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Detection of Subtle Changes in the Brains of Infants and Children via Subvoxel Registration and Subtraction of Serial MR Images

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PURPOSE: To compare conventional two-dimensional multisection images with registered three-dimensional volume and subtraction images for detecting subtle changes in the brains of infants and children. **METHODS:** Twenty-six patients (24 with hemorrhagic/ischemic lesions) and one each with perinatal infection and Sturge-Weber disease were examined on two or more occasions with conventional multisection T1- and T2-weighted sequences as well as with 3-D T1-weighted volume sequences. A registration program was used to match the volume images to subvoxel dimensions, and subtracted images (second volume set minus the first) were obtained. The multisection images were compared with the 3-D and subtracted images and graded for detection of changes in a variety of brain structures. **RESULTS:** In 16% to 33% of comparisons of different structures, the multisection images and the 3-D registered and subtracted images showed changes equally well. The 3-D registered and subtracted images were better than the multisection images in 67% to 84% of comparisons for detection of changes in the cerebral hemispheres, ventricles, brain stem, cerebellum, and in lesions. Statistically significant differences were found between the graded performance of the registered 3-D images and the conventional 2-D images in detecting cerebral infarction and hypoxic ischemic encephalopathy. In the late phase following neonatal cerebral infarction (1 to 11 months), the 3-D registered and subtracted images revealed growth of the brain at the margins of the lesions. **CONCLUSION:** Subvoxel registration of serial MR images may be of value in detecting subtle changes in the brains of infants and children.

Index terms: Brain, magnetic resonance; Magnetic resonance, in infants and children; Magnetic resonance, subtraction

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Recognition of large changes to the brain on follow-up magnetic resonance (MR) images of infants and children is usually straightforward, but detection of small changes may present considerable difficulty. Even with great care in patient positioning, MR images acquired on follow-up examinations are usually obtained at slightly different angles and levels from the first examination, and these differences in misregistration may be larger than the changes being sought. Subtraction of images is not usually of help in this situation, because this process does not distinguish changes in the brain from those caused by misregistration.

We have implemented a registration program that aligns serial three-dimensional MR images of the brain to within one hundredth of a millimeter (1, 2), reducing misregistration artifacts to the image noise level and allowing small differences to be recognized. To assess the potential of this technique for detecting subtle changes in the brains of infants and children, we studied 26 patients with different diseases on two or more occasions and compared their conventional MR images with the precisely registered and subtracted ones.

Subjects and Methods

Permission for this study was obtained from the Research Ethics Committee of the Royal Postgraduate Medical School and informed consent was obtained in each case.

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The patients' clinical diagnoses are summarized in the Table. Infants with hypoxic ischemic encephalopathy (HIE) were graded according to Sarnat and Sarnat criteria (3). Infants with grade I HIE had transient feeding difficulties and minor disturbances of tone; those with grade II had more marked disturbances of tone and seizures, while those with grade III were comatose and unresponsive with seizures.

All studies were conducted on a 1.0-T unit. Conventional two-dimensional axial multisection T1-weighted spin-echo (620–920/20/2 [repetition time/echo time/excitations]), T1-weighted inversion-recovery (2500–3500/30/2) (inversion times were 600–950), and T2-weighted spin-echo (2700/120/2, 2500/20,80/2) images were obtained in each case. The section thickness was 5 mm, the matrix was 192 × 256, and the field of view was 20 to 24 cm. In addition, radio frequency spoiled T1-weighted 3-D volume images (21/6/2) with a 35° flip angle and a 154 × 192 × 256 matrix were obtained in each case and displayed in the axial and sagittal planes. Contrast material (dimeglumine gadopentetate 0.1 mmol/kg) was administered to three patients (one each with HIE, perinatal infection, and Sturge-Weber disease).

A registration technique described previously (1, 2) was used with volume imaging for noncontrast and contrast-enhanced images and for follow-up studies. The first stage consisted of copying the initial (baseline) image and using a semiautomated segmentation computer program to remove the skull, scalp, and surrounding facial structures, leaving zero values in all voxels except those representing brain and cerebrospinal fluid (CSF). The registration software then automatically determined the positional change required to match the follow-up images to the isolated brain in the segmented baseline image. This was achieved by using a χ^2 test of voxel intensity differences between the images. The optimal spatial match is defined as the position that produces the minimum value of χ^2, since this maximizes the correspondence between the intensity distributions in the two images. The fit was automatically improved by using different translations and rotations to minimize χ^2. When an optimal fit was obtained, the second image was reformatted using sinc interpolation to match the first image. The first image was then subtracted from the reformatted second image.

