Original Article

Laboratory results in the elderly: the Sydney Older Persons Study

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Abstract

Background The use of laboratory intervals based on younger and healthier populations is of questionable validity in older populations. The aim of this study was to examine haematological and biochemical profiles in a sample of community-dwelling older people and to study the impact of age, disease, disability and medications.

Methods Basic haematological and biochemical values were obtained for 338 survivors of a random sample of community-living people aged 75 years or over at time of recruitment. These values were compared to the laboratory reference intervals and the effects of age, disease, medication and disability examined.

Results The distribution of the 35 parameters measured differed from those described by the laboratory reference intervals in all but four of the variables. The values showed few significant age associations but did show associations with disease, disability and drug use.

Conclusions Abnormalities identified in haematological and biochemical testing are not due to age but to age-related illnesses. This is contrary to previous studies reporting a change in haematological and biochemical parameters purely on the basis of age. In the presence of abnormalities, identification and clarification of disease states should be made.

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Introduction

Laboratory tests are often used to screen for disease in the elderly, particularly in the setting of non-specific presentation of acute illness. The normality or otherwise of such common laboratory tests depends on the laboratory reference interval. The reference intervals are usually derived statistically from populations of healthy individuals (typically younger and independently mobile), raising the issue of their appropriateness to sick, older people.[1,2]

Usual laboratory reference intervals are constructed in a way that defines 5% of people who are normal as lying outside the reference interval. Parametric methods based on two standard deviations of the mean and non-parametric methods are used in their definition. Reference intervals are derived from healthy people and are assumed to represent people free of disease. Recently some have suggested that use of hospital populations or intra-individual changes may be more appropriate.[1,3–5] However, if the person has not previously presented to the institution and no prior parameters are available for comparison, the latter may not be possible. It has been postulated and sometimes demonstrated that the elderly show increased heterogeneity with age of biochemical and haematological parameters,[6–11] though this appears to be related to the population studied. One study of the very healthy showed little increased heterogeneity,[4,5] while those who studied patients either in acute hospital or in long-term care found greater deviations from reference intervals.[6,7] Few randomly selected community sample studies have been performed.

We have studied a randomly selected sample of community-living older people, recruited at age 75 years and over, the survivors of whom were venesected 5 years later (aged 80 years and over). In this random sample, which is representative of community-dwelling elderly that are not acutely unwell, results were compared to the usual laboratory reference intervals. It was hypothesized that the community elderly would demonstrate an excess of abnormal

values (outside reference intervals) and this paper aimed to examine the contributions of age, disease and drug use.

Methods

Population

Between 1991 and 1993, a community-dwelling cohort of people aged 75 years and over in central Sydney were recruited by random sampling methods[12–14] for a longitudinal survey of health and well-being (Sydney Older Person Study, SOPS1). The survey included a social science interview and also an at-home medical assessment by a physician trained in geriatric medicine, which included a history, structured clinical examination and medication review. The clinician recorded presence or absence of a range of systemic and neurodegenerative disorders, and also their severity and impact on function. An informant was interviewed for each participant, regarding health, social and functional issues.

Blood collection

Of the original SOPS1 sample ($n = 647$), 404 underwent a second assessment in 1994–1996 and 338 of these were successfully visited at place of residence by a registered nurse in 1996–1997. Of the sample, 31 were resident in a nursing home at the time of blood collection. The nurse repeated the drug history and collected the blood samples. Samples for routine haematology were collected into EDTA tubes and serum samples for biochemical analyses into SST-gel tubes (Becton Dickinson, North Ryde, Australia). Specimens for glucose analyses were collected into fluoride–oxalate tubes to minimize storage changes. All samples were transported to the hospital laboratory on ice within 4 h of collection. Biochemistry tubes were centrifuged upon receipt. Standard analyses were performed on the day of receipt; aliquots were taken and either stored at 4°C overnight, or frozen at −20°C for less frequently performed tests.

