.

Cytogenetic studies: The karyotype was determined using a Giemsa banding technique (Institute of Medical Genetics, University of Oslo) and was found to be normal for the proband and her son.

Discussion

Do the described anomalies in certain members of this family represent a true syndrome? The evidence presented above seems to point to the affirmative. First, in the proband and her affected son all the described features are present although some doubt exists as to the type of headache in the son (Table 1). Secondly, the clinical bleeding tendency, the ichthyosis and dyslexia are present in all four generations (V,2, IV,2, III,2, II,2). Miosis is present in three (V,2, IV,2 and II,2). Muscle defect and asplenia are only documented in the two youngest generations.

We have not been able to retrieve other members of this kindred with any of the described features. Although not all components are present in each generation, it is reasonable to conclude that the abnormalities constitute a true syndrome. None of the defects has been assigned to a specific chromosome or linkage group. The heredity is obviously autosomal dominant.

The hemorrhagic diathesis: Despite considerable effort, the basic platelet defect has not yet been unravelled. The studies have shown, however, that the thrombocytopathia is different from all hitherto reasonably characterized platelet dysfunctions (Stormorken et al., to be published).

The muscle dysfunction: The increased muscle fatigue and spasms seem to be of myo-

Table 1

Expressivity and relative degree of various features

	V,2	IV,2	III,2	II,2
Clinical bleeding tendency	+	+	+	+
Muscle fatigue	++	++	+?	?
Miosis	+	+	−	+
Asplenia	+	+	−	?
Headache	+	++	+	++
Dyslexia	++	+	+	+
Ichthyosis	++	+	++	+

genic origin. Leg spasm is a typical sign of metabolic muscle disorders, like McArdle's disease (deficiency of muscle phosphorylase, McArdle 1951). Low back pain and red urine (myoglobinuria), typical additional features of McArdle's disease during attacks, are not present in these patients, however. This also excludes other forms of myoglobinuria.

The defect seems to be different from other recognized inherited muscular disorders, but so far no clue has been provided as to the basic causative factor. Further investigations are in progress by Sjaastad and coworkers.

The red cell abnormality and asplenia: The erythrocyte morphology in the proband and affected son strongly indicated absence of the spleen. As this was confirmed by computed tomography, it is reasonable to consider the red cell abnormalities as secondary to the asplenia.

Congenital, but not inherited asplenia has been described associated with severe heart disease and various other pathologies (bilateral rightsidedness, situs inversus, etc.) usually designated Ivemark's syndrome or the asplenia syndrome (Monie 1982). Since, except for the asplenia, neither heart nor other internal organ abnormalities are present in our family, the syndrome clearly differs from Ivemark's. Moreover, patients with Ivemark's syndrome rarely survive their first year, whereas survival seems quite normal in our family (III,2 and IV,2 > 70 years). The cause of Ivemark's syndrome is considered to be infections during pregnancy. This family therefore seems to be the first described with in vivo documented *inherited asplenia.* The possibility of a postnatal atrophy cannot be entirely ruled out, but none of the conditions known to lead to such atrophy are present (Corrigan et al. 1983).

In view of the role of the spleen in the development of the immune defence system it is interesting that in none of the affected members of this family is there evidence of decreased resistance to infections. A detailed study of their immune apparatus will appear elsewhere (Frøland & Stormorken, to be published).

The miosis presents itself as a marked dysfunction of dilator pupillae. Hereditary miosis is an extremely rare occurrence (Polomeno & Milot 1979, Dick et al. 1983). Although not verified through biopsy, which would be unethical in our patients because of the tendency to bleeding, it is assumed that the dilator muscle is anatomically absent or grossly reduced. The fact that there is practically no dilation even with strong stimulation supports this assumption. Moreover, since there is no ptosis and the reaction to heating was normal, a sympathetic deficiency (Horner's syndrome) does not seem to be the mechanism underlying the miosis. The constrictor function seems to be normal.

Due to the miosis and consequent restricted light admittance the nature and degree of other visual pathologies registered remain obscure. The pathological ERG and visual field defects may, however, indicate true retinal involvement.