Changes in signal intensity on difference images derived from properly aligned source images may arise from changes in signal intensity and/or changes in brain size, shape, or site (2).

Three experienced observers who were blinded to the patients' histories assessed the conventional 2-D T1- and T2-weighted images as a group and compared them with the registered 3-D T1-weighted volume and subtraction images. Images were compared for changes in the cerebral hemispheres, ventricles, brain stem, and cerebellum, as well as for changes in lesions, and graded in conference on a four-point scale: 0 = none (no change), 1 = mild (definite change but of limited degree), 2 = moderate (full-scale change but not extensive), and 3 = marked (extensive full-scale change) (2). These gradings were then compared using *t* tests to determine whether there were significant differences in the performance of multisection and 3-D registration methods across the patient populations.

Results

Twenty-six infants or children had MR imaging; 20 were term and six were preterm (less than 37 weeks' gestational age). Of the 26 infants, 24 had hemorrhagic and/or ischemic brain lesions, one had perinatal infection (group B streptococcus), and one had Sturge-Weber disease (Table 1). The breakdown of clinical diagnoses of the 24 infants with hemorrhage and/or ischemic lesions is as follows: premature intraventricular hemorrhage (n = 5), premature periventricular leukomalacia (PVL) (n = 1), term intracerebral hemorrhage (n = 1), term infarction (n = 6), and HIE (n = 11).

The age at initial examination varied from 26 weeks' gestational age to 6 years, 11 months. The follow-up periods (apart from the three patients who had contrast-enhanced studies at the same examination) varied from 1 day to 7 months. The total number of examinations was 64, with 12 patients having more than one follow-up examination. Thirty-eight sets of images were matched using the registration program.

Overall, the detection of changes in the cerebral hemispheres was the same with 2-D images and 3-D volume and subtraction images in nine comparisons and better with 3-D volume and subtraction images in 29 (76%) of the instances. The corresponding figures for the ventricles were six and 32 (84%); for the brain stem, 11 and 27 (71%); for the cerebellum, 11 and 27 (71%); and for lesions, 11.5 and 25.5 (67%). In no case were the registered images worse than the conventional images for detection of changes. The grades obtained from the images for these changes are presented in Table 1. Statistically significant improvement was noted with registration and subtraction images in detection of infarction (n = 6) for ventricular, brain stem, cerebellar, and lesional changes. Statistically significant advantages of registration and subtraction were also seen in cases of HIE (n = 11) in the cerebral hemispheres, ventricles, brain stem, and cerebellum, and in lesions.

Although all the subjects in this study were patients, we also observed changes that were probably the result of normal growth and development, such as an increase in the size of the

