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Laboratory parameters of Italian centenarians

The Italian Multicentric Study on Centenarians (IMSC)[1,2]

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Abstract

A consortium of 20 university departments of geriatrics and gerontology conducted the Italian Multicentric Study on Centenarians (IMSC), in order to assess the socio-economic, clinical and biological conditions of the Italian centenarians. The investigation involved 382 subjects randomly selected from a total of 1162 centenarians (234 men and 928 women), recorded by a census carried out until 31 December, 1993. Their case history, clinical and socio-economic data were recorded on a computerized clinical case sheet. Blood samples for the purpose of the present investigations were drawn from 257 of them. A great proportion (79%) of these latter subjects displayed satisfactory general conditions in their laboratory parameters, 18.3% of them had fairly good clinical conditions even with slightly modified laboratory parameters. Only a low percentage (2.8%) had poor general conditions with a marked anemia, hyperazotemia and uric acid levels. Long duration diabetes was practically absent, and only 5.5% of our centenarians displayed hyperglycemia with a mean duration time of 9.3 years. The prevalence of subjects with hypercholesterolemia was 31.1%. Only 4.3% of centenarians was affected by mixed form of dyslipidemia (hypertriglyceridemia associated with hypercholesterolemia), confirming that elevated blood lipid contents jeopardize really long survival.

Keywords: Italian centenarians; Laboratory parameters in centenarians; Hypertriglyceridemia; Hypercholesterolemia

[1] Participants of IMSC are listed in Appendix 1.

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1. Introduction

The progressive increase of the number of healthy elderly subjects in the industrialized countries during the last decades rendered necessary the systemic analysis of the socio-economic, clinical and biological conditions of the Italian centenarians. For this purpose, 20 university centers of gerontology and geriatrics organized a research program called the Italian Multicentric Study of Centenarians (IMSC, 1995), coordinated by the Institute of Internal Medicine and Geriatrics, University of Catania, Italy. The basis of the work of IMSC was a partial census conducted during March–December 1993 on a population of 1654182 inhabitants of Italy: this census recorded 1162 centenarians, and extrapolated that the total number of centenarians in the whole Italian populations should amount to 4004 subjects. The results obtained by the IMSC have already been in part published (IMSC, 1998). The present paper reports on the main laboratory parameters obtained by blood analyses. Since specific reference values are available for the oldest old persons neither in the clinical practice, nor in the scientific literature, these results could be compared only to the general, adult reference values.

2. Subjects and methods

Case history, clinical and socio-economic data were recorded for all the 1162 centenarians included in the census. The laboratory tests described here could be carried out on 257 centenarian subjects (57 men and 200 women). The main criteria of inclusion (or exclusion) in this study were:

1. Birth date on or before 31st December 1893.
2. Italian citizenship.
3. Informed consent to perform blood sampling.

The centenarians were visited at their own homes, and blood samples were taken after 14 h of fasting. The results were compared to the available standard laboratory reference values valid for the general adult population (Grasbeck and Saris, 1969). Red and white blood cells, as well as thrombocyte counts, hemoglobin content, hematocrit and mean red cell volume (MCV) were determined by using an automatic Coulter Counter (Forestier et al., 1984). Total protein and albumin/globulin ratio were measured by using the Biuret method. Automatic seroprotein electrophoresis determined the percentages of albumin, α1-, α2-globulins, β- and γ-globulins (Ciampi et al., 1988). Renal parameters (azotemia and uricaemia) were measured by automatic enzymatic and colorimetric methods, respectively (Baldinelli et al., 1988). Total cholesterol (TC), high-density lipoprotein (HDL)-cholesterol (HDL-C) and triglycerides (TG) were determined by using enzymatic-colorimetric methods (Edora and Rockerbie, 1975; Savoldi et al., 1976). The HDL-C measurement took place after precipitation of very low density lipoproteins (VLDL) and the low density lipoproteins (LDL) by phosphotungstate (Austin et al., 1984). Apo-B and Apo-al were assessed by nephelometric method (Marcovina et al., 1994). Liver enzymes such as aspartate aminotransferase (AST), alanine amino-

transferase (ALT), and alkaline phosphatase (ALP) were determined by optimized standard methods (Weisshaar et al., 1974). Glucose levels were measured by an automatic enzymatic method (Kohler and Miksch, 1971). Serum sodium and potassium contents were determined by a potentiometric method (Koch et al., 1983), and serum calcium content was measured by an automatic colorimetric method (Ripoll, 1976). Thyroid stimulating hormone (TSH) was determined by radioimmunoassay (RIA) (Bansal, 1989). Serum iron and ferritin contents were measured by an automatic colorimetric method, and ELISA method, respectively (Fortier et al., 1979).

