The management of acute necrotizing encephalitis: a review of 369 cases

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Introduction

Acute necrotizing encephalitis (ANE) has a highly fatal outcome and the importance of cerebral oedema as a cause of death has been clearly recognized (Pierce et al., 1964; Page, Tyler & Shillito, 1967; Delmas-Marsalet et al., 1968). Signs of brain herniation are common and have been well documented (Haymaker et al., 1958; Bloedhorn et al., 1962). This happens even in the absence of clinical signs of cerebral hypertension.

Van Bogaert, Radermecker & Devos (1955), Brihaye (1958) and Haymaker et al. (1958) had already noticed the close similarities between ANE and herpes encephalitis, but ANE was thought to be a mode of reaction against several viral aggressions rather than the unique expression of herpes simplex virus (HSV) infestation (Bergouignan, Julien & Vital, 1968a). Growing evidence for the identity of the two diseases has been brought to light by little. From 1965 up to 1970, out of thirty-nine cases where electron microscopy was performed, thirty-six showed the typical herpes-like particles (Rappel et al., 1971) and to date more than ten cases must be added to this series (Caulet et al., 1971; Laterre, 1972, Vital, 1972). Virus isolation and especially immunofluorescence techniques (Tomlinson & McCallum, 1969; Liu et al., 1971; Longson, 1973) have brought further evidence so that it can be assumed—with the possible exception of three cases (Duckett, Kelly & Grant, 1963; Scheid & Jochheim, 1956; Heathfield et al., 1967)—that ANE is of herpetic origin.

Therefore a correct therapeutic approach will include on the one hand the relief of the raised intracranial pressure, either surgically or medically or by both means; on the other hand, the inhibition of growth of the virus by cytotoxic compounds and/or interferon-inducers. In the present article, the term ‘treatment’ includes decompressive therapy and antiviral treatment with the exclusion of brain biopsy performed through a burr hole; as well as all the supportive treatments such as antibiotics and cardio-respiratory support.

Decompressive therapy

The presenting symptoms of ANE are often those of a temporal lobe mass (Pierce et al., 1964; Carmon, Behar & Beller, 1965; Potter 1969) and/or of raised intracranial pressure (Haymaker et al., 1958; Drachman & Adams, 1962; Castleman & McNeely, 1964; Blackwood et al., 1966). In similar situations, i.e. glioblastoma (Hitchcock & Sato, 1964) or acute hemorrhagic leukoencephalitis (Coxe & Luse, 1963) decompressive therapy followed or not by lobectomy will be performed.

Recently, Long et al. (1972a) have observed that in experimental brain oedema, early excision of the lesion prevented the development of swelling. Surgery performed later was as good as steroids, whereas after 24 hr, excision had no effect. However, in clinical situations, decompressive therapy itself can be a harmful procedure, allowing a sudden ‘mushroom-like’ billowing out of the cerebral matter through the opened skull. Such swelling will impair even more the local cerebral circulation and break down further the blood-brain barrier, increasing as a result the pre-existing oedema and leading to necrosis of the herniated brain (Fox, 1964).

Therefore medical decompression by hypertonic solutions of urea or mannitol, or by steroids are used pre- and per-operatively. Hypertonic solutions act rapidly and briefly (Goldstein et al., 1964; McQueen & Jeans, 1964) whereas steroids show a slower but more sustained action (Kofman, et al., 1957). Therefore, the first ones are used in acute situations, whereas the latter are preferred in more chronic conditions. Hydrocortisone, prednisolone and dexamethasone are clinically active at initial dosage of 100, 50 and 10 mg respectively, to be repeated (Fox, 1964).

The benefit gained from steroid therapy does not seem to depend upon their anti-oedema properties; ubiquitous effects are more likely, through their protective action on cell membranes (Long, Maxwell & French, 1972b; Demopoulos et al., 1972). Some experimental work suggests that the beneficial effect of dexamethasone does not appear to be mediated by its effects on oedema (Lewin, Pappius & Hansebout, 1972; Pappius, 1972). However, Clasen et al. (1972) suggest that in inflammatory and necrotic lesions the response to dexamethasone might not be as good as in oedema of other origin.

In experimental herpes encephalitis, hydrocortisone did not have a beneficial effect in guinea-pigs (Tokumaru, 1967) neither did prednisolone have any effect in ninety-two cases of viral encephalitis (Hohenegger, 1967). On the other hand, Crompton & Teare (1965) reported two cases of herpes encephalitis after the reduction of steroid maintenance therapy in chronic diseases.

**Antiviral therapy**

**Idoxuridine**

Idoxuridine (5-ido-2′-deoxyuridine; IUDR, IDU, SKF 14-287) a pyrimidine analogue was, like other halogenated derivates (FUDR, BUDR), primarily prepared for studies on cancer therapy, but has shown only moderate tumour-inhibitory effect (Calabresi et al., 1961). On the other hand halogenated pyrimidines were found to be—*in vitro*—good inhibitors of DNA-containing viruses (Herrmann, 1961; Lerman, Doyle & Doyle, 1962; Rapp, 1964; Buthala, 1964).