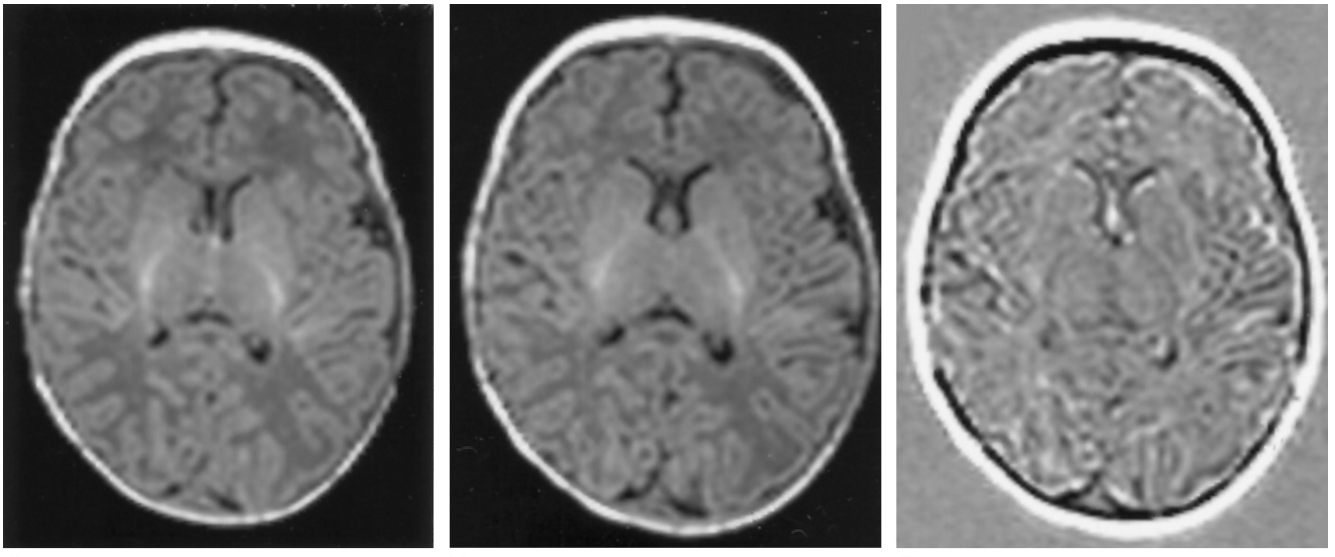

Fig 1. Case 20: Grade II HIE.

Registered T1-weighted 3-D images (21/6/2) at 2 weeks (*A*) and 5 weeks (*B*) with subtracted (*B* − *A*) image (*C*). The white rim around the brain on the difference image (*C*) is a measure of brain growth. The peripheral brain in *B* occupies the site previously occupied by CSF in *A*. Subtraction of *A* from *B* gives the high signal margin in *C*.

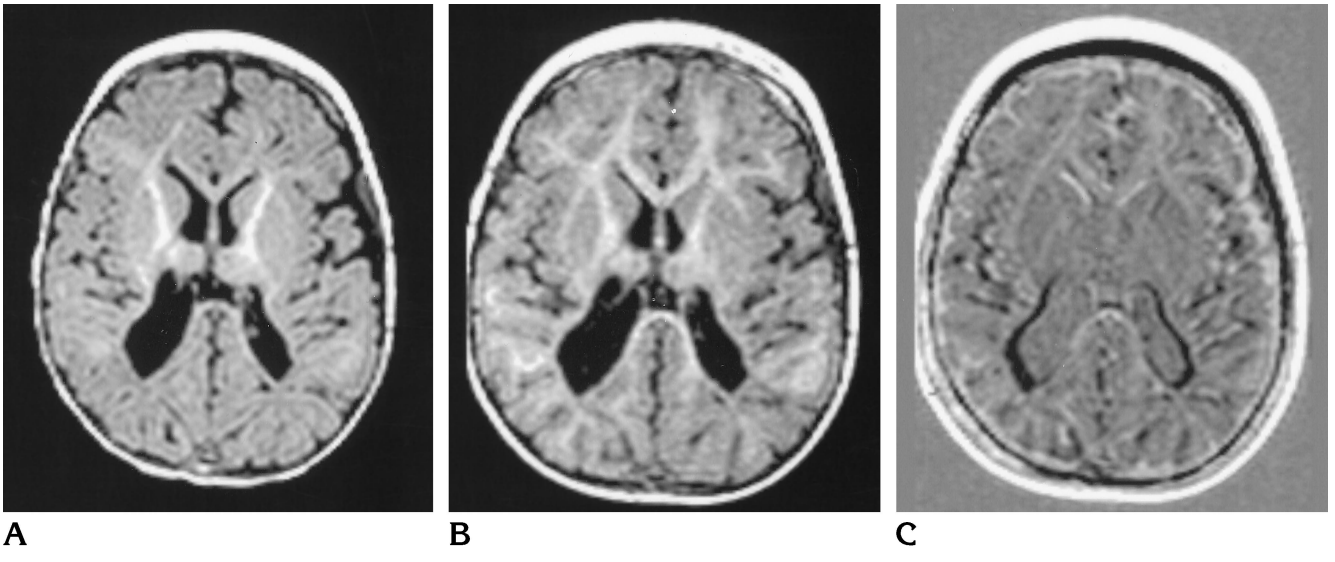

Fig 2. Case 6: Premature PVL.

Registered T1-weighted 3-D images (21/6/2) at 8 (*A*) and 15 (*B*) months with difference (*B* − *A*) image (*C*). Evidence of growth is seen at the periphery and there is differential change in the ventricular system with reduction anteriorly and dilatation posteriorly.

hemispheres (Fig 1) and brain stem, and increased signal on difference images, which was probably due to a decrease in T1 with or without an increase in myelination.

