Quebec Cooperative Study of Friedreich's Ataxia.

Clinical Laboratory Findings in Friedreich's Ataxia

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SUMMARY: *All clinical laboratory tests carried out in 4 groups of patients with the diagnosis of typical or atypical Friedreich's ataxia have been found to be within the normal range. In this prospective study of 50 patients, a number of findings previously reported to be abnormal in the literature, have not been confirmed.*

RÉSUMÉ: *Tous les tests de laboratoire clinique accomplis sur 4 groupes de patients ayant le diagnostic d'ataxie de Friedreich "typique" ou atypique s'avérèrent entièrement à l'intérieur des limites normales. Cette étude prospective de 50 patients nous a permis d'éliminer, en tant que phénomène caractéristique de la maladie, un grand nombre de données que l'on avait préalablement rapporté dans la littérature mondiale, comme étant anormales.*

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INTRODUCTION

It is widely believed that genetically transmitted degenerative disorders are the result of inborn errors of metabolism. As part of a program to delineate the hematologic and biochemical characteristics of Friedreich's ataxia, a series of tests were carried out on 36 patients with the typical disease and 14 with the atypical form. In additon to routine clinical laboratory tests (liver and renal function, etc.), several specific investigations were conducted in those cases where abnormal results had previously been reported in Friedreich's ataxia. Such determinations included the measurement of the activity of certain serum enzymes, a search for the presence of acanthocytotic red cells, serum protein electrophoresis and serum lipid levels. It was hoped that the results of this series of tests could serve as a useful basis in a continuing search for a biochemical abnormality in Friedreich's ataxia, which could be used as predictive marker.

SUBJECTS AND METHODS

Serum lactate dehydrogenase (LDH), alkaline phosphatase, creatinine, urea, uric acid, Ca^{2+}, Na^{+} and K^{+} were measured by technicon SMA 12/60. Ceruloplasmin and transferrin activities were measured immunochemically by the method of Mancini et al. (1965). Serum glutamate oxaloacetate transaminase (SGOT), glutamate pyruvate transaminase (SGPT) and creatinine phosphokinase (CPK) were estimated using the Abbott 100 apparatus. Aldolase activity was measured using the kit of Boehringer-Mannhein. Serum protein electrophoresis was performed by a standard technique using a Beckman microzone apparatus. Vitamin B_{12} levels were estimated by radioassay using the Schwarz-Mann kit. Total serum cholesterol was measured by the Technicon procedure; serum triglycerides were estimated by the semi-automated method of Kraml and Cosyns (1969). The 50 patients studied have been described in detail in a previous paper with the criteria for their selection.

RESULTS

Hematology

Distribution of ABO/Rh blood groups types for the Friedreich's ataxia group is shown in Table 1. As is evident, the only differences between the groups are the slight increase in type 0^{+} in Group Ia (typical Friedreich's ataxia) and the marked increase in blood type A^{+} in groups IIa and IIb. Other hematologic data are shown in Table 2. A single patient showed signs of anemia (RBC count 3.4 x $10^6/mm^3$, hemoglobin 8.2g./100 ml., hematocrit 26.9%). Otherwise, all patients studied had hematologic profiles within normal limits. No sign of acanthocytosis was seen in any of the 23 cases studied.

Biochemistry

Serum enzyme activities, together with the levels of creatinine, urea, uric acid, electrocytes and vitamin B_{12}, were studied in 50 patients with suspected Friedreich's ataxia. Results are shown in Table 3. Electrolyte and B_{12} levels were within normal limits in all. Serum creatinine

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was found to be elevated in 5 cases (1.6, 1.3, 3.3, 1.5, 1.6). Urea levels, however, were within normal limits. Serum uric acid was found to be elevated in only one case (9.7 mg %). Ceruloplasmin was at or below the lower limit of normal in the serum of 8 patients from Group Ia and 2 of Group IIb. Five patients showed elevated serum SGOT (64, 66, 68, 175, 75 i.u.) and only 3 patients had elevated serum SGPT activities (54, 52, 47 i.u.). However, SGPT values are often low in group Ia and IIa, 9/21 and 4/6 patients respectively being at or below the lower limit of normal. This point will be discussed in a later paper. Aldolase activity was within normal limits in all cases. Serum LDH activity was found to be elevated in 11 patients, 9 in Group Ia (298, 288, 293, 403, 253, 286, 250, 294 i.u.), and one each in Group Ib (288 i.u.) and Group IIb (288 i.u.).