This was confirmed in animals (Perkins et al., 1962; Kaufman, 1962; Calabresi, McCollum & Welch, 1962, 1963a, b; Kaufman & Maloney, 1963). In man good results have been obtained in herpetic keratitis (Maxwell, 1963; Thomas, Purnell & Rosenthal, 1965), in severe cutaneous herpes (Longson, 1970) and in stomatitis (Douglas, Condemi & Balduzzi, 1971). IDU was also found active against vaccinia-zoster virus (Juel-Jensen et al., 1970).

In encephalitis, the systemic route must be used. Idoxuridine is poorly soluble in water, unless the solution is alkalinized at pH 8.5–9. The compound acts as a false thymidine and blocks the duplication of the virus, but has in counterpart a toxic effect on a variety of rapidly proliferating tissues such as hair-follicles, bone-marrow and epithelial cells of the oral mucosa. The effects are often mild and transient at the usual dosage of 400–600 mg/kg body weight (Calabresi et al., 1961), although severe side-effects have been reported (Dayan & Lewis, 1969).

IDU can reverse the deleterious effects of corti-

**Cytosine-arabinoside**

Cytosine-arabinoside (1-β-d-arabinofuranosylcytosine, cytarabine, cytosar, Ara-C, C-A, U-19–220A) was also first used in cancer therapy (Evans et al., 1961; Talley & Vaitkevicius, 1963) but its antiviral activity was rapidly recognized (Underwood, 1962; Rapp, 1964; Buthala, 1964; Butel & Rapp, 1965) and its use in varicella-zoster and HSV infections advocated (Kaufman & Maloney, 1963; McKelvey & Kwaan, 1969; Hall et al., 1969; Miller, Sloan & Silverman, 1969; Juel-Jensen, 1970a, b; Foerster & Hryniuk, 1971) in spite of some doubts cast about its effectiveness (Seligman & Rosner, 1970; Mann, 1971).

Buthala (1964) has demonstrated that cytarabine and IDU had only additive effect, but Ara-C was able to eliminate even the IDU-resistant viruses (Underwood, Wisner & Weed, 1964).

Because of the high toxicity of the drug when given in continuous perfusion, single daily rapid intravenous injections are now preferred. The schedule proposed by Juel-Jensen (1971), i.e. respectively 10, 8, 8, 8, and 6 mg/kg body weight appears to be safe.

In cell culture infected by HSV, Ara-C was found much more active than IDU (Buthala, 1964) whereas as in rats, inoculated with vaccinia, IDU only was active (Calabresi et al., 1963b). In herpes simplex keratitis in the rabbit, Ara-C was found to be at least as effective as IDU (Underwood, 1962).

Almost all the cases of herpes encephalitis in adults are due to HSV type I (Craig & Nahmias, 1973). Walker et al. (1970) have demonstrated that in HSV type I and type II infections, better results were obtained with IUDR and FUDR respectively, whereas Ara-C inhibited both type of viruses. The existence of IDU-resistant strains (Buthala, 1964a), that can be overcome by Ara-C (Underwood et al., 1964), is in favour of the latter drug as well as its simple preparation, compared with the painstaking and time-consuming preparation of IDU solution. However, in the present state of knowledge, there is no definite superiority of one drug over the other which has been demonstrated in herpes encephalitis.

**Interferons**

Interferons, discovered by Isaacs & Lindenmann (1957), are peptides produced by most animals—including man—and play a significant role in the protection against viral diseases (Isaacs & Hitchcock, 1960; Scientific Committee on Interferon, 1962;
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The usefulness of interferon, or of the synthetic inducers, has been demonstrated against many viruses, including herpes (Cantell & Tommila, 1960; Jones, Galbraith & Al-Hussaini, 1962; Park & Baron, 1968; Lindh et al., 1969; De Clercq & Merigan, 1970b; Kruger & Mayer, 1970). Its protective activity in experimental herpes encephalitis has been demonstrated by Catalano & Baron (1969).

Unfortunately repeated exposure to stimulation led to the development of hyporeaction, tolerance or refractoriness of the interferon-forming cells (Ho, 1970). This in turn has to be overcome by other drugs (Grossberg, 1972).

Human cell culture seems not to be affected by Poly-I–Poly-C (Hilleman, 1970a); careful and limited experimentation in man have shown only moderate toxic effects (fever, slight liver changes, disorders of coagulation) (Hilleman, 1970b; Merigan, 1970).

