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Real time validation of paediatric biochemical reports using the Valab-Biochem® system

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SUMMARY. Validation of biochemical reports must be fast and clinically accurate to be of assistance to clinicians. Considerable skill is required to analyse the consistency of different data in the report and to consider influences on the data. When performed throughout the day, such analysis is time-consuming and uncertain. We therefore decided to use a computer-assisted validation system, Valab-Biochem®. Its decisions result from a decision tree based primarily on the intrinsic consistency of the data, validation ranges and patients' sex, age and hospital ward. Three hundred randomly chosen reports were simultaneously submitted to Valab-Biochem and to five biologists in order to analyse the computer's findings.

The sensitivity of Valab-Biochem was 80% compared to biologists' consensus decision, which was taken as the gold standard. The specificity was 78%. This system provided autonomous assessment of the reports and could be used as an initial screen to assist biologists and focus attention on potentially inconsistent reports.

Additional key phrases: expert system; computer-assisted validation

Validation of laboratory data is the last step before results are transmitted to clinicians. It follows the analytical validation performed by the technical staff in charge of monitoring quality control results, checking the accuracy of the data provided by analysers and correcting any erroneous results caused by equipment problems. Biologists (clinical biochemists) examine the data themselves (their intrinsic consistency, correlation with previous results and with the other parameters concerned), demographic factors (age, race, sex) and clinical factors (reference values, hospital department and diseases concerned). They not only validate apparently normal reports, but also pathological ones when there is good agreement between the different factors listed above. Unvalidated data may require technical verification concerning (for instance) sample identification and integrity and analytical validity, as well as additional laboratory tests and clinical investigation requiring telephone contact with the practitioner.[1] Most procedures involved in the technical validation are largely automated and can be completed quickly. Clinical validation, on the other hand, is slower and time consuming and its schedule throughout the day is uncertain. Several expert systems using artificial intelligence have already been tested to help biologists in the analytical process and with troubleshooting of instruments[2–4] and also to validate and interpret results.[5–7] Since the initial ethical problems and integration difficulties seem to be partially solved,[8,9] we decided to integrate a computer-assisted validation system called Valab-Biochem® into our paediatric biochemistry laboratory. A prototype of this system had been previously tested on some biochemical data from adults.[10] In this work, we present the results of our experience using this expert system in paediatrics.

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MATERIALS AND METHODS

The concept of computer-assisted validation

An expert system may be defined as a computer program that gives advice in a well-defined area of expertise. It is able to explain its reasoning, which is controlled by an algorithm and depends on a knowledge base.

TABLE 1. *Biochemical parameters studied by Valab-Biochem*

Ionogram	Sodium, potassium, chloride, carbon dioxide, total protein
	Calcium, phosphate, magnesium
	Creatinine, urea
	Anion gap
Enzymes	Alanine aminotransferase, aspartate aminotransferase, alkaline phosphatase, γ-glutamyl transferase
	Amylase
	Creatine kinase, lactate dehydrogenase
Other parameters	Cholesterol, triglycerides, apoliprotein A, apoliprotein B
	C-reactive protein, α-1 acid glycoprotein
	Total bilirubin, unconjugated bilirubin
	Glucose
	Uric acid
	Iron

consistent reports among those validated): major error (i.e. the percentage of validated reports among all the inconsistent reports): minor error (i.e. the percentage of unvalidated reports among all the consistent reports).[10]

Statistical methods

Variables of interest were described by their 95% confidence intervals and kappa-statistics (K) were used for the evaluation of inter-observer agreement.

RESULTS

Valab-Biochem integrated well into our computerized laboratory and its daily routine use is easy. The system works quickly since it requires 50 ms to validate a report and can study several reports at the same time. The reason why Valab-Biochem refuses to validate a report is always stated and is usually easy to investigate. The most frequent arguments for its refusal of automatic validation concern the delta check and validation ranges (Table 2).

Final decisions which varied from one biologist to another were statistically in moderate agreement ($K=0{\cdot}41$, $P<0{\cdot}0001$) and therefore used to determine the median biologist's decisions. We compared Valab-Biochem findings to the median biologist's ones and to the consensus findings they agreed upon as reference (Table 3 A).

The performance of the expert system was not statistically different from the median biologist performance. However, analysis of the raw data suggested the following comments. The sensitivity of the expert system was slightly greater than the biologist's sensitivity. Valab-Biochem only validated a few incoherent reports, fewer than the biologist, leading to a smaller major error. However, the specificity of Valab-Biochem is lower than the biologist's specificity, with an increased minor error. Consequently, the expert system proved to be more severe and therefore quantitatively less efficient since it refused to validate a larger number of reports than the biologist, even if those reports were consistent. Valab-Biochem therefore had a negative predictive value greater than that of the biologist but its positive predictive value was slightly lower (Fig. 1).