Of the five patients who had a history of intraventricular hemorrhage, two had hemorrhage at the time of examination. Change in the hemorrhage was seen better in one patient (case 2) after 4 days on registered subtracted images.

The patient with premature PVL (case 6) was of interest because the registered image showed differential growth between the anterior and posterior horns of the lateral ventricles (Fig 2).

The six cases of term infarction were of considerable interest. Two phases of evolution were apparent. The first phase was seen in three patients who were examined initially at 2 to 6 days of age and followed up at 1 day to 3 weeks. In this initial phase, an increase in T1 was present,

Clinical details and MR imaging results

Patient	Age at Imaging		Clinical Diagnosis	Abnormal MR Findings	Cerebral Hemispheres			Ventricles			Brain Stem			Cerebellum			Lesion(s)		
	1st Study	2nd Study			2-D	Reg 3-D	Subtr	2-D	Reg 3-D	Subtr	2-D	Reg 3-D	Subtr	2-D	Reg 3-D	Subtr	2-D	Reg 3-D	Subtr
1	26 wk GA	27.5 wk GA	Premature IVH	1) IVH	2	2	2	2	2	2	2	2	2	1	1	1	1) 3	3	3
				2) Parenchymal hemorrhage													2) 3	3	3
				3) Ventricular enlargement													3) 3	3	3
2	31.5 wk GA	32 wk GA	Premature IVH	1) IVH	0	0	0	0	0	0	0	0	0	0	0	0	1) 0	0	2
				2) Parenchymal hemorrhage													2) 0	0	2
				3) Subdural hemorrhage													3) 0	0	2
				4) Ventricular enlargement													4) 0	0	0
3	7.5 mo	11 mo	Premature IVH	Ventricular dilatation	2	2	3	2	2	3	1	2	2	1	2	3	2	2	3
4	21 mo	27 mo	Premature IVH	Ventricular enlargement	0	0	2	1	1	3	0	0	2	0	0	1	1	1	3
5	6 y, 11 mo	7 y, 6 mo	Premature IVH	Ventricular enlargement	0	0	2	0	0	3	0	0	0	0	0	0	0	0	3
6	8 mo	15 mo	Premature PVL	PVL	1	1	3	1	1	3	0	1	2	0	0	1	1	2	2
7	9 mo	15 mo	Intracerebral hemorrhage (term)	Parenchymal hemorrhage and cysts	2	3	3	0	2	2	0	1	2	1	2	2	2	2	2
8	2 d	3 d	Infarction	Infarction	0	0	1	0	1	2	0	0	0	0	0	0	2	2	3
	3 d	10 d			0	0	1	0	1	2	0	0	0	0	0	1	2	2	3
9	4 d	8 d	Infarction	Multiple infarction and brain swelling	0	1	2	0	1	2	0	0	0	0	0	0	0	1	2
	8 d	27 d			2	2	2	0	0	2	0	0	2	1	2	2	3	3	3
10	6 d	1 mo	Infarction	1) Hemorrhagic infarction (frontal and parietooccipital)	0	1	1	1	1	2	0	1	1	0	1	1	1) 1	1	2
																	2) 1	1	2
	1 mo	3 mo		2) Ventricular enlargement	1	2	3	1	2	3	0	2	3	0	2	2	1) 1	2	3
																	2) 1	2	3
11	4 wk	14 wk	Infarction	Infarction	1	2	3	1	2	3	0	1	2	0	0	1	2	2	3
	14 wk	25 wk			1	2	3	1	2	2	0	0	1	0	0	1	2	2	3
12	5 wk	3 mo	Infarction	Superficial L fronto/parietal and occipital L temporoparietal infarction	0	1	2	1	2	3	0	1	3	0	0	1	1	1	2
13	11 mo	17 mo	Infarction	Infarction	0	0	2	0	0	2	0	0	1	0	0	1	1	2	2
14	4 d	5.5 wk	HIE, I	1) Parenchymal hemorrhage	0	1	2	2	2	3	0	0	2	0	0	2	1) 2	2	2
																	2) 2	3	3
	5.5 wk	20 wk		2) Ventricular enlargement	2	2	3	2	2	3	1	1	3	1	1	3	1) 2	2	2
																	2) 2	3	3
15	2 mo	3 mo	HIE, I	No lesions	0	1	2	1	2	2	0	1	2	0	1	2	0	0	0
	3 mo	6 mo			0	1	2	0	1	1	0	1	2	0	1	2	0	0	0