Serum protein profiles are shown in Table 4. Values for albumin, globulins and immunoglobulins were found to fall within normal limits in all cases.

Finally, serum cholesterol and triglycerides were studied in detail because of the reported low values in such entities as familial hypobeta-lipo-proteinemias who often present with similar phenotypes. There were no significant differences for cholesterol levels (a control, age matched, group of 17 normal subjects was also run in the same laboratory because of the known age-variability of these measurements. In this control group, mean serum cholesterol was 163 mg % and mean triglyceride level 75 mg %). Triglycerides values tended to be elevated in Groups Ia and IIa, but this rise did not attain significance. Despite this, it should be remarked that two families (Group Ia, cases 8-9 and Group IIb, cases 6-7-8) had consistantly low levels of serum triglycerides (below 50 mg %) in all members, without acanthocytosis. Average cholesterol and triglyceride levels in the 5 patients involved were 159.4 mg % and 38.8 mg %, respectively.

DISCUSSION

Although, no abnormalities of either a hematologic or biochemical

TABLE 1

DISTRIBUTION OF ABO/Rh BLOOD GROUPS
(% DISTRIBUTION)

GROUP	NORMAL POPULATION OF QUEBEC (Quebec Red Cross data)	EXPERIMENTAL PATIENTS			
		GROUP Ia	GROUP Ib	GROUP IIa	GROUP IIb
n	—	33	2	6	7
A^+	35	33.3	–(1)	66.7	71.4
A^-	6	6.1	–(1)	0.0	14.3
O^+	38	48.5	–	16.7	14.3
O^-	7	6.1	–	0.0	0.0
B^+	9	3.0	–	16.7	0.0
B^-	2	0.0	–	0.0	0.0
AB^+	3	3.0	–	0.0	0.0
AB^-	1	0.0	–	0.0	0.0

TABLE 2

HAEMATOLOGIC FINDINGS IN FRIEDREICH'S ATAXIA

	FRIEDREICH'S ATAXIA (all cases)		
	MEAN	RANGE	NORMAL RANGE
Leucocyte count /mm^3	6520	4900-12500	5000-10000
% neutro	60	21-80	54-62
Baso	1	0-2	0-1
Eosino	2	0-9	1-6
Lympho	31	11-69	20-45
Mono	6	1-13	2-10
Red Blood cell count (x 10^6) /mm^3	4.7	3.4-6.2	4.5-6.5
Haemoglobin (g/100 ml)	13.5	8.6-16.2	13.5-18.0 ♂ 11.5-16.5 ♀
Haematocrit (%)	39.6	26.9-46.7	40.0-48.0
MCV (μ^3)	86.7	74.0-100.0	80.0-100.0
% mean cell haemoglob. (g/100 ml)	34.0	29.3-35.4	32.0-37.0
Serum iron (mg %)	114.0	50.0-202.0	70.0-195.0
Acanthocytosis	NIL	NIL	NIL

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TABLE 3

BIOCHEMICAL DATA
(mean ± S.D.)