Valab-Biochem has been modified in order to decrease the number of incoherent reports it validated (Table 3 B). No more then three incoherent reports were then validated by the system, leading to a major error of 2% and without increasing its minor error. Its findings agreed with the reference ($K=0{\cdot}6$, $P=0{\cdot}0001$). When 300 different reports were submitted to Valab-Biochem, similar results were obtained (Table 3 C).

Among the 29 blood parameters studied (Table 1), a few were frequently responsible for the divergence between the validation of the biologists and that of Valab-Biochem. These parameters were potassium, total protein, C-reactive protein creatinine and magnesium (Table 2). These items were important for validation or its refusal and their importance depended on the patient's hospital department and the disease suspected (e.g. creatinine, potassium in connection with nephrology).

DISCUSSION

The implementation of artificial intelligence in clinical laboratories is increasing rapidly and several operational expert systems have already

TABLE 2. *The most frequent reasons for refusal of automatic validation by Valab-Biochem*

Biochemical parameters	Reasons for refusal of automatic validation			Total
	Delta check	Validation ranges	Correlation	
Sodium	2			2
Potassium	6	6	2	14
Carbon dioxide	1	2		3
Total protein	10	2	2	14
Calcium	2			2
Phosphate	2	2	2	6
Magnesium	8			8
Creatinine	8		4	12
Urea	4	2		6
Alanine aminotransferase	6		2	8
Aspartate aminotranferase	6		2	8
Alkaline phosphatase	2	4		6
γ-Glutamyl transferase	2	2	2	6
Lactate dehydrogenase	2			2
Cholesterol		4	2	6
Triglycerides		4	2	6
Apolipoprotein A		4	2	6
Apolipoprotein B		2	2	4
C-reactive protein	10	2	2	14
Total bilirubin	2	6		8
Uric acid	2	2		4
Total	75	44	26	

The expert system always states why it refuses to validate a result. The reasons may include the delta check with previous results, the validation ranges and the acceptability limits or a bad correlation with the results for related analytes.

been tested.[1,5,6,7,18] A prototype of the computer-assisted validation system called Valab-Biochem was first developed on an adult blood electrolytes profile validating the knowledge base construction and the interface engine reasoning.[15] In this work, we have evaluated the clinical efficiency of the latest commercial software of Valab-Biochem sold by EREMS and reported our personal experience using this system in a computerized paediatric biochemistry laboratory and improved its routine operation.

Integration of the system into our laboratory was easy and the hardware was installed without difficulty. The hardest step was to adapt the knowledge base in order for the system to assimilate the wide variations in different analytes with age in children from one day old to sixteen years;[18] for example, Valab-Biochem's interpretation of liver function tests is based on the determination of serum bilirubin concentration and the correlation between aspartate aminotransferase, alanine aminotransferase, alkaline phosphatase and γ-glutamyl transferase activities. However, in paediatrics, and particularly in the pubertal growth period, wide variations of alkaline phosphatase activity are observed (up to 650 IU/L) because the bone isoform activity is increased. Since Valab considers only the hepatic fraction, it does not validate this physiological isolated increase in alkaline phosphatase activity if γ-glutamyl-transferase activity is unchanged. In addition, the evaluation of the renal function by Valab-Biochem in premature babies and neonates can be erroneous if technician and biologists are not vigilant to the analytical interference of haemolysis or bilirubin on creatinine determination. High concentrations of serum bilirubin up to 260 μmol/L are common in the first 5 days of life and lead to a false decrease of creatinine due to analytical interference with the Jaffé method. This may impair detection of abnormal maturation of renal function in premature babies who have higher serum creatinine concentrations than term infants, which decrease rapidly during the first 3 weeks of life. These difficulties clearly indicated that, before using an expert system, each laboratory should first establish its precise validation ranges for all parameters according to its own practice and the analysers used.

TABLE 3. *Evaluation of the expert system Valab-Biochem. We randomly evaluated 300 reports as true negative (T−), true positive (T+), false positive (F+) or false negative (F−) [A]. Valab-Biochem® was then readjusted and the system examined these 300 reports again [B] and 300 other reports [C]. Figures in parentheses are 95% confidence intervals. E = error; PV = predictive value*

System	Accepted	Rejected	T−	T+	F−	F+	Sensitivity (%)	Specificity (%)	PV+ (%)	PV− (%)	Major E (%)	Minor E (%)
Valab-Biochem	158	142	131	106	27	36	80 (73-87)	78 (72–84)	75 (68–82)	83 (77–89)	20 (13–27)	23 (17–29)
A												
Expert 1	150	150	108	91	42	59	68 (60-76)	65 (58-72)	61 (53–69)	72 (65–79)	32 (24–40)	35 (28–42)
Expert 2	156	144	138	115	18	29	86 (80-92)	83 (77–89)	80 (73–87)	89 (84–94)	13 (7–19)	12 (7–17)
Expert 3	180	120	130	83	50	37	62 (54-70)	78 (72–84)	69 (61–77)	72 (65–79)	38 (30–46)	22 (16–28)
Expert 4	156	144	144	121	12	23	91 (86-96)	86 (81-91)	84 (78–90)	92 (88–96)	9 (4–14)	14 (9–19)
Expert 5	198	102	156	91	42	11	68 (60-76)	93 (89-97)	89 (84–94)	79 (73–95)	32 (28–36)	7 (3–11)
Median ($n = 5$)	168	132	135	100	33	32	75	81	77	81	25	18
Consensus	167	133	167	133	0	0	100	100	100	100	0	0
B												
Valab-Biochem	149	151	146	130	3	21	98 (96-100)	87 (82–92)	86 (80–92)	98 (96–100)	2 (0–4)	13 (8–18)
C												
Valab-Biochem	148	152	144	129	4	23	97 (94-100)	86 (81-91)	85 (79–91)	97 (94–100)	3 (0–6)	14 (9–19)