Continued

Patient	Age at Imaging		Clinical Diagnosis	Abnormal MR Findings	Cerebral Hemispheres			Ventricles			Brain Stem			Cerebellum			Lesion(s)		
	1st Study	2nd Study			2-D	Reg 3-D	Subtr	2-D	Reg 3-D	Subtr	2-D	Reg 3-D	Subtr	2-D	Reg 3-D	Subtr	2-D	Reg 3-D	Subtr
16	2 d	18 d	HIE, II	1) Parenchymal hemorrhage (basal ganglia)	1	2	2	2	2	3	0	0	1	1	1	2	1) 2	2	2
				2) Brain swelling													2) 2	2	3
17	5 d	12 d	HIE, II	Parenchymal hemorrhage in basal ganglia	0	0	1	0	0	1	0	0	0	0	0	0	1) 2	2	3
	12 d	6 wk			0	0	2	0	0	2	0	0	1	0	0	1	1) 2	2	3
18	9 d	16 d	HIE, II	1) Subdural hemorrhage	2	2	2	1	1	1	0	0	0	0	0	0	1) 3	3	3
																	2) 1	1	2
	16 d	6 wk		2) Infarction (posterocerebral)	2	2	2	1	2	2	0	1	1	0	1	1	1) 3	3	3
																	2) 1	2	2
	16 d	3.5 mo			1	2	3	1	1	2	0	1	2	0	1	2	1) 1	1	2
																	2) 1	1	2
19	2 wk	7 wk	HIE, II	Small parenchymal hemorrhage	0	2	2	1	2	2	0	1	2	0	1	1	2	2	2
	7 wk	12 wk			0	2	2	1	2	2	0	1	2	0	1	1	1	2	2
20	2 wk	5 wk	HIE, II	Parenchymal hemorrhage	0	0	2	0	1	2	0	0	1	0	0	0	1	2	2
21	2 mo	6 mo	HIE, II	1) Hemorrhagic infarction	0	1	3	1	2	3	0	1	2	0	1	2	1) 1	2	3
				2) Ventricular enlargement													2) 1	2	3
	6 mo	9.5 mo			0	1	3	1	2	3	0	1	2	0	1	2	1) 1	2	3
																	2) 1	2	3
22	10 mo	14 mo	HIE, II	1) Ventricular enlargement	0	1	3	0	1	3	0	0	2	0	0	2	1) 0	1	3
																	2) 0	0	0
	14 mo	19 mo		2) Lentiform nucleus cyst	0	1	3	0	1	3	0	0	2	0	0	2	1) 0	1	3
																	2) 0	0	0
23	1 d	1 d	HIE, III: died	1) Brain swelling	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
	1 d	3 d		2) Parenchymal hemorrhage	1	1	2	2	2	3	0	2	2	0	2	2	1) 2	2	3
																	2) 1	1	2
24	1 d	6 d	HIE, III: ? metabolic: died	1) Parenchymal hemorrhage (basal ganglia)	0	0	1	1	2	3	0	1	2	0	0	1	1) 2	2	2
				2) Ventricular enlargement													2) 1	2	3
25	9 d	9 d	Perinatal (group B streptococcus) infection	Abscesses and meningeal enhancement	0	0	0	0	0	0	0	0	0	0	0	0	3	3	3
26	3 mo	3 mo	Sturge-Weber disease	Sturge-Weber disease	0	0	0	0	0	0	0	0	0	0	0	0	0	0	2

Note.—Reg indicates registered; subtr, subtraction; GA, gestational age; IVH, intraventricular hemorrhage; HIE, hypoxic ischemic encephalopathy; and PVL, periventricular leukomalacia. Grading of change: 0, none; 1, mild; 2, moderate; 3, marked.