Laboratory analysis

All analyses were performed in the laboratories of Central Sydney Laboratory Service (CSLS). The primary site for analysis was Concord Hospital, a teaching hospital of the University of Sydney and an accredited pathology provider under the Commonwealth Government of Australia. Routine biochemistry tests included electrolytes, urea, creatinine, glucose, albumin, calcium, magnesium and iron. These were all performed by standard techniques on a Beckman Synchron CX7 analyser (Beckman-Coulter, Gladesville, Australia) on the day of collection. Vitamin B_{12} and folate assays were carried out on a Beckman Access (Beckman-Coulter), transferrin on a Beckman Array (Beckman-Coulter) and ferritin on an Abbott AxSYM (Abbott Diagnostics, Lane Cove, Australia) after overnight storage of serum at 4°C. The haematology profile of haemoglobin, white cell, differential and platelet counts was performed on a Coulter STKS blood autoanalyser (Beckman-Coulter) on the same day of collection. Testing for selenium, zinc, vitamins A and E and glycosylated haemoglobin (HbA_{1c}) was performed off-site at the Royal Prince Alfred campus of CSLS, a second teaching hospital within the Central Sydney Area Health Service. Selenium and zinc were measured using mass spectrometry inductively coupled plasma, vitamins A and E using a high-performance liquid chromatography (HPLC) ultraviolet detector and HbA_{1c} was measured with HPLC.

The standard reference intervals in use for all tests had been derived either from local population studies or those provided by the analytical system manufacturers. In this latter case, reference interval data had been validated by smaller population studies. This validation had occurred at both the major teaching hospitals (i.e. Concord and Royal Prince Alfred) and 'area reference ranges' and had been standardized on a predominantly ambulant, adult outpatient population of Central Sydney Area Health Service – a geographical area serving the central and inner west of greater Sydney. All instrumentation in use was less than 4 years old, and the validation of reference intervals had been confirmed at the time of commissioning the instrumentation using the same collection techniques, tubes and pre-analytical steps as in this sample population.

Statistical analysis

For each of the haematology and biochemistry measures obtained, the values for the population sampled were compared to the laboratory reference interval (gender-specific intervals were used where applicable). The number of results above and below the reference interval was identified. Results for which more than 5% were either above or below the reference interval were considered to be significantly different from a population perspective.

To study the effects of age, the sample was divided into approximately equal 20% age bands. Mean values of each measured biochemical and haematological parameter were compared in each centile using analysis of variance. For each parameter a linear contrast test[15] was used to identify if there was a significant linear trend with age. To assess further the effect of age, standard deviations for each measure were examined using Levene's test for heterogeneity of variance.[15] This test identifies whether the standard deviation is equal across the age bands for each measured parameter. A statistically significant finding indicates that there is a difference in the standard

deviation and therefore in the spread of results within each age band. A statistically significant result where there are increasing standard deviations with increasing age bands indicates an increase in the spread of results with increasing age, thereby supporting the contribution of age to abnormal test findings.

To study the effects of diseases and drugs, we used the data from the 1994–1996 clinician assessment. To develop a measure of illness burden, we derived three summary variables: total number of diagnoses, total disability score and total number of medications taken. At the completion of the medical assessment, all diagnoses were coded using ICD-9[16] and a summary variable of the total number of diagnoses was created. Disability was assessed by the clinician during the medical interview using the Kilsyth Disability Scale.[17,18] This scale measures disability in mobility, continence, instrumental activities of daily living (meal preparation, housework, shopping) and activities of daily living (dressing, feeding, toileting). All components of this scale were summed to give a measure of total disability. All medications were reviewed by the clinician at the assessment and the total number was recorded. We also identified a group likely to be more ill than the whole population as those now resident in nursing homes ($n = 31$) and compared them to those still living in the community ($n = 309$). Two analyses were performed. First, total diagnosed diseases, total disability and total number of drugs consumed were compared to the total number of laboratory tests outside the reference interval for each individual. Second, the individual and total laboratory test results of those resident in nursing homes were compared with those still living in the community with regard to results outside the reference interval. *t*-Tests were used to make these comparisons. All analyses were done using Statistical Package for the Social Science, Version 6.1.3 (SPSS Inc., Chicago, IL, USA).

Results

Blood samples were obtained on 338 subjects. Their mean age was 84·9 years (range 78·9–100·1 years). Table 1 shows the values obtained on biochemical and haematological tests.