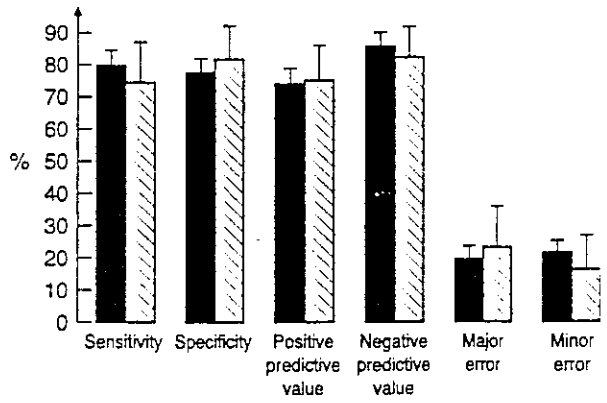

FIGURE 1. *Comparison of the sensitivity, specificity, predictive values and errors of Valab-Biochem* ■ *with the median biologist values* ▨. *The differences observed are not statistically significant* ($P > 0.05$).

Furthermore, Valab-Biochem has to be tailored to the characteristics of each laboratory and the caseload of the hospital before being put into routine use.[12,20]

In this work, Valab-Biochem showed greater sensitivity than the biologist and smaller major error. Consequently, the expert system succeeded in one important aim, avoiding the validation of inconsistent reports. However, the specificity of the system was below that of the biologist, with an increased minor error. Valab-Biochem was more severe and validated fewer reports than the biologist did, even if they were consistent. These results agree with those reported previously[8,10] and Valab-Biochem statements are statistically identical to those of biologists. The 27 inconsistent reports validated by the expert system indicate a few drawbacks to its routine use: first, it cannot evaluate the time elapsed since the preceding result in the delta check determination, if this time has not been well established for each parameter before being integrated into Valab-Biochem.[13] In addition, its access to all clinical information and its interpretation of the reference values may be restricted, for instance when the patient moves from one hospital department to another or simultaneously develops several diseases. Thus, the appreciation of parameter values and their consistency by the expert system and by biologists is not the same. Valab-Biochem only refers to its own knowledge base and does not fully possess the biologist's capacity to consider each parameter in relation to its medical importance (e.g. potassium compared to alkaline phosphatase in nephrology), and to its analytical determination (e.g. total bilirubin as a possible interference on creatinine determination). This shows the importance, for computer systems, of reference ranges, acceptability limits and validation criteria. If the basic rules of the system are permanent, the values of biological parameters can be programmed (e.g. the initial delta-check and the duration of the validity of the previous results), thus making Valab-Biochem flexible and adaptable to different types of medical activity.

To increase the specificity of the expert system and try to decrease its major error, we asked the EREMS to fit a new delta check, better validation ranges and useful additional items of clinical information to each parameter. After these changes, only three of the 27 inconsistent reports found previously were still validated by the expert system and no remarks by clinicians were recorded concerning the reports validated after these modifications. In this way, Valab-Biochem relieves the load on supervisors in charge of data validation. Since 50% of the reports are automatically validated, this system helps biologists focus their attention on the reports that it rejects. Its very fast reproduction of human reasoning pathways (50 ms to validate a report) saves considerable time (about 2 h per day). Since the expert system does not get tired, it gives more consistent results than its human counterparts and increases the accuracy of the validation process. However, several problems still remain when using this expert system, for example, difficulties in specifying the exact nature of the interference mechanisms, or in identifying the biologists who provided and interpreted the expertise.

CONCLUSION

In our experience, the clinical efficiency of the latest commercial release of Valab-Biochem software is good in a paediatric setting, since the knowledge base and knowledge acquisition process have been well adapted to the hospital and the laboratory concerned. Final results agree with those obtained in the reference sites. The manufacturer's findings are generally similar to ours, with a loss of efficiency but an identical accuracy and an increased regularity. Thus, this system can be used in first screening to validate consistent reports automatically and submit the reports it rejects to the biologists. Furthermore, the use of such a flexible and user-friendly expert system is not restricted to biochemistry as a similar system called Valab-Haemato[R] is used in haematology.[21]

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