DETERMINATION		GROUP Ia		GROUP Ib		GROUP IIa		GROUP IIb	
NAME	UNITS	N	RESULT	N	RESULT	N	RESULT	N	RESULT
1. Ceruloplasmin	mg%	32	29.43 ± 9.17	—	—	6	31.17 ± 7.17	5	24.0 ± 5.29
2. Transferrin	mg%	15	282.87 ± 56.36	—	—	4	275.0 ± 51.96	5	261.4 ± 16.65
3. SGPT	i.u.	21	20.28 ± 15.36	—	—	6	25.0 ± 8.73	3	27.33 ± 3.51
4. SGOT	i.u.	33	39.33 ± 14.38	3	96.67 ± 68.64	6	25.0 ± 5.62	8	36.25 ± 12.65
5. Aldolase	i.u.	20	1.89 ± 1.66	—	—	6	1.78 ± 0.84	3	6.80 ± 2.19
6. CPK	i.u.	21	58.43 ± 42.61	—	—	5	44.20 ± 23.59	3	110.67 ± 54.92
7. Alk. Phosph.	i.u.	33	96.09 ± 59.75	3	120.67 ± 50.52	6	58.83 ± 24.77	8	106.50 ± 33.45
8. L.D.H.	i.u.	32	205.91 ± 65.23	3	232.33 ± 63.68	6	153.0 ± 33.88	8	222.0 ± 36.50
9. Creatinine	mg%	27	1.00 ± 0.56	3	0.6 ± 0.0	6	1.05 ± 0.31	5	0.84 ± 0.17
10. Urea	mg%	29	29.38 ± 5.70	3	26.33 ± 6.80	6	24.66 ± 10.61	5	30.8 ± 3.89
11. Uric Acid	mg%	33	5.22 ± 1.55	3	5.07 ± 0.46	6	4.47 ± 1.05	8	5.29 ± 0.80
12. B_{12}	pg/ml	26	571.88 ±151.81	3	658.33 ±142.63	5	595.00 ± 67.19	8	587.5 ± 52.12
13. Ca^{++}	mEq/L	33	9.88 ± 0.65	3	10.00 ± 0.62	6	9.97 ± 0.56	8	9.90 ± 0.63
14. K^{+}	mEq/L	28	4.27 ± 0.31	3	4.77 ± 0.50	6	4.03 ± 0.37	5	4.38 ± 0.16
15. Na^{+}	mEq/L	28	140.86 ± 2.91	3	143.00 ± 2.64	6	141.33 ± 2.50	5	141.20 ± 1.30
16. Schilling	%	20	20.01 ± 8.34	—	—	6	25.85 ± 7.05	3	25.0 ± 4.58
17. Cholesterol	mg/100 ml	33	169.57 ± 29.75	3	185.33 ± 16.44	6	163.50 ± 27.27	8	187.50 ± 23.75
18. Triglycerides	mg/100 ml	32	87.81 ± 35.43	3	83.33 ± 42.35	6	101.17 ± 39.84	5	66.20 ± 39.00

TABLE 4

SERUM PROTEINS IN FRIEDREICH'S ATAXIA

	FRIEDREICH'S ATAXIA (all cases)		NORMAL
	MEAN	RANGE	RANGE
Total protein (g%)	7.2	6.5-8.5	6.0-8.2
Albumin (%)	60.7	52.6-67.8	49.0-62.0
α_1-Globulin (%)	3.9	1.7-5.3	2.9-6.0
α_2-Globulin (%)	9.3	6.7-13.4	6.0-13.0
β-Globulin (%)	12.0	9.9-16.1	10.0-18.0
γ-Globulin (%)	14.1	9.7-18.7	12.0-21.0
IgA (mg%)	171.7	80.0-400.0	90.0-450.0
IgG (mg%)	110.5	791-1575	800-1800
IgM (mg%)	127.5	37.0-435.0	60.0-280.0

nature were uncovered by the clinical laboratory studies reported, there are some interesting observations which are potentially of use in the diagnosis of Friedreich's ataxia, and other results which point the way for further studies.

Previously, serum ceruloplasmin activity had been reported (Badiu, 1972) to be decreased in 15 patients with spino-cerebellar degeneration, 13 of whom were diagnosed as Friedreich's ataxia. It was noted that the decreased ceruloplasmin activity was related to the duration of the condition. In the present study, although 4 patients had ceruloplasmin activity below the usual lower limit of normal, the decreased activity was not related to the duration of the illness nor were values decreased to the extent seen in Wilson's disease. The lowest value recorded was 18 mg%.