For the 16 basic haematology tests, only neutrophil and eosinophil counts had 95% of subjects within the laboratory reference interval. Most values outside the reference intervals were low, including haemoglobin (14·8% low, none high), red cell count (35·3%), haematocrit (32·3%) and lymphocyte count (42·1%). Only the mean corpuscular volume (MCV) had an excess of values above the reference interval (10·7%). The haematinic-related vitamins also showed an excess of low values: B_{12} concentrations (22·2%), serum folate concentrations (10·1%) and red cell folate concentrations (16·5%).

For the 19 biochemistry tests, only serum sodium and calcium had 95% of subjects fitting the laboratory reference interval. Increased high values were seen for potassium (16%), magnesium (26·2%), urea (42·6%), creatinine (15·6%), glucose (10·0%) and HbA_{1c} (14·8%). Routine testing of HbA_{1c} is recommended in diabetic populations. This finding indicates the high prevalence of poor glycaemic control within an older community-dwelling population where the majority of subjects are not diabetic. An excess of low values was seen for iron (22·4%), transferrin saturation (29·6%) and serum albumin (29·5%). Of the less often measured vitamins, there were 12·4% low vitamin A levels and one low vitamin E levels (20% high).

Age differences

There were few statistically significant age effects identified. These are shown in Table 2. When examining the mean values, only platelets and total CO_2 showed significant differences across the age bands. When examining for a linear trend with age, only total CO_2 and ferritin were statistically significant. Thus, only total CO_2 showed significant mean differences across the age bands and a significant trend with decreasing total CO_2 levels with advancing age. However, given the number of statistical tests performed, one would expect one or two of them to be spuriously significant when no genuine age effects existed, raising the possibility that these may respresent type 1 errors.

When examining the standard deviations across the age bands, eight laboratory tests showed changes in the range of values (*see* Table 2). However, many of these did not show an increasing or decreasing change in the distribution of values with age (i.e. only one age band showed a different distribution to the others). For example, mean corpuscular haemoglobin (MCH) showed a reduced standard deviation in the 85·2–87·8-year-olds, but there was no clear trend for a decrease in the standard deviations with age.

Effects of diseases and drugs

The total number of drugs and total disability scores of all subjects were significantly correlated to the number of test results outside the reference intervals ($r = 0·15$, $P = 0·007$, and $r = 0·24$, $P < 0·001$, respectively), while the number of diagnoses correlated significantly but less strongly ($r = 0·14$, $P = 0·012$). Nursing home residents had more laboratory values in total outside the reference intervals than those still residing in the community (*see* Table 3). The results for individual laboratory tests showed the nursing home population had significantly lower haemoglobins and

Table 1. Reference intervals and number of results above and below reference interval

