Acanthocytosis, normolipoproteinaemia and multiple tics

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Summary

A chronic degenerative neurological disorder is described which is characterized by tics, grimacing, involuntary movements, a severe disturbance of swallowing and a concurrent malformation of the erythrocytes. This condition is clearly different from familial hypo-betalipoproteinaemia and abetalipoproteinaemia, the two previously described neurological disorders associated with abnormal red cells.

Introduction

Neurological disease and normolipoproteinaemic acanthocytosis has been reported in two families, the G family from New England (Kuo & Bassett, 1962; Rovito & Pirone, 1963; Levine, 1964; Estes *et al.*, 1967; Engel *et al.*, 1967; Levine, Estes & Looney, 1968) and the St family from Eastern Kentucky (Critchley *et al.*, 1968). The neurological and systemic manifestations separate this syndrome from the ataxic disorder of early life associated with abetalipoproteinaemia (Salt *et al.*, 1960), and from familial hypo-betalipoproteinaemia (Mars *et al.*, 1969). This report describes the clinical and laboratory findings in a third individual, the first to be recognized in the United Kingdom.

Case report

The patient, Si., a woman aged 30 years, was referred to the Neurological department in August 1969. Her parents were unrelated, one from Lancashire and the other from Lincolnshire. Until her marriage in 1965 her medical history had been unremarkable and she had held a semi-skilled job assembling electronic valves. However, her husband had noticed during their courtship that her walk was ungainly and had avoided drinking with her in company because of her tendency to slobber.

After the birth of her first child in 1967 she became forgetful and unreliable and was twice accused of

neglecting her child. At times she would have difficulty in coordinating movements and would bump into objects or, when sitting quietly, suddenly fall to the floor. Her husband became increasingly irritated by grunting noises of which at first she was unaware. During her second pregnancy she developed hypertension and in November 1968 gave birth prematurely at home after 7 months' gestation. She was unable to get to the telephone to call the doctor. On her own volition she had attended the ENT and Psychiatric clinics in 1968 complaining of intermittent difficulty in swallowing, thinking that it was due to cancer. There was no history suggestive of steatorrhea.

When examined in September 1969 she was noted to be thin with high arched feet, 5 ft 4 in in height and weighing only 126 lb. She was alert and oriented, yet appeared unkempt and dishevelled. Many of her symptoms distressed her but there were others of which she was apparently unaware until her attention had been directed to them. Most disturbing were the wide variety of oro-facial tics. At times these appeared compulsive or even hysterical. They were continually present during waking hours though fluctuating in severity from day to day and partially improved by benzhexol and diazepam. Her speech was dysarthric, partly broken by the involuntary movements. She would also grunt, suck, cluck, make repetitive sounds, bite her tongue and lower lip (Fig. 1), or struggle to control the pooling of saliva. The involuntary limb movements were sometimes dystonic and sometimes choreiform with hyperextension and flexion of her trunk and throwing out of an arm or leg. She performed purposive movements fairly well despite an apparent loss of manual and finger dexterity. Her visual acuity was normal, the visual fields full and there was no evidence of retinitis pigmentosa. There were no Kayser-Fleischer rings and the pupils reacted to light and accommodation. There was no

FIG. 1. Proband. Note especially her bitten lip.

nystagmus. The jaw jerk was present. She had normal tone and power in her limbs without wasting. The reflexes were just present and the plantars were flexor. She was not ataxic and sensation was intact. She could hop on either foot. Romberg's test was negative. Her blood pressure was 160/100 mmHg. Heart, chest and abdomen were normal and there were no glands palpable.