Serum transaminases have been reported to be elevated in Friedreich's ataxia (Gautier and Richterich, 1963; Krongrad and Joos,

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1972). In the present study, 3 out of 30 patients showed elevated SGPT and 5 out of 50 patients had elevated SGOT activities. Robinson et al. (1965) reported elevated SGOT in the serum of 5 patients out of 19. The latter authors point out, that in view of the muscular disability suffered by many patients, altered levels of aldolase, SGOT and LDH would not be surprising. In this study, aldolase activity was within normal limits, whereas serum LDH activity was found to be higher than 225 i.u. in 18 out of 49 patients, particularly in the younger ones. No consistent pattern within groups was observed. LDH activity had previously been reported as normal (Robinson et al., 1965) or elevated (Badiu and Cherciulescu, 1969). It remains to be established if these LDH changes are related to the known cardiac abnormalities associated with Friedreich's ataxia. In one report (Badiu et al., 1969), persistent elevation of LDH isoenzyme-5 (cardiac specific) was reported in the serum of a seven year old girl with Friedreich's ataxia. Other serum enzymes which have previously been studied and found to have activities within normal limits in Friedreich's ataxia, include phosphoglucose isomerase, 5¹-nucleotidase, adenosine triphosphatase and β -glucuronidase (Robinson et al., 1965).

Badiu and Cherciulescu (1969) determined protein profiles by paper electrophoresis in 20 cases of spinocerebellar degeneration (including Friedreich's ataxia, Pierre Marie's ataxia and patients with the Roussy-Levy syndrome) and found a significant decrease in serum and CSF albumins as well as a significant increase in CSF β-globulins. No correlation was found between these changes and the clinical form or the degree of functional impairment in the disease. Lafon et al. (1956), however, had previously been unable to demonstrate any changes in CSF proteins in Friedreich's ataxia. In the present study, serum electrophoretic patterns in all 23 cases studied showed no significant differences from normal values. CSF proteins were found to be significantly increased in group II patients (Table 5).

TABLE 5
CSF Proteins

	Group I n = 11	Group II n = 5
mean	30 mg %	66 mg %
range	18-57 mg %	20-96 mg %
normal range	0-45 mg %	

Abnormalities of lipid metabolism have been claimed in Friedreich's ataxia. Badiu and Cherciulescu (1969), for example, reported a marked increase in amounts of chylomicrons in the serum of 10 patients. Findings in the proband included low serum cholesterol and β-lipoproteins and the absence of acanthocytosis. Serum, low, very low and high density lipoproteins and their apoproteins showed no major differences from normal. Other reports include normal (Podolsky et al., 1964) and elevated (Krongrad, 1972) serum cholesterol in association with Friedreich's ataxia; serum triglycerides have similarly been reported as normal (Podolsky et al., 1964) and elevated (Badiu and Cherciulescu, 1969). In addition to this confused situation, the neurological picture in the Bassen-Kornzweig syndrome (familial a-betaliproteinaemia) may resemble Friedreich's ataxia. Differential diagnosis is not difficult when typical findings are present (acanthocythosis, lack of serum β -lipoproteins, diminished plasma lipid levels). It is more difficult, however, when such typical findings do not appear, or appear only partially. In the present study, mean serum cholesterol was within normal limits for all 4 groups. In only one case (94 mg %) was serum cholesterol considered to be abnormally low. Serum triglycerides, on the other hand, showed a much wider range of values in the Friedreich's ataxia group as compared to controls. These findings of normal serum cholesterol and triglycerides together with the absence of acanthocythosis serve as one way of differentiating between Friedreich's ataxia and the familial hypobetalipoproteinaemias. They also indicate that these rare syndromes are apparently not present within our group of experimental subjects.

In conclusion, it can be stated that all routine hematological and biochemical tests performed in Friedreich's ataxia were within normal limits. Although some variations outside these limits did occur, they were neither constant nor frequent and did not indicate the presence of definable sub-groups of patients. Moreover, this prospective survey, although negative, does not confirm previously reported abnormalities based on the study of small numbers of patients. This is so for abnormal levels of serum ceruloplasmin, electrophoresis, cholesterol, triglycerides and certain serum enzymes which have been found normal for a large group. No diagnostic criteria have been obtained from a study of these substances in patients or asymptomatic siblings.

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