Test	Limits		Frequencies: n (%)		
	Low/normal	Normal/high	Low	Normal	High
Haematology					
Haemoglobin (M/F) (g/L)	13/11·5	18/16·5	50 (14·8)	287 (85·2)	0 (0)
RCC (M/F) ($\times 10^{12}$/L)	4·5/3·8	6·5/5·8	119 (35·3)	218 (64·7)	0 (0)
Haematocrit (M/F) (%)	0·4/0·37	0·5/0·47	109 (32·3)	224 (66·5)	4 (1·2)
MCHC (M/F) (g/L)	33/32	36	27 (8·0)	310 (92·0)	0 (0)
MCV (F)	79	98	4 (1·2)	297 (88·1)	36 (10·7)
MCH (pg)	27	34	9 (2·7)	313 (92·9)	15 (4·4)
White cell count ($\times 10^9$/L)	4	11	11 (3·3)	318 (94·3)	8 (2·3)
Neutrophil count ($\times 10^9$/L)	2	7·5	6 (1·8)	321 (95·2)	10 (3·0)
Lymphocyte count ($\times 10^9$/L)	1·5	4	142 (42·1)	193 (57·3)	2 (0·6)
Monocyte count ($\times 10^9$/L)	0·2	0·8	0 (0)	304 (90·2)	33 (9·8)
Eosinophil count ($\times 10^9$/L)	0	0·4	0 (0)	321 (95·3)	16 (4·7)
Basophil count ($\times 10^9$/L)	0	0·1	0 (0)	335 (94·6)	2 (0·6)
Platelet count ($\times 10^9$/L)	150	450	31 (9·4)	299 (90·3)	1 (0·3)
Serum vitamin B_{12} level (pmol/L)	185	815	58 (22·2)	261 (77·4)	18 (5·3)
Serum folate level (nmol/L)	7	39	34 (10·1)	279 (83·3)	22 (6·6)
Red cell folate level (nmol/L)	320	1270	55 (16·5)	269 (80·8)	9 (2·7)
Biochemistry					
Sodium (mmol/L)	135	145	17 (5·0)	322 (94·7)	1 (0·3)
Potassium (mmol/L)	3·5	5·0	3 (0·9)	283 (83·2)	54 (15·9)
Chloride (mmol/L)	100	110	45 (13·2)	288 (84·7)	7 (2·1)
Total carbon dioxide (mmol/L)	22	32	4 (1·2)	319 (93·8)	17 (5·0)
Urea (mmol/L)	3·3	7·6	4 (1·2)	191 (56·2)	145 (42·6)
Creatinine (mmol/L)	0·05	0·12	1 (0·3)	286 (84·1)	53 (15·6)
Glucose (mmol/L)	3·0	8·0	1 (0·3)	305 (89·7)	34 (10·0)
Albumin (g/L)	33	47	92 (29·5)	220 (70·5)	0 (0)
Calcium (mmol/L)	2·10	2·60	2 (0·6)	311 (95·1)	14 (4·3)
Magnesium (mmol/L)	0·65	0·90	3 (0·9)	236 (72·8)	85 (26·2)
Iron (mmol/L)	11	31	76 (22·4)	258 (76·6)	3 (0·9)
Transferrin (g/L)	1·7	2·9	12 (3·6)	300 (89·0)	25 (7·4)
Transferrin saturation (%)	20	50	99 (29·6)	231 (69·0)	5 (1·5)
Ferritin (mg/L)	30	284	42 (12·3)	254 (75·4)	42 (12·3)
Ferritin* (mg/L)	30	284	42 (12·9)	254 (77·9)	30 (9·2)
Selenium (mmol/L)	0·70	1·35	28 (8·4)	259 (77·8)	46 (13·8)
Zinc (mmol/L)	10	18	25 (7·5)	297 (89·5)	10 (3·0)
Vitamin A (mmol/L)	1·4	4·0	41 (12·4)	287 (87·0)	2 (0·6)
Vitamin E (mmol/L)	8	30	1 (0·3)	263 (79·7)	66 (20·0)
Glycosylated haemoglobin** (%)	4·2/3·5	7·2/6·0	16 (4·7)	272 (80·5)	50 (14·8)

*Values greater than 500 excluded. **Ranges before/after 26 February 1997. RCC = red cell count; MCHC = mean corpuscular-haem concentration; MCV = mean corpuscular volume; MCH = mean corpuscular haemoglobin.

other red cell indices [MCV, mean corpuscular haem concentration (MCHC), MCH] but higher neutrophil counts and platelet counts. They had lower albumin levels, as well as lower selenium, calcium, iron and transferrin concentrations and transferrin saturation. Their HbA_{1c} concentrations were also lower.

Discussion

The main finding of this study is that few reference intervals for haematology and biochemistry tests can be applied directly to community-living elderly subjects who are not acutely unwell without finding an excess of out-of-range values. This study has identified that these abnormalities are significantly correlated with disease, disability and drug use. However, in the acute hospital setting the significance and clinical impact of such biochemical and haematological abnormalities may be difficult to interpret in isolation. We would support the previous contention that intra-individual differences may be of greater validity in older populations[2,3] rather than interpreting results within the context of reference intervals. While some of the findings may reflect processing delays, there was only one low glucose result and more might have been expected if processing was abnormally delayed.