Investigations

The blood indices were as follows: Hb 13.1 g/100 ml, MCHC 34%, WCC 4400/ μ l (normal differential), platelets 182,000/ μ l, reticulocytes 3%, ESR (Westergren) 8 mm in 1 hr. A Romanowsky stained blood film showed acanthocytosis and rouleaux formation (Fig. 2). In a fresh saline preparation acanthocytes made up 40–60% of the red cell population. The red cell deformity was corrected by the addition of 20% albumin or the non-ionic detergent, Tween 80. No intracellular inclusions were noted either in wet preparations or after incubation with methyl violet. The red cell osmotic fragility, incubated and non-incubated, was normal but a slight increase in auto-haemolysis was noted after 48 hr incubation. This was corrected by the addition of ATP. The acanthocytes stood out well under the scanning electron microscope (Figs. 3 and 4). They comprised about

FIG. 2. Wet preparation to show acanthocytes, light microscopy, $\times 510$.

45% of the cells, the other cells appeared normal. No membrane defects were seen.

The serum bilirubin was normal (0.5 mg/100 ml), but a slight reduction in haptoglobin was noted on starch gel electrophoresis. The levels of erythrocyte glucose-6-phosphate dehydrogenase, creatinine phosphokinase and triose phosphate isomerase were normal or slightly elevated. Haemoglobin electrophoresis and serum vitamin B₁₂ and folate levels were also normal.

The biochemical studies were normal apart from an increased fibrinogen level at 813 mg/100 ml. The serum cholesterol was 225 mg/100 ml, vitamin A 26 micrograms/100 ml, fasting vitamin E 1.2 mg/100 ml; the total serum proteins were normal at 7.0 g/100 ml with a raised globulin fraction on electrophoresis. Using paper electrophoresis the alpha-lipoprotein was 271 mg/100 ml and beta-lipoprotein slightly raised at 740 mg/100 ml. Serum triglycerides were also estimated nephelometrically by the method of Stone & Thorp (1966), and the lipoprotein pattern was determined as described by Stone *et al.* (1970). The

FIG. 3. Electron microscopy, $\times 4900$. FIG. 4. Electron microscopy, $\times 12,800$.

results are shown in Table 1. The serum electrolytes were normal: sodium 138 mEq/l, potassium 4.5 mEq/l, chlorides 101 mEq/l, calcium 9.8 mg/100 ml, and magnesium 3.4 mg/100 ml, with serum urea 34 mg/100 ml, glucose 138 mg/100 ml and creatinine 0.6 mg/100 ml. The serum iron was 120 μ g/100 ml, copper 147 μ g/100 ml and copper oxidase 395 units. The creatinine clearance was 119 ml/min, without aminoaciduria and the faecal fat excretion was 3.4 g/24 hr.

TABLE 1.

Estimation	Concentration in mg/100 ml of serum	
	(1)	(2)
Total serum cholesterol	198	246
Serum triglycerides	158	116
Beta lipoproteins (Sf 0-20)	370 (Normal)	481 (Normal)
Pre-beta lipoproteins (Sf 20-400)	187 (Slightly raised)	132 (Normal)
Chylomicrons (Sf > 400)	6 (Normal)	8 (Normal)

Psychometric tests were performed on two occasions. The verbal I.Q. (Wechsler Adult Intelligence Scale) was 91, performance 81 and full scale 86. The Minnesota perceptuo-diagnostic test at 58 and the scatter of the Wechsler subtests suggested organic deterioration. This was not confirmed by pneumoencephalography which showed a normal ventricular system with intact caudate bulges. The CSF showed only 1 wbc/ μ l and a protein content of 15 mg/100 ml. The Wassermann and Lange reactions were negative. Electromyographic and nerve conduction studies, electrocardiography, muscle and liver biopsies were all normal. Cinematographic studies performed on two separate occasions when swallowing thick barium confirmed the difficulty in initiating deglutition and showed lack of co-ordination, weakness and flaccidity involving the soft palate and hypopharynx.

No acanthocytes were seen in the peripheral blood of her brother, father or two children. The presence of a serum factor affecting platelet function in this condition is the subject of a separate report (Betts, Critchley & Nicholson, 1970).