Statsitical analysis was performed using descriptive statistical methods, categorial analysis (Agresti, 1984), and Chi-square methods (Dixon and Massey, 1983).

3. Results and discussion

The main blood parameters are shown in Table 1. Most of the parameters of centenarians fell within the standard ranges valid for the healthy adult population, with only several exceptions: the hemoglobin content and red cell count in males, and the latter also in females were somewhat lower. The sex-dependent difference in red blood cell counts seen usually in younger adults in favor of males was not observed in centenarians, which may find its explanation in the postmenopausal increase of hemoglobin levels in females.

When examining the single subjects with low blood hemoglobin contents, we identified 13 cases (5%) out of 257, who displayed on average only 7.74 g/dl hemoglobin content. Two of them were in poor physical and mental condition, another two showed fair physical and poor mental condition, while the remaining nine cases displayed fair or good physical and mental condition.

Table 1
Hemocytometric results of centenarians (mean ± S.D.)

Parameters	Total pool	Females (F)	Males (M)	Reference values
Number	257	200	57	
Hemoglobin (g/dl)	12.4 ± 1.7	12.4 ± 1.8	12.5 ± 1.7	F: 12.0–16.0; M: 14.0–18.0
Hematocrit (%)	39.6 ± 22.0	39.8 ± 24.5	39.0 ± 4.9	F: 36.0–46.0; M: 38.0–47.0
Red cell count (10^{12}/l)	4.1 ± 0.6	4.1 ± 0.7	4.2 ± 0.6§	F: 4.2–5.4; M: 4.5–6.3
MCV (fl)	91.6 ± 9.0	91.2 ± 8.5	92.9 ± 8.6	82.0–98.0
Leukocytes (10^9/l)	6.3 ± 2.0	6.1 ± 1.9	7.0 ± 2.5	4.0–10.0
PMN (%)	61.0 ± 13.0	60.4 ± 12.7	63.4 ± 12.7	50.0–65.0
Lymphocytes (%)	28.4 ± 11.0	28.9 ± 11.0	26.9 ± 11.1	20.0–35.0
Platelets (10^6/l)	208.4 ± 71.0	211.6 ± 71.8	197.4 ± 66.4	130–400

PMN = polymorphonuclear leukocytes.
Sources of the reference values are listed in Section 2.
§Indicates values outside the reference intervals.

Table 2
Clinical chemistry results of centenarians (mean ± S.D.)

Parameters	Total pool	Females (F)	Males (M)	Reference values
Number	257	200	57	
Urea (mg/dl)	49.1 ± 22.1	46.6 ± 20.7	58.2 ± 25.6§	18.0–50.0
Uric acid (%)	5.9 ± 4.1	5.6 ± 3.5	7.1 ± 5.6§	F: 2.4–5.6; M: 3.4–7.0
Glucose (mg/dl)	89.0 ± 24.4	88.5 ± 25.7	91.2 ± 19.7	70.0–110.0
AST (U/l)	19.4 ± 10.0	19.0 ± 10.0	21.0 ± 10.0	00.0–37.0
ALT (U/l)	11.4 ± 8.0	11.0 ± 8.0	13.0 ± 7.0	00.0–40.0
ALP (U/l)	198.5 ± 141.6	195.3 ± 137.5	209.7 ± 156.4	98.0–279.0
Total protein (g/dl)	6.90 ± 0.7	6.9 ± 0.7	6.8 ± 0.9	6.0–8.0
A/G	1.3 ± 1.5	1.4 ± 1.7	1.2 ± 0.3	1.3–2.1
Electrophor. A (%)	53.2 ± 6.8§	53.5 ± 6.2§	52.0 ± 7.4§	62.0–70.0
α1-globulin (%)	3.3 ± 0.9	3.3 ± 0.8	3.3 ± 1.1	2.1–3.3
α2-globulin (%)	10.2 ± 2.3§	10.1 ± 2.4§	10.6 ± 2.2§	4.7–8.3
β-globulin (%)	12.2 ± 2.6§	11.9 ± 2.0§	12.5 ± 3.0§	4.6–8.3
γ-globulin (%)	19.4 ± 5.4§	19.1 ± 5.4§	20.7 ± 5.2	11.4–17.8
Serum Na^+ (μ/l)	140.4 ± 4.6	140.1 ± 4.4	141.5 ± 4.7	135.0–145.0
Serum K^+ (μ/l)	4.8 ± 2.5	4.9 ± 2.8	4.4 ± 0.4	3.5–5.0
Serum Ca^{++} (μ/l)	8.1 ± 5.9	8.4 ± 6.4	6.6 ± 2.4§	8.1–10.4
TSH (mU/l)	1.6 ± 0.9	1.6 ± 0.9	1.6 ± 0.9	0.25–3.1
Serum Fe (μg/dl)	70.2 ± 25.5	71.4 ± 25.6	66.2 ± 25.5§	F: 60.0–120.0; M: 70.0–140.0
Ferritin (ng/ml)	114.7 ± 115.3	104.7 ± 95.1	149.8 ± 181.8	15.0–300.0