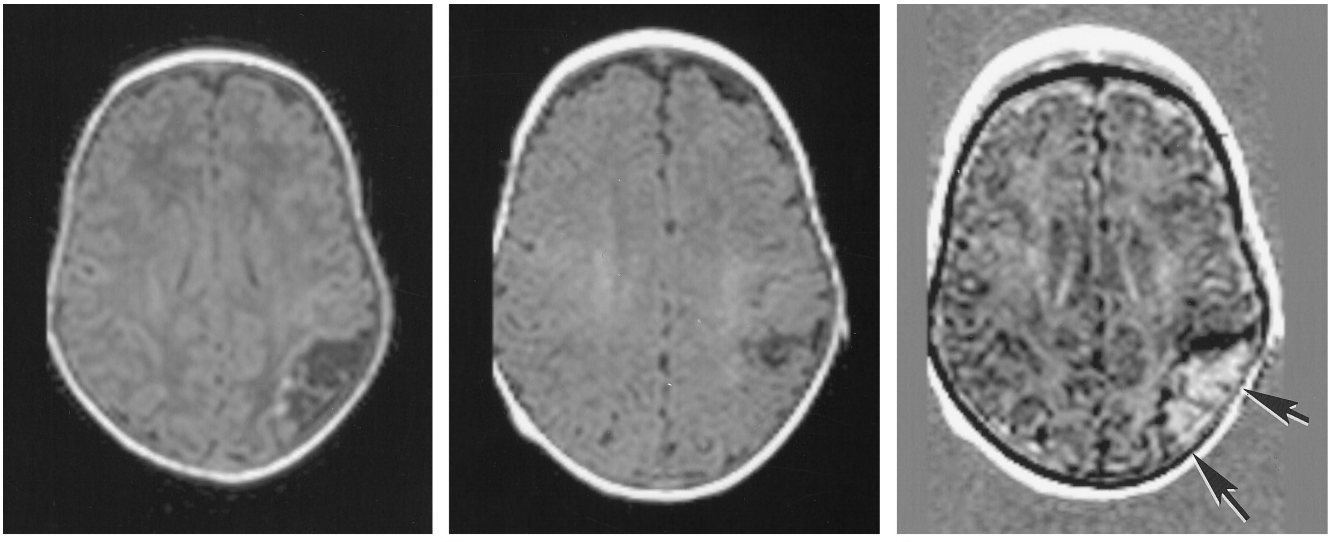

Fig 3. Case 11: Late phase of infarction.

Registered T1-weighted 3-D images (21/6/2) at 4 (*A*) and 14 (*B*) weeks with difference (*B* − *A*) image (*C*). The high signal area (*arrows*) shows increased growth in the region of the infarction relative to the changes elsewhere on the image.

which produced a well-demarcated homogeneous or nearly homogeneous region of low signal intensity on the registered T1-weighted images. The second phase of evolution was observed in four patients on images obtained at 4 weeks to 11 months of age and with follow-up examinations ranging from 2 to 6 months. On these studies, there was a marked decrease in the low signal region and evidence of an increased rate of growth in relation to the area of infarction (eg, Fig 3). This was particularly well seen at the margins of the infarct but could also be seen in the general location of the infarction.

A variety of patterns in addition to resolution of brain swelling was seen between 2 and 18 days in the 11 patients with HIE. The distribution and pattern of evolution of bilateral basal ganglia hemorrhage was seen better on the registered images than on the 2-D images.

In the two patients with HIE, multiple or more extensive areas of infarction developed in the late phase. Accelerated growth was again seen but with a wider distribution than in patients with isolated infarction (Fig 4).

Contrast enhancement was equally well seen with both conventional and registration subtraction techniques in two cases and better seen on the registered subtracted images.

Discussion

The registration technique used here provided precise matching of volume images and allowed small differences to be detected more frequently than with conventional unregistered images. Subtracted images produced from precisely registered images were particularly helpful in identifying regions of change that could then be studied in context by using the corresponding anatomic sections. Image registration also allowed the use of thinner sections, since it ensured that the anatomy displayed was matched as far as possible throughout the image planes. This reduced partial volume effects and helped in the detection of small and geometrically complex structures.

The application of this technique to infants and children is more complicated than in adults because of the large changes in brain size that occur with growth and development and the less well defined subarachnoid space, which makes differentiation of the brain from the scalp and skull more difficult.