Discussion

The normolipoproteinaemic syndrome differs from the two other neurological disorders associated with abnormal red cells in that there is no evidence of a concurrent disturbance of lipid metabolism. The disturbance of lipid metabolism seen in abetalipoproteinaemia is severe with impaired transport of fats across cell membranes and a decrease in all serum lipids with absence of the betalipoprotein moiety (Salt *et al.*, 1960), and in some cases an accompanying abnormality in the red cell phospholipids (Phillips, 1962). The clinical presentation resembles that of Friedreich's ataxia. As only one family has been reported with familial hypo-betalipoproteinaemia, observations on this syndrome are necessarily limited. The clinical manifestations simulate multiple sclerosis, the serum lipids are reduced and the red cells readily resume a normal shape in hyperlipaemic solutions (Mars *et al.*, 1969).

Historically it had been assumed that the present

syndrome also formed part of the spectrum of lipid abnormality. Kuo & Bassett (1962) originally presented the New England family as an example of hypo-betalipoproteinaemia. The younger brother had had loose stools since childhood with three times the normal amount of fat in the faeces (18 g/24 hr), and loose stools were seen in most of the acanthocytotic but neurologically normal relatives. However, repeated investigations subsequently showed normal lipoprotein levels and intestinal biopsies were likewise normal. Neither the present patient nor any member of the Kentucky family (Critchley *et al.*, 1968) had a history of steatorrhoea or loose stools. The acanthocytes of this syndrome are stable in hypo- and hyper-lipaeamic solutions. Their behaviour when exposed to the detergent Tween 80 is similar to that of other acanthocytes but this finding is not pathognomonic of a lipid abnormality: other morphologically similar cells such as pyknocytes and burr cells occasionally regain a normal shape in the presence of detergents (Rowland, 1967).

The distinctive clinical feature of the normolipoproteinaemic syndrome is an extra-pyramidal movement disorder with dystonic, choreiform and athetoid movements and a wide variety of oro-facial tics. No swallowing difficulties were experienced in the patient described by Levine *et al.* (1968) although there were roving tongue movements and the speech was dysarthric and interrupted. The oro-pharyngeal abnormalities in the present patient are mild by comparison with those of the proband in the Kentucky family. He had a gnawed tongue and severe lacerations on his lips and held a rag to his mouth to prevent further damage. Since the original publication a further study of his swallowing difficulties has been made (Critchley, E.M.R., 1968, unpublished). He would initiate deglutition by throwing his head backwards to straighten the curvature of the oro-pharynx. In the cine-films, the partially amputated tongue was relatively immobile. Discordant movements were seen involving the tongue, palate and posterior pharyngeal wall but these failed to result in a normal peristaltic wave. Beyond the hypopharynx rhythmic muscular contractions were present.

The compulsive monosyllabic utterances in these patients never suggested coprolalia despite the disinhibiting influence of the dementia, but there is a close resemblance to the Gilles de la Tourette syndrome, and it is of interest that tongue biting has also been reported in this condition (Striner, 1927). We can anticipate the discovery of other patients with normolipoproteinaemic acanthocytosis if a wet preparation of the peripheral blood is examined on all patients with oro-facial tics and involuntary movements. The condition appears to follow an

autosomal recessive mode of inheritance, and, in the other two families, there is evidence of partial expression in the heterozygous form. The importance of the syndrome lies in the association of chronic degenerative neurological disease with biochemical and haematological anomalies, largely unexplored, yet amenable to further study.

Acknowledgments

We wish to thank in particular, Doctors D. P. Oakley, A. F. Ollerenshaw, W. G. Owen, V. Bhushan and J. A. Gatt, B.Sc. at Preston Royal Infirmary for their help and interest, Dr J. K. Lloyd at Great Ormond Street Hospital for vitamin E estimations, Dr M. C. Stone at Leigh Infirmary for nephelometry, and Doctors A. J. Salisbury and J. A. Clarke at St Bartholomew's for electronmicroscopy. Requests for reprints should be addressed to E.M.R.C.

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