A: albumin; G: globulin; Other abbreviations are explained, and sources of the reference values are listed in Section 2.
§Values outside the reference intervals.

Table 2 lists the chemical parameters measured. Most of those parameters also fell within the normal ranges of the healthy adult population, although with some exceptions, as follows:

1. Average urea and uric acid were slightly higher in males. This is due to the fact that 21 subjects (8.2%) had an elevated urea (mean: 91.5 ± 11.8 mg/dl), and 19 subjects (7.4%) showed an increased uric acid content (mean: 9.1 ± 8.4 mg/dl) out of the 257 centenarians investigated. An elevated uricemia is probably due to an increased catabolism and reduced clearance of the products of purine metabolism. Both parameters proved to be elevated in ten centenarians (3.9%). Of them, only three displayed poor physical and mental condition, whereas the remaining subjects had fair or good physical and mental condition.
2. Total average protein contents were in the normal range, although in 14 cases (5.4%) we found lower protein concentrations (mean: 5.06 ± 0.02%). Out of these cases, three were in poor physical and mental condition, two of them had fair physical but poor mental condition, and the rest showed fair or good physical and mental condition.

3. Average albumin contents were somewhat lower in both sexes, whereas all globulin fractions were considerably higher, except the α1-globulin, the average of which was at the upper limit of the reference ranges. Low albumin contents may probably be signs of a deficient nutrition, while increased globulin-concentrations may confirm the tendency of a progressive polyclonal activity of B lymphocytes during aging (Paganelli et al., 1992).
4. Calcium and iron contents were lower in males.

Lipoprotein profiles of centenarians are shown in Table 3. The average TC, HDL-C and TG values were in general low, however, higher in females than in males, whereas mean HDL-C and Apo-1 were in the normal upper range (Table 3). Nevertheless, the study population was inhomogeneous in the lipoprotein contents: for example, 80 centenarians (31.1%) displayecl 227.3 ± 22.3 mg/dl TC, and 11 of them (4.3%) also showed elevated TG values: 257.0 ± 55.3 mg/dl, and seven of these latter 11 subjects had another risk factor, too, i.e. mean HDL-C 32.7 ± 5.4 mg/dl. These 11 centenarians were in fair physical conditions, although two of them had poor cognitive functions. Since VLDL-C and LDL-C are atherogenic lipoproteins, and HDL-C is antiatherogenic, the centenarians in general, have a favorable lipoprotein profile compatible with the longevity and the absence of atherotrhombotic diseases.

The Catania and Bari Centers determined lipoprotein(a) (Lp(a)) as a factor of independent atherogenic risk for cardiovascular diseases and observed higher levels in centenarians (39.6 ± 3.5 mg/dl), than found in the adult population (Capurso et al., 1990; Malaguarnera et al., 1996).

One can conclude from this data that our centenarians have quite normal general hematological and clinical chemical parameters, revealing their health status rather than their age. Our data agrees with the results of a Finish study (Louhija et al., 1994) on a group of centenarians, describing TC, LDI-C and HDL-C levels as 178, 93, and 58 mg/dl, respectively. Other studies have described a reduction of TC, LDL-C and HDL-C levels, and an increase of HDL-C level above 70 years of age (Nikkila and Heikkinen, 1990; Rifkind et al., 1990). The findings on centenarians confirm this natural trend. Therefore, low TC, LDL-C and HDL-C levels may be considered as markers of longevity. Our mean values for these parameters fall in the normal range, and are lower than observed in the octagenarians of the same

Table 3
The lipoprotein profiles of centenarians (mean $\pm$ S.D.)