In this study all subjects were patients and so it was not possible to define normal patterns of growth and development. Nevertheless, features were observed that are usually associated with growth and development, and these were more readily observed on the registered and subtracted images than on the conventional images. These included increase in size of the brain as well as increased image signal intensity due to decreased T1 and/or myelination.

The technique was particularly sensitive to changes in ventricular size. Such changes were

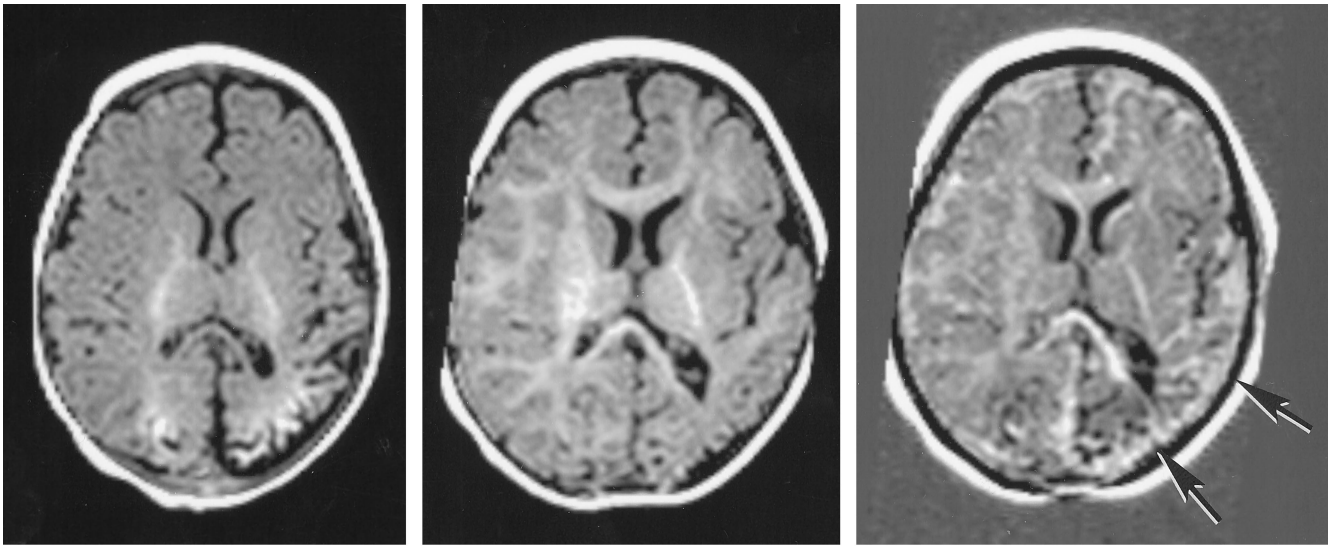

Fig 4. Case 21: Grade II HIE.

Registered T1-weighted 3-D images (21/6/2) at 2 (*A*) and 6 (*B*) months with difference (*B* − *A*) image (*C*). There is evidence of increased growth in the left hemisphere (*arrows* in *C*).

observed with the registered images when they were not apparent with conventional imaging. A spontaneous decrease in ventricular size was observed as well as a decrease following treatment with acetazolamide.

Changes in signal intensity of hemorrhage could be observed on difference images even when the lesion was of high signal and appeared off the scale on the conventional images. The use of thinner, accurately aligned sections also helped in defining anatomic location.

Of particular interest was the evidence of growth seen around infarction in the late phase. This rapidly proliferating tissue did not have the features of gliosis (long T1 and T2) and followed the configuration of the brain. In studies obtained after prenatal surgical removal of the frontal association cortex in rhesus monkeys, Goldman and Galkin (4) observed the formation of new sulci and gyri at the borders of the lesion. The surgical lesions were created at about 100 to 110 days' gestation, when the rhesus monkey brain is relatively lissencephalic. Because of the difference in species, stage of gestation, nature of the primary lesion, and other factors, it is difficult to extrapolate from these results to our patients, but it is of interest that this type of change has previously been observed in developing primates.

Conclusion

Subvoxel registration is likely to be of considerable value in detecting subtle changes in the brains of infants and children. It allows serial examinations to be placed in a well-defined context and viewed as part of a unified data set. The subtracted images allow areas of change to be clearly seen against a neutral background produced by precise cancellation of signals from unchanged structures. Applications of registration will include studies of normal as well as pathologic growth and development.

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