Table 2. Laboratory measures where an age effect on either means or standard deviations within 20 centile age bands was identified

Laboratory parameter	20 centile age bands (years) 78·9–81·6	81·7–83·2	83·3–85·1	85·2–87·6	87·7–100·1	Anova P	Linear P	Levene's P
Means across age bands								
Platelets ($\times 10^9$/L)	212·4	234·8	240·0	214·5	217·8	0·036	0·665	
Total CO_2 (mmol/L)	28·9	29·1	28·5	28·2	27·9	0·048	0·004	
Ferritin (mg/L)	159·9	164·5	151·7	136·9	102·8	0·115	0·007	
Standard deviations across age bands								
MCH (g/L)	0·73	0·75	0·59	0·55	0·6			0·041
Monocyte ($\times 10^9$/L)	0·2	0·24	0·19	0·17	0·17			0·032
Basophil ($\times 10^9$/L)	0·04	0·05	0·05	0·04	0·07			<0.001
Platelets ($\times 10^9$/L)	52	80	60	68	50			0·023
B_{12} (pmol/L)	286	253	169	350	299			0.013
Total CO_2 (mmol/L)	2·5	2·3	2·3	2·9	3			0·052
Ferritin (mg/L)	158	169	168	159	87			0.044
Selenium (mmol/L)	0·22	0·32	0·29	0·32	0·2			0.006

MCH = mean corpuscular haemoglobin.

Table 3. Comparison of mean laboratory parameters between community and nursing home subjects

	Community (n = 308)	Nursing home (n = 31)	P
Total high/low	5·54	7·00	0·006
Laboratory parameter			
Haemoglobin (g/L)	13·5	12·9	0·027
MCV (F)	92·9	90·5	0·01
MCH (pg)	31·3	30·1	0·011
MCHC (g/L)	33·6	33·3	0·001
Neutrophils ($\times 10^9$/L)	4·2	5·1	0·027
Platelets ($\times 10^9$/L)	219	267	0·007
Albumin (g/L)	34	31	<0.001
Calcium (mmol/L)	2·40	2·35	0·008
Iron (mmol/L)	15	10	0·000
Transferrin (g/L)	2·3	2·2	0·023
Transferin saturation (%)	25·5	18·9	<0.001
Selenium (mmol/L)	1·08	0·97	0·03
HbA_{1c} (%)	5·7	5·3	0·026

MCV = mean corpuscular volume; MCH = mean corpuscular haemoglobin; MCHC = mean corpuscular haem concentration.

A possible interpretation of these results is that age alone accounts for the abnormalities identified and that older people are more likely to have renal impairment, or relative dehydration, to be prone to glucose intolerance and to be relatively malnourished with deficiencies in haematinics, mild anaemia and lymphocytopenia. However, the failure to find mean values regularly increasing or decreasing with age suggests that these effects are not due to age but to age-related pathological changes. This is supported by the examination of heterogeneity of variance with age, which did not show either an increasing or a decreasing variance with age for the majority of values. The lack of an age-related effect is also supported by the results considering diagnoses, disability, drugs and nursing home residence. The total number of drugs, total disability scores and the number of diagnoses all correlated significantly with abnormal test results. This indicates that, rather than age, it is age-related disease and its accompanying disability and need for therapy that account for abnormal test results. The nursing home population may have been more subacutely unwell, with raised platelets and neutrophil counts. They had lower albumin, iron, iron saturation, selenium, vitamin A and HbA_{1c}, suggesting greater malnutrition.

The strengths of this study are that the sample is a non-hospital-based population, whose subjects were thoroughly assessed by clinicians diagnosing a wide range of conditions independently of the laboratory results. While it is important in individual cases to understand the aetiology of abnormal test findings, it is beyond the scope of this paper to ascertain the myriad of diseases accounting for the abnormal results identified in this study.

The findings from this study suggest that clinicians need to consider any test result in an older person in the context of their individual illnesses. Abnormal results in biochemical and haematological parameters should not be attributed to age but to age-related diseases. Therefore, when results outside the reference intervals are found, identification of disease states should be made. As the older population often suffers from multiple comorbid chronic illnesses, the use of intra-individual ranges, which permit better clinical interpretation of values in the setting of acute

illness, may enhance patient assessment and management.

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