However, the problem of the toxicity/activity ratio of the inducers is still a preoccupying factor which prevents their generalized use (Levy, 1970; Hill et al., 1971) and will perhaps restrict them to the treatment of life-threatening virus infections (Finter, 1970).

Other compounds

In recent years, several compounds have been tested against viruses. Rifampicin has shown antiviral properties (Heller et al., 1969; Subak-Sharpe, Timbury & Williams, 1969) and some derivatives, like rifamycines and aminopiperazines, are active against HSV (Lancini, Cricchio & Thiry, 1971). L-asparaginase has also proved its effectiveness (Maral & Werner, 1971) and extracts of Burkitt’s lymphoma cell culture have been successfully used in ocular herpes simplex infection in rabbits (Albert & Rabson, 1971).

It must be pointed out that most of the above antiviral compounds show also some antitumour activity (Calabresi et al., 1961; Evans et al., 1961; Adamson et al., 1969; Levy et al., 1969; Adamson, 1971; Crowther, 1971) and some of them paradoxically depress both specific (immunologic) and non-specific (interferon system) mechanisms of defence against infection, while their action on chromosomes is still a matter of controversy (Kilbourne, 1955b; Immam and Hammon, 1957b; Kilbourne, Smart & Pokorny, 1961; Holmes, Gilson & Deinhardt, 1964; Kabak, Saksela & Mellman, 1964; Hilleman, 1965; Levy, Axelrod & Baron, 1965; Mitchell et al., 1969; Berenbaum, 1970; Chakrabarty & Friedman, 1970; Ho, 1970).

Results and discussion

369 cases of ANE have been reviewed and the results are summarized in Tables 1 and 2. The figures suggest that any treatment is better than no treatment at all. However, these rough results deserve some comments. Most of the cases—either published

<table>
<thead>
<tr>
<th>TABLE 1. Outcome of 369 cases of ANE</th>
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<tbody>
<tr>
<td>Treatment</td>
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<tr>
<td>-----------</td>
</tr>
<tr>
<td>Untreated</td>
</tr>
<tr>
<td>Treated</td>
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<table>
<thead>
<tr>
<th>TABLE 2. Outcome of 101 treated cases</th>
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<tr>
<td>Treatment</td>
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<tr>
<td>-----------</td>
</tr>
<tr>
<td>Surgery only</td>
</tr>
<tr>
<td>IDU only</td>
</tr>
<tr>
<td>Ara-C only</td>
</tr>
<tr>
<td>Steroids only</td>
</tr>
<tr>
<td>Steroids + surgery</td>
</tr>
<tr>
<td>IDU or Ara-C + surgery</td>
</tr>
<tr>
<td>IDU or Ara-C + steroids</td>
</tr>
<tr>
<td>IDU or Ara-C + surgery + steroids</td>
</tr>
<tr>
<td>Poly-I–Poly-C</td>
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</table>

or the subject of personal communications—have been referred to hospital because of the severity of the disease, and indeed coma was one of the most common presenting symptoms. Therefore the high mortality rate observed in ANE may have been biased by a preselection of the worst cases. It must be remembered that ANE was first—and sometimes still remains—a necropsy diagnosis, even though it is now becoming a bedside diagnosis. In 1958, Haymaker et al. reviewed all the cases of ANE in adults known at the time; until then thirty-seven cases had been collected. To date more than 400 cases have been reported, and nearly thirty new cases are added every year (see Table 4). This more likely reflects improvement in diagnosis rather than higher
prevalence of the disease, for many cases may have been unrecognized in the past (Nolan, Carruthers & Lerner, 1970; Upton, Barwick & Foster, 1971).

A few authors have published relatively large series of untreated patients with survival (Meyer et al., 1960; Leider et al., 1965; Miller, Hesser & Tompkins, 1966; Olsen et al., 1967). These cases probably represent the less severe form of the disease. Miller et al. (1966) points out that in their series ten out of thirteen comatose patients died, whereas only one of the seven non-comatose patients died. A benign form of the disease, presenting like a more or less transient temporal lobe impairment may have been wrongly diagnosed as 'stroke' (Rappel & Violon, 1973). Therefore, if severer cases of ANE have been missed, milder cases may also have been overlooked, so that the true incidence, natural history and mortality rate of the disease remains largely unknown.

On the other hand, the terms 'alive' and 'dead' do not give a full account of the outcome of the disease. Table 3 gives the survival time in 172 deaths. In untreated patients, the death rate amounts to 80% within 3 weeks, 84% within a month and 90% within 2 months. Within 6 months, all but one patient had died. In treated patients, the mortality rates are 57%, 67-5% and 80% for 3 weeks, 1 and 2 months respectively. At 6 months, 12.5% are still alive. This seems to indicate that treating the patients will increase the survival time.

However, Table 4 shows that 70% of all the treated cases have been reported within the last 5 years. The part played in that period of time by the improvement of supportive treatment, especially cardio-respiratory, is difficult to assess. One must point out that as far as the presenting symptoms and the severity of the disease are concerned the treated group was in no way different from the untreated group.