Parameters	Total pool	Females (F)	Males (M)	Reference values
Number	257	200	57	
TC (mg/dl)	181.9 ± 39.0	185.3 ± 40.3	170.1 ± 33.2	up to 200.0
HDL-C (mg/dl)	60.3 ± 31.0	63.8 ± 44.0	48.2 ± 17.8	F: 45.0–60.0; M: 35.0–50.0
TG (mg/dl)	114.4 ± 50.0	119.6 ± 51.0	96.0 ± 40.3	up to 170.0
ApoB (mg/dl)	100.1 ± 35.0	103.1 ± 36.3	89.6 ± 28.2	F: 60.0–145.0; M: 55.0–165.0
ApoA-I (mg/dl)	141.6 ± 29.0	145.5 ± 29.5	128.1 ± 24.3	F: 110.0–230.0; M: 95.0–200.0

Sources of the reference values are listed in Section 2.

geographical area (Louhija et al., 1994). Furthermore, our results fully agree with those obtained on Hungarian centenarians, by using similar methods to our ones, and revealing substantial homogeneity of clinical phenotypes, regardless of the ethnic origin (Németh et al., 1990).

As regards diabetes mellitus, its presence in our centenarian population was assessed on the basis of the criteria of the National Diabetes Data Group (1979), and of the World Health Organization (WHO Study Group, 1986), according to which fasting glycemia above 140 mg/dl indicates diabetes. We detected 21 diabetic subjects (5.5%) (1 male and 20 females). Mean duration of diabetes was 9.3 years, with a onset around 94 years of age (except two diabetic centenarians who had this disease earlier). The general conditions were poor only in six (28.5%) of the 21 diabetics. The ILSA study (Amaducci and Scarlato, 1993) conducted on 5632 randomly chosen Italian subjects between 65 and 84 years of age, revealed a diabetic prevalence of 13.6%, with the onset of the disease at all ages. Diversely, the onset of diabetes was very late in centenarians. This data confirms that diabetes jeopardises longevity.

In conclusion, our study differentiated unhealthy centenarians in the final stages of aging, and healthy centenarians who could overcome the life-long effects of negative environmental factors, since they represent a well-defined, advantageous genetic profile. The laboratory parameters of the healthy centenarians fall within the range of the healthy adult population, demonstrating that unaltered physiological patterns favor the healthy mental and physical aging even above 100 years.

Appendix A

Twenty Italian University Centers have been collaborating in the Italian Multicentric Study on Centenarians (IMSC). The present report was made possible by their enthusiastic cooperation in preparing the case sheets, recording and processing the great number of data. The merits of the successful completion of IMSC should be shared equally among all the members of the study centers, listed below in alphabetical order of the participating cities: Bari: A. Capurso, A.M. Colacicco, V. Solfrizzi: University of Bari, Institute of Geriatrics, Piazza G. Cesare, 11, I-70124 Bari. Bologna: A. Gaddi, S. D'Addato, C. Galletti: University of Bologna, Policlinico S. Orsola-Malpighi, Via Massarenti, 9. I-40138 Bologna. Brescia: M. Trabucchi, S. Boffelli, R. Rozzini: Geriatric Research Group, Ospedale Richiedei. Via Pinidolo, 23. I-25064 Brescia. Catania: L. Motta, R. Rapisarda, F.B. Tomasello: University of Catania, Department of Internal Medicine and Geriatrics, Ospedale Cannizzaro, Via Messina 829. I-95126 Catania. Catanzaro: R. Mattace, M. Motta, L. Pansini: University of Catanzaro, Department of Experimental and Clinical Medicine, Policlinico "Mater Domini", Via T. Campanella, I-88100 Catanzaro. Firenze: G. Masotti, N. Marchionni, E. Petruzzi: University of Florence, Institute of Gerontology and Geriatrics, Ospedale Ponte Nuovo, Via Oblate, 4. I-50134 Firenze. Genova: S. Bertolini, M. Agretti, P. Costelli: University of Genova, Department of Internal Medicine, Viale Benedetto XV, 6. I-16132 Genova. Milano:

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