The headache: The headache is not unlike common migraine. As platelet serotonin has been implicated in the pathogenesis of migraine (Hanington et al. 1981), a connection between the headache and the observed platelet serotonin transport abnormality is feasible. Furthermore, since platelets are a well established model for serotonergic neurons (da Prada et al. 1981), neuronal dysfunction could also be its underlying cause.

The dyslexia and related problems: The pathogenesis of dyslexia is still obscure (Committee on Children with Disabilities,

1984), but the general notion is that somatic disturbances are the main underlying mechanism in dyslexia and similar syndromes, e.g. minimal brain dysfunction and attention deficit disorder (Shaywitz et al. 1978). It is of interest that Koike et al. (1984) have described a platelet defect in minimal brain dysfunction.

Hallgren (1950) showed that dyslexia may be dominantly inherited, as in the present family, but generally the heredity pattern is disputed and complex (Jørgensen 1983).

Ichthyosis: Clinically, the ichthyosis strongly resembles ichthyosis vulgaris, which is also known to be inherited in an autosomal dominant manner. Histological and biochemical characterization is underway. Ichthyosis is present in several syndromes (e.g. Sjögren-Larsson syndrome, Rud's syndrome, Refsum's syndrome) which also have neurological components.

Note on the Common Denominator

The described abnormalities affect organs derived from different germ layers. The responsible genetic deviation must therefore reside in a constituent concerned with early embryogenesis. With such wide variation in pathologies it is not easy to find a common denominator from our present state of knowledge. Since three of the features (the dyslexia and related problems, the headache and the thrombopathia) may be serotonin-related, the recently recognized family of serotonin-binding glycoproteins, serotonectins (Gershon & Tamir 1984), could in some way be implicated.

References

Committee on Children with Disabilities (1984). Learning disabilities, dyslexia and vision. *Pediatrics* **74**, 150–151.

Corrigan, J. J. Jr., D. B. van Wyck & W. H. Crosby (1983). Clinical disorders of splenic function: The spectrum from asplenism to hypersplenism. *Lymphology* **16**, 101–106.

Da Prada, M., J. G. Richards & R. Kettler (1981). Amine storage organelles in platelets. In *Platelets in Biology and Pathology* 2. J. L. Gordon (ed). Elsevier/North Holland, pp. 107–145.

Dick, D. J., P. K. Newman & P. G. Cleland (1983). Hereditary spastic ataxia with congenital miosis: four cases in one family. *Br. J. Ophthalmol.* **67**, 97–101.

Gershon, M. D. & H. Tamir (1984). Serotonectin and the family of proteins that bind serotonin. *Biochem. Pharmacol.* **33**, 3115–3118.

Hallgren, B. (1950). Specific dyslexia ("congenital word blindness"). Clinical and genetic study. *Acta Psychiat. Scand.* (suppl). **65**.

Hanington, E., R. J. Jones, J. A. L. Arness & B. Wachowicz (1981). Migraine: a platelet disorder? *Lancet* **i**, 720–723.

Jørgensen, G. (1983). Legasthenie aus der Sicht der Genetik. *Med. Welt* **34**, 1162–1166.

Koike, K., A. K. Rao, H. Holmsen & P. S. Mueller (1984). Platelet secretion defect in patients with the attention deficit disorder and easy bruising. *Blood* **63**, 427–433.

McArdle, B. (1951). Myopathy due to a defect in muscle glycogen breakdown. *Clin. Sci.* **10**, 13–35.

Monie, I. W. (1982). The asplenia syndrome: an explanation for absence of the spleen. *Teratology* **25**, 215–219.

Polomeno, R. C. & J. Milot (1979). Congenital miosis. *Can. J. Ophthalmol.* **14**, 43–46.

Shaywitz, S. E., D. J. Cohen & B. A. Shaywitz (1978). The biochemical basis for minimal brain dysfunction. *J. Pediatr.* **92**, 179–187.

Address:

Professor Helge Stormorken
Research Institute for Internal Medicine
Rikshospitalet
0027 Oslo 1
Norway