However, the patients of the latter group have been usually reported as part of series collected over several years (Haymaker et al., 1958; Bennett, Zurhein & Roberts, 1962; Drachman & Adams, 1962; Flamant-Durand, Capon & Coers, 1965; Leider et al., 1965; Miller et al., 1966; Olsen et al., 1967; Roy & Wolman, 1969) thus preventing any time/outcome correlation. Until now, no controlled trial has ever been performed, but some reports deserve our interest.

Nolan et al. (1970) had better results in the treated than in the untreated patients observed during the same period of time. Two of the three survivors reported by Carmon et al. (1965) were treated. The only survivors in the series of Bergouignan et al. (1968b) and Delmas-Marsalet et al. (1968) were also the only patients operated upon.

Another point in favour of the effectiveness of treatment is that the first signs of recovery often appeared 12–72 hr after therapy was begun (Adams & Jennett, 1967; Evans et al., 1967; Marshall, 1967; Duffy, 1969; Rappel & Brihaye, 1969; Goldman et al., 1970; Masquin, 1970; Nolan et al., 1970; Silk & Roome, 1970; Bellanti, Catalano & Chambers, 1971; Chow et al., 1971; Gurwith, Harman & Merigan, 1971; Habel & Brown, 1972; Upton et al., 1971; Laterre, 1972). This phenomenon was not observed in untreated patients. After initial improvement some patients died several weeks or months later from causes not directly related to ANE (Duffy, 1969; Bellanti et al., 1971; Rappel et al., 1971). In the present review they are considered as treatment-failures. Indeed their increased sensitivity to dramatic and fatal infections can be considered as a remote effect of their initial illness. The quality of survival is discussed elsewhere in this issue (Oxbury & MacCallum, 1973) and will therefore not be commented on in the present study.

In the present state of knowledge no treatment seems to be preferable to the others. In Case A described by Gurwith et al. (1971), the patient deteriorated whilst on dexamethasone and recovered shortly after IDU therapy had begun. In Case I of Laterre (1972) IDU was of no help, but external decompression and lobectomy had an obvious beneficial effect. In Case I (J.S.) described by Rappel et al. (1971) the situation deteriorated despite surgery, but responded rapidly to IDU.

Today's treatment should not be confined to only one approach to the disease but will include surgery and drug therapy. Surgery has the advantage of allowing a large view of the affected area, often

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**Table 3. Survival time—data available from 172 patients out of 257 deaths**

<table>
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<tr>
<th>Death within</th>
<th>Untreated patients</th>
<th>Treated patients</th>
</tr>
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<tbody>
<tr>
<td>1 week</td>
<td>26</td>
<td>5</td>
</tr>
<tr>
<td>2 weeks</td>
<td>52</td>
<td>9</td>
</tr>
<tr>
<td>3 weeks</td>
<td>27</td>
<td>9</td>
</tr>
<tr>
<td>1 month</td>
<td>6</td>
<td>4</td>
</tr>
<tr>
<td>2 months</td>
<td>7</td>
<td>5</td>
</tr>
<tr>
<td>6 months</td>
<td>13</td>
<td>3</td>
</tr>
<tr>
<td>1 year</td>
<td>0</td>
<td>3</td>
</tr>
<tr>
<td>1 year</td>
<td>1</td>
<td>2</td>
</tr>
</tbody>
</table>

**Table 4. Cases of ANE published**

<table>
<thead>
<tr>
<th>Year</th>
<th>Untreated patients</th>
<th>Treated patients</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Dead</td>
<td>Alive</td>
</tr>
<tr>
<td>1967</td>
<td>36</td>
<td>18</td>
</tr>
<tr>
<td>1968</td>
<td>13</td>
<td>4</td>
</tr>
<tr>
<td>1969</td>
<td>16</td>
<td>—</td>
</tr>
<tr>
<td>1970</td>
<td>9</td>
<td>5</td>
</tr>
<tr>
<td>1971</td>
<td>2</td>
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</tbody>
</table>
permitting a per-operative diagnosis. On the other hand the necrotic tissues can be easily removed, and intracranial pressure better controlled. Drug therapy will include medical decompensation and virus growth inhibition. The possible usefulness of combined therapy like Ara-C and l-asparaginase, discussed in this issue by Cappel, Thiry & Klastersky (1973), suggest that the future lies in polychemotherapy. We must also bear in mind that the treatment should be started as early as possible in order to prevent irreversible damage taking place before therapy (Charnock & Cramblett, 1970).

The present review is intended to demonstrate the difficulties, the biases, the loopholes and the limits of a retrospective study. The time has now come to encourage the undertaking of prospective and collaborative studies, for the advancement of our knowledge and for the sake